# Sepsis requiring Intensive Care Unit admission

Studies on temporal trends in epidemiology, cancer, elective surgery and local infectious outbreaks

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**Thesis for the degree of Philosophiae Doctor**

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UNIVERSITY OF ICELAND
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# Sýklasótt sem krefst innlagnar á gjörgæsludeild

## Þróun faraldsfræði yfir tíma, krabbamein, valaðgerðir og áhrif einstakra faraldra

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# Ágrip

Sýklasótt (sepsis) er ein algengasta ástæða innlagna á gjörgæsludeildir í heiminum og er dánartíðnin há þrátt fyrir framfarir í stuðningsmeðferð. Mikil vitundarvakning hefur verið um heilkennið á síðastliðnum 20 árum í kjölfar birtinga fjölda rannsókna sem sýndu fram á betri lifun með tiltölulega einfaldri meðferð, til dæmis skjótri gjöf vökva og sýklalyfja. Þessi vitneskja varð hvatinn að alþjóðlegu átaki í meðferð sýklasóttar sem hafði það að markmiði að draga úr dánartíðni vegna sjúkdómsins. Nokkur fjöldi rannsókna á síðastliðnum árum hefur sýnt vaxandi nýgengi sýklasóttar, ásamt lækkandi dánarhlutfalli. Þessar rannsóknir hafa margar verið byggðar á greiningarkóðum í sjúkraskrám, en talið er að hin nýlega vitundarvakning um sýklasótt geti skekkt niðurstöður slíkra rannsókna vegna bættrar skráningar. Sýklasótt er þekktur fylgikvilli ýmissa læknismeðferða sem hafa áhrif á varnir líkamans, til dæmis krabbameinslyfjameðferða og skurðaðgerða. Sjaldgæft er að sjúklingar veikist af völdum mengaðra áhalda, íhluta eða lyfja en stöðug árvekni gagnvart sýkingum er nauðsynleg til að uppgötva slík tilfelli fljótt.

Heildarmarkmið þessa verkefnis var að lýsa faraldsfræði sýklasóttar sem leiðir til innlagna á gjörgæsludeildir hjá heilli þjóð hér á Íslandi og skoða sérstaklega nokkra undirhópa. Metið var hvort breytingar hefðu orðið á nýgengi, meðferð og afdrifum sjúklinga yfir tíma, auk þess að lýsa nánar krabbameinssjúklingum með sýklasótt, sjúklingum sem fengu sýklasótt í kjölfar valskurðaðgerða og áhrifum hópsýkinga tengdum vélindaómtæki.

Rannsóknirnar fjórar (I-IV) sem ritgerð þessi byggir á voru allar aftursæjar áhorfsrannsóknir á tveimur stórum hópum sjúklinga. Farið var yfir gögn allra sjúklinga sem lögðust inn á gjörgæsludeildir á Íslandi og metið hvort þeir uppfylltu skilyrði fyrir alvarlegri sýklasótt eða sýklasóttarlosti við innlögn. Rannsóknartímabilið voru árin 2006, 2008, 2010, 2012, 2014 og 2016 og var stuðst við gögn í sjúkraskrám sjúklinga. Þessi gagnagrunnur tók til 971 sýklasóttarsjúklings og var notaður í rannsóknum I-III. Fyrir rannsókn III var að auki fenginn listi yfir allar skurðaðgerðir sem framkvæmdar voru á Landspítala sömu ár. Fyrir rannsókn IV voru fundnir allir sjúklingar sem gengist höfðu undir opna hjartaaðgerð á Íslandi á árunum 2013-2017 og voru þeir 973.

Í rannsókn I voru helstu niðurstöður þær að nýgengi sýklasóttar á íslenskum gjörgæsludeildum breyttist ekki yfir 11 ára rannsóknartímabilið og dánarhlutfall var einnig stöðugt. Nokkrar breytingar sáust í meðferð sjúklinga yfir rannsóknartímann, svo sem skjótari mælingar á mjólkursýru í blóði eftir komu á bráðamóttöku og minni notkun sterkjulausna og blóðhluta, en engin

breyting varð hins vegar á tímalengd að gjöf sýklalyfja eftir komu á bráðamóttöku.

Niðurstöður rannsóknar II sýndu að 24% allra sýklasóttarsjúklinga á gjörgæsludeildum hafa undirliggjandi krabbamein og innlögnum krabbameinssjúklinga með sýklasótt fjölgaði á seinni hluta rannsóknartímabilsins. Eðli sýkinga og afdrif sjúklinga voru mismunandi eftir tegundum krabbameina. Sjúklingar með meinvörp voru síður líklegri til að fá meðferð með öndunarvél, legutími þeirra á gjörgæsludeild var stuttur og dánartíðni há.

Í rannsókn III reyndist tíðni sýklasóttar eftir valaðgerðir á Landspítala vera lág, eða 0,19%, en hún var mjög breytileg milli aðgerðartegunda. Hæst var tíðnin eftir bris- og skeifugarnarbrottnám (Whipple aðgerð) og brottnám á vélinda en mesti fjöldi sjúklinga í rannsóknarhópnum hafði gengist undir brottnám á ristli. Dvalartími á gjörgæsludeild var langur og dánartíðni sambærileg við aðra sýklasóttarsjúklinga. Tíðni ófullnægjandi fyrstu sýklalyfjameðferðar var há.

Tilefni rannsóknar IV voru tvær hópsýkingar sem tengdar voru lækningatæki, ómhaus sem notaður er við hjartaómskoðun um vélinda í öllum hjartaaðgerðum. Í örfínum sprungum á tækinu lifðu bakteríur af hefðbundna sótthreinsun og bárust í sjúklinga. Birtingarmynd þessara sýkinga var oftast lungnabólga á fyrstu dögum eftir aðgerð en sýklasóttarlost og hjartaþelsbólga komu einnig upp. Til að meta áhrif þessara hópsýkinga var tekinn saman gagnagrunnur yfir allar opnar hjartaaðgerðir yfir fimm ára tímabil. Tíðni sýkinga eftir hjartaaðgerðir á Íslandi var 20%, algengastar voru lungnabólgur og grunnar skurðsárasýkingar.

Af þessum rannsóknum, sem byggja á vönduðum faraldsfræðigögnum fyrir heila þjóð, má álykta að faraldsfræði sýklasóttar sem leiðir til innlagna á gjörgæsludeildir hefur ekki breyst yfir 11 ára tímabil. Nýlegt átak í meðferð leiddi ekki til mikilla breytinga. Krabbamein eru algeng hjá sýklasóttar-sjúklingum en takmarkaðri gjörgæslumeðferð var beitt hjá sjúklingum með langt genginn sjúkdóm. Stærri kviðarholsaðgerðir vegna krabbameina voru algengasta orsök sýklasóttar eftir valaðgerðir og vanda þarf val fyrstu sýklalyfja hjá þessum sjúklingahópi. Hópsýkingar eftir hjartaaðgerðir sýna fram á mikilvægi þess að vera vakandi fyrir óvanalegu mynstri sýkinga.

**Keywords:**

Faraldsfræði, árangur gjörgæslumeðferðar, krabbamein, valaðgerðir, hjartaaðgerðir.

# Abstract

Sepsis is a leading cause of admission to *intensive care units* (ICU) worldwide and mortality rates remain high despite advances in organ support. Awareness of the syndrome has increased substantially in the past 20 years, after the publication of several studies that showed improved outcome with relatively simple measures, such as early administration of fluid and antibiotics. These studies were the impetus for an educational treatment campaign with the goal of reducing mortality from sepsis. Several studies in recent years have shown an increasing incidence of sepsis, and declining mortality rates. Many of those are based on diagnosis codes with risk of bias due to increased use of sepsis codes as a result of this heightened awareness of sepsis. Medical care may contribute to the development of sepsis, not only by weakening host defences with immunosuppressive therapy and surgical procedures, but also on rarer occasions by contamination, highlighting the importance of scrutinous observation of hospital-acquired infections.

The overall aim of this thesis was to create a broad overview of sepsis requiring admission to intensive care units in a nationwide cohort in Iceland, with a special focus on several patient groups. Trends in incidence, treatment and outcome were assessed, with special consideration given to cancer patients with sepsis, patients developing sepsis after surgery and the detection of nosocomial infection clusters and their impact.

The four studies (I-IV) were retrospective cohort studies using two cohorts of patients. For the first cohort, all ICU admissions in Iceland were screened for the presence of severe sepsis or septic shock on admission during calendar years 2006, 2008, 2010, 2012, 2014 and 2016 using clinical criteria and chart review. This database of sepsis patients (971 patients) was used in studies I,II and III. Additionally, for study III, the number and type of all surgical procedures performed at the largest hospital in Iceland, Landspitali, during the same study years were collected. For study IV, a second database was constructed for all patients who underwent open-heart surgery in Iceland from 2013-2017 (973 patients).

In study I the population incidence of sepsis requiring intensive care did not change over the 11-year study period and mortality rates remained stable as well. Changes in treatment observed over the study period included earlier measurements of serum lactate and a reduction in the use of colloids and blood products, but no change was seen in the timing of antibiotic administration.

In study II it was observed that 24% of all sepsis patients admitted to the ICU had an underlying malignancy and the prevalence of such admissions was higher in the latter half of the study period. Patient characteristics and outcome varied between cancer types. Patients with metastatic disease were less likely to receive invasive mechanical ventilation, had a short duration of stay in the ICU and high mortality.

In study III, the overall incidence of sepsis requiring intensive care after elective surgery was low (0.19%) at Landspitali, but varied considerably between surgical procedures. The highest incidence was observed after pancreaticoduodenectomy and oesophageal resections, but the largest number of patients had undergone colorectal surgery. ICU length of stay was long, with similar mortality rates as in other sepsis patients. The rates of insufficient initial empirical antimicrobial therapy were high.

In study IV, two nosocomial clusters of infections are described that were related to the use of surface-damaged TEE (transoesophageal echocardiography) probes used during cardiac surgery. Clinical presentation was most often postoperative pneumonia but fulminant septic shock and cases of endocarditis were seen as well. The overall incidence of postoperative infections after cardiac surgery in Iceland was 20%, most frequently pneumonia and superficial wound infections.

From these studies it is concluded that by using clinical criteria in a nationwide cohort, the incidence and outcome of sepsis requiring admission to intensive care units did not change over an 11-year period. Recent treatment campaigns had limited effect on sepsis management. Cancer is a frequent comorbidity in sepsis patients but the extent of intensive care was limited in patients with advanced disease. Major oncological procedures are the most common cause of postoperative sepsis following elective surgery, and the choice of empirical antimicrobial therapy needs careful consideration in this setting. Examples of nosocomial outbreaks of infections are described which emphasize the importance of continuous infection surveillance systems.

**Keywords:**

Epidemiology, critical care outcomes, neoplasms, elective surgical procedures, cardiac surgical procedures

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# Contents

# List of abbreviations

| | |
|---|---|
| ACCP | American College of Chest Physicians |
| APACHE | Acute Physiology and Chronic Health Evaluation |
| aPTT | Activated Partial Thromboplastin Time |
| AKI | Acute Kidney Injury |
| ALT | Alanine aminotransferase |
| ARDS | Acute Respiratory Distress Syndrome |
| AST | Aspartate aminotransferase |
| AVR | Aortic Valve Replacement |
| BMI | Body Mass Index |
| CABG | Coronary Artery Bypass Grafting |
| CI | Comorbidity Index |
| CI | Confidence Interval |
| CNS | Central Nervous System |
| CRP | C-Reactive Protein |
| CVP | Central Venous Pressure |
| ECMO | Extracorporeal Membrane Oxygenation |
| ED | Emergency Department |
| *e.g.* | Exempli gratia (Latin: for example) |
| EGDT | Early Goal-Directed Therapy |
| FiO2 | Fraction of Inspired Oxygen |
| DIC | Disseminated Intravascular Coagulation |
| IABP | Intra-Aortic Balloon Pump |
| ICD | International Statistical Classification of Diseases |
| ICU | Intensive Care Unit |
| *i.e.* | Id est (Latin: that is) |

| | |
|---|---|
| IL | Interleukin |
| INR | International Normalized Ratio |
| IMV | Invasive Mechanical Ventilation |
| IQR | Interquartile Range |
| KDIGO | Kidney Disease: Improving Global Outcomes |
| LOS | Length of stay |
| MAP | Mean Arterial Pressure |
| ml | Milliliters |
| MVR | Mitral Valve Replacement |
| NIV | Non-Invasive Ventilation |
| NO | Nitric oxide |
| NYHA | New York Heart Association |
| OPCAB | Off-Pump Coronary Artery Bypass |
| PCR | Polymerase Chain Reaction |
| PaO2 | Partial pressure of oxygen in arterial blood |
| RNA | Ribonucleic Acid |
| RRT | Renal Replacement Therapy |
| SBP | Systolic Blood Pressure |
| SCCM | Society of Critical Care Medicine |
| $S_{cv}O_2$ | Central venous oxygen saturation |
| SD | Standard Deviation |
| SIRS | Systemic Inflammatory Response Syndrome |
| SOFA | the Sequential Organ Failure Assessment |
| SSC | Surviving Sepsis Campaign |
| TEE | Transoesophageal Echocardiography |
| TNF | Tumour Necrosis Factor |

# List of figures

# List of tables

# List of original papers

This thesis is based on the following original publications, which are referred to in the text by their Roman numerals (I-IV).

I. **Vesteinsdottir E**, Sigurdsson MI, Gottfredsson M, Blondal A, Karason S. *Temporal trends in the epidemiology, management and outcome of sepsis – a nationwide observational study.* Acta Anaesthesiol Scand 2022;66:497-506. DOI:10.1111/aas.14026

II. **Vesteinsdottir E**, Sigurdsson MI, Gottfredsson M, Blondal A, Karason S. *A nationwide study on characteristics and outcome of cancer patients with sepsis requiring intensive care*. Submitted for publication.

III. **Vesteinsdottir E**, Gottfredsson M, Blondal A, Sigurdsson MI, Karason S. *Sepsis after elective surgery – Incidence, aetiology and outcome.* Acta Anaesthesiol Scand 2021;65:457-465. DOI: 10.1111/aas.13747

IV. **Vesteinsdottir E**, Helgason KO, Sverrisson KO, Gudlaugsson O, Karason S. Infections and outcomes after cardiac surgery – The impact of outbreaks traced to transesophageal echocardiography probes. Acta Anaesthesiol Scand 2019;63:871-878. DOI: 10.1111/aas.13360

In addition, some unpublished data are presented:

All papers are reprinted by kind permission of the publishers.

## Declaration of contribution

For paper I, the doctoral student, Edda Vésteinsdóttir (EV), planned the study with professor emeritus Gísli H. Sigurðsson (GHS) and supervisor Sigurbergur Kárason (SK). EV screened all intensive care unit admissions for sepsis and included patients into the study under guidance of GHS and with advice regarding diagnosis and management of infections from Magnús Gottfreðsson. EV registered patient data for a large part of the cohort and supervised medical students Íris Kristinsdóttir, Perla Steinsdóttir, Hrafnkell Óskarsson and Hildur Ólafsdóttir in collecting the rest of the patient data on pre-printed study forms. EV entered data into an electronic database, did statistical analysis with advice from Martin Ingi Sigurdsson and wrote the manuscript with input from all co-authors.

For paper II, EV planned the study with supervisor SK and co-authors. The same database as in study I was used. EV collected additional data, did statistical analysis and wrote the manuscript with input from co-authors.

For paper III, the same sepsis database as in study I was used. EV planned the study with supervisor SK and co-authors. EV collected additional data on surgical procedures in Iceland, did the statistical analysis and wrote the manuscript with guidance from co-authors.

For paper IV, EV planned the study with supervisor SK and co-authors. EV collected data on cardiac surgery patients in Iceland, did statistical analysis and wrote the manuscript with input from co-authors. Kristján Orri Helgason and Ólafur Guðlaugsson managed genetic analysis of the bacterial strains.

The doctoral student, EV, wrote this thesis with guidance from supervisor SK and the doctoral committee.

*"Except on few occasions, the patient appears to die from the body's response to infection rather than from it"*

William Osler (The Evolution of Modern Medicine 1904)

# 1 Introduction

Sepsis is a syndrome caused by infection but the clinical manifestation is highly variable, from a rapidly progressing multiorgan failure to the more subtle initial presentation of weakness and confusion commonly seen in the elderly.[1,2] It is a leading cause of admission to intensive care units worldwide (12-28% of all admissions),[3-6] with high mortality rates (30-40%)[3-6] and survivors can be affected by substantial long-term morbidity.[7] Sepsis is an area of very active research, as any intervention that would consistently reduce morbidity and mortality due to it would be of immense global benefit.

This thesis is based on four epidemiological studies on sepsis from a nationwide population in Iceland with different perspectives. The primary aim was to assess recent trends in incidence, treatment and mortality, in addition to providing data on certain patient groups that have not been described in this manner before. Also, two infectious outbreaks in surgical patients in the ICU are portrayed.

This introduction starts with a brief historical overview of sepsis, before moving on to the topics of pathophysiology, epidemiology and some aspects of sepsis management. All of these could easily be the subject of an entire independent thesis, on this highly researched, but complex syndrome.

## 1.1 Sepsis – a brief history

Infectious diseases, the illnesses caused by pathogens or their toxic products, have been the leading cause of death in humans throughout the ages and still are in low-income regions.[8] The word “sepsis” origins from ancient Greek, *σηψιω*, pertaining to the decomposition of organic matter.[9] Hippocrates noted the similarities between the smell of festering wounds and the foul air emerging from swamps. This process was at that time thought to arise spontaneously or from “bad air” (miasma theory).

Francisco Redi, physician in Florence, refuted this theory with his experiments on the putrefaction of meat in 1668. He showed that exposure to open air (and thus flies) was essential for the process. Maggots were not seen in meat covered with gauze or stored in an air-tight container.[10] Some years previously, Girolamo Fracastoro from Verona, had published his theory on the “seeds of disease” that could be spread by contact, fomites or air and rapidly multiplied (“De contagione et contagiosis morbis” in 1546).[11] These

ideas, however, failed to achieve widespread influence. It wasn't until a century later (1674) that the Dutch self-taught scientist, Antoni van Leeuwenhoek discovered protozoa, and later bacteria, with his microscope[12] (**Figure 1**).

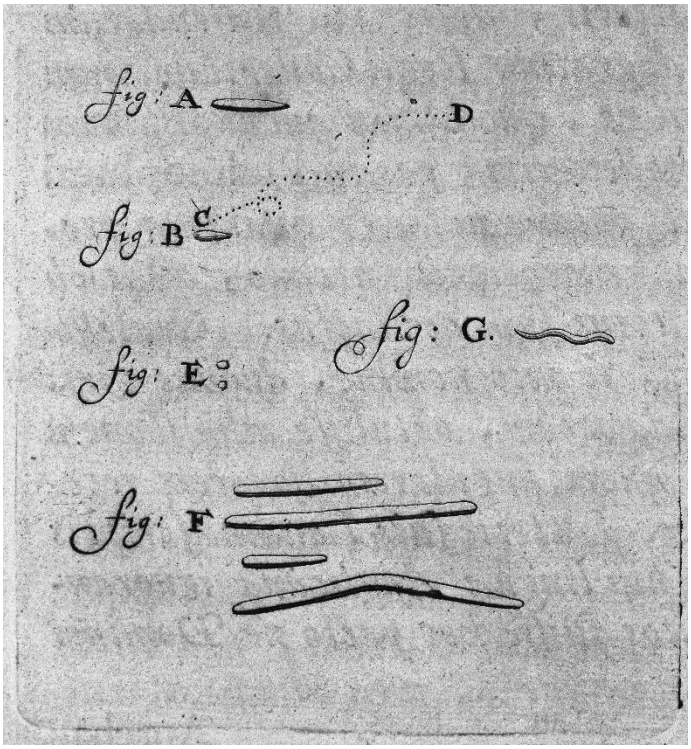


**Figure 1:** The first drawings of the "animacules" Antoni van Leeuwenhoek visualized with his microscope in 1674, which marked the beginning of modern microbiology. Figure courtesy of Wellcome collection.[13]

In the nineteenth century, several important discoveries were made within a short time. Although not accepted by the medical community at the time, Semmelweis made the connection between puerperal sepsis and contamination from the hands of physicians and medical students who assisted births immediately after performing autopsies on women who had died from sepsis. At that time, childbirth in hospital was associated with up to 10-15% maternal mortality rates from "maternal fever", which dropped to under 2% after the implementation of hand disinfection with a chlorine solution.[14] In the same era, close to half of all surgical patients died of wound infections. By adding carbolic acid to wound dressings, Joseph Lister, managed to reduce these death rates[15] (**Figure 2**). He had been inspired by

Louis Pasteur's recent work which showed that microbial contamination was essential for fermentation.[16] Further progress and final proof of the germ theory of disease was made by Robert Koch, who developed techniques for culture of microorganism. He manage to grow anthrax bacilli from the blood of infected sheep and inoculate healthy sheep with them, leading to disease.[17]

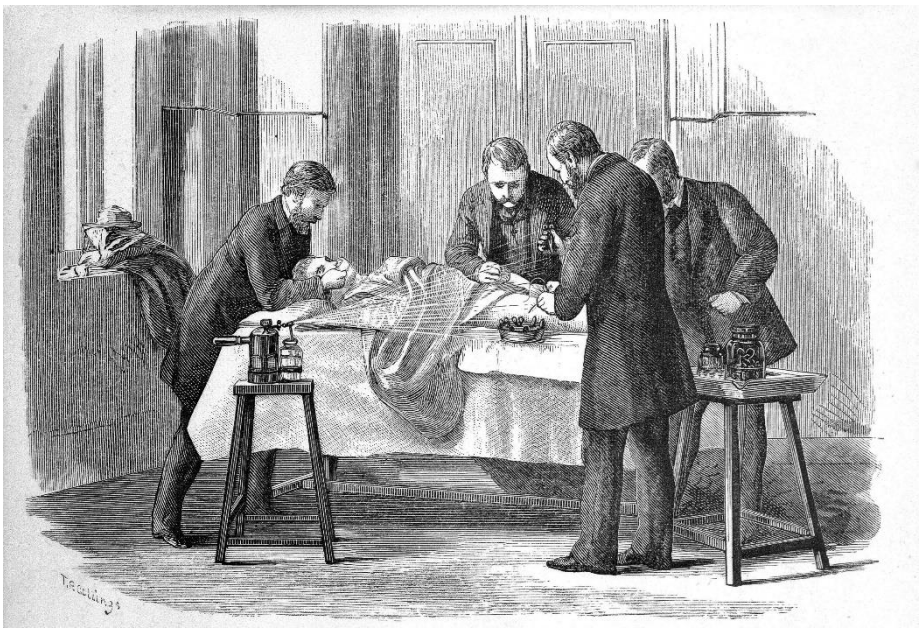

**Figure 2:** Surgeons working in the 1870s. A carbolic acid spray is in use in an attempt to prevent wound infections. Unknown author, figure courtesy of Wellcome Collection.[13]

With the germ theory of disease accepted, attention turned to producing agents capable of eradicating germs without harming the host. The first successful antimicrobial agent was arsphenamine ("Salvarsan") discovered in 1909 by Paul Ehrlich and was active against syphilis.[18] This was followed by the discoveries of penicillin in 1928, the sulfonamides in 1932 and the later revolutionary introduction and widespread use of penicillin in the 1940s.[19] Deaths from sepsis continued, however, despite active antimicrobial therapy. Animal studies on the pathogenesis of *Vibrio cholerae* showed that immunized animals injected with the bacteria would still die despite no viable organism detected in their abdominal cavity. It seemed that some substance in the bacterial cell wall, released with cell death, was responsible for toxic effects.[19] That substance was named "endotoxin" and its role, and the role of

host defences, in the pathophysiology of sepsis have been elucidated successively.

## 1.2 The pathophysiology of sepsis

Sepsis is caused by a systemic inflammatory response to an invading pathogen, most often bacteria or fungi, although viruses and protozoa can elicit a similar response. Immune responses are mediated by leukocytes which are derived from the bone marrow. Haematopoietic stem cells give rise to both the lymphocytes responsible for adaptive immunity and circulating granulocytes (including neutrophils) and macrophages, which are responsible for the innate immune response that triggers systemic inflammation.[20]

These cells contain cell membrane receptors that detect certain molecular patterns expressed on microbes (but not host cells) that have been conserved through evolution. An example of these receptors is the family of Toll-like receptors which recognize viral *ribonucleic acid* (RNA) strands and lipopolysaccharides from bacterial cell walls (i.e. endotoxin) among many other foreign molecules.[21] The activation of these receptors triggers production and release of inflammatory mediators, *cytokines*, which are small proteins that act in various manner on other cells. Important cytokines released from macrophages include the interleukins: *Interleukin*-1 (IL-1) and IL-6, and *Tumour necrosis factor-α* (TNF-α). They mediate fever, increased vascular permeability and attraction of additional immune system cells, such as neutrophils who phagocytose bacteria. Furthermore they trigger coagulation of blood which can hinder the spread of pathogens.[20] Concurrently to this local inflammatory response, a compensatory anti-inflammatory response is activated to downregulate the production of cytokines, modulate their effects and restore homeostasis. Patients with sepsis may even show a degree of immunosuppression with delayed clearence of infections and increased susceptibility to new infections (**Figure 3**).[22]

Certain infections are severe enough to cause inflammatory mediators to appear in the systemic circulation.[23] Their mechanisms, intended to locally contain an infection, instead act systematically with widespread vasodilation, capillary leak of plasma and inappropriate activation of the coagulation system. Factors such as the causative organism, timing of therapy, patient health status and genetic predisposition may explain why the inflammatory response remains localized in some infections but becomes widespread and triggers multiorgan failure in others.[24]

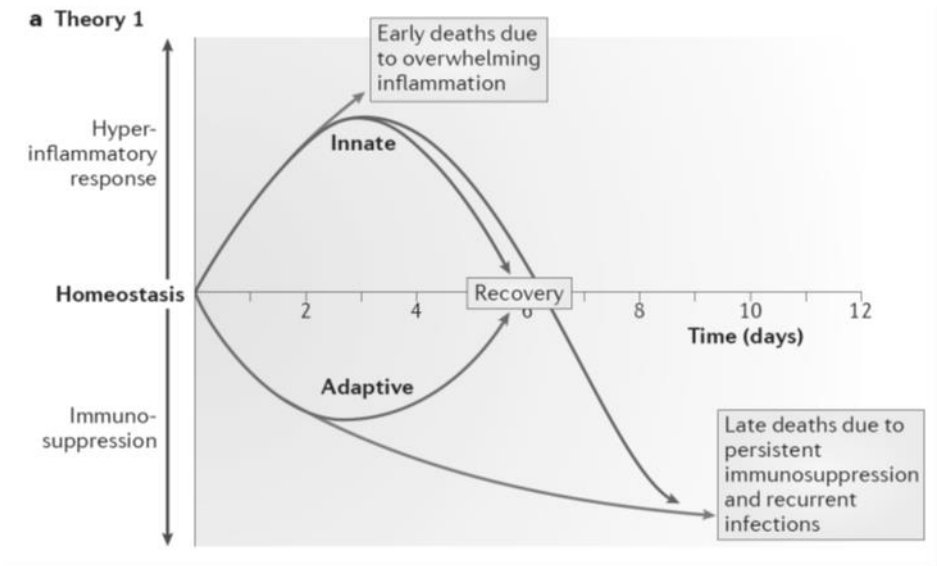


**Figure 3:** In sepsis there is concurrent activation of the pro- and anti-inflammatory immune response. The intensity of the response depends on both patient and pathogen factors. It may lead to early deaths due to hyperinflammation and organ failure but also to late deaths related to inability to clear new infections. Figure reproduced with permission from Hotchkiss et al,[25] copyright Springer Nature.

## 1.3 Organ dysfunction in sepsis

Self-administration of purified endotoxin in a laboratory worker led to the development of haemodynamic shock with pulmonary oedema, abnormalities in hepatic and renal function and disseminated intravascular coagulation.[26] The pathways leading from the initial immune response to organ failure are not fully elucidated, but cytokine induced production of *nitric oxide* (NO) in various cells is likely an important factor. In vascular endothelium its production results in profound vasodilation.[27] The ensuing classical clinical picture of a circulatory shock with high cardiac output and low systemic vascular resistance was first described in 1965.[19] This presentation is, however, often complicated with hypovolemia from extravasation of fluids and the myocardial depressive effects of NO and other mediators,[27] leading to low cardiac output states.

Activation of the coagulation system is an integral part of the innate immunity response. Systemic activation results in the widespread formation of microvascular thrombi with rapid consumption of platelets and coagulation factors, resulting in the clinical syndrome of *disseminated intravascular coagulation* (DIC) where thrombosis and bleeding can co-exist.[28]

The increased vessel permeability induced by cytokines affects the pulmonary circulation as well as the systemic. Transudation of fluids into alveoli compromises gas exchange and further dysfunction is mediated by neutrophil accumulation and loss of surfactant production. This injury can be further aggravated by alveolar trauma from mechanical ventilation.[29,30] Pneumonia and sepsis are the most common causes of the *acute respiratory distress syndrome* (ARDS), characterized by hypoxia of acute onset, bilateral pulmonary infiltrates and pulmonary hypertension.[30-32]

Decreased renal blood flow causing tubular injury, alterations in microcirculatory flow and formation of microthrombi all contribute to the development of *acute kidney injury* (AKI) injury in sepsis.[33-35] Microvascular dysfunction has also been demonstrated in sepsis[36] and is thought to contribute to organ dysfunction and so are disturbances in oxygen utilization of mitochondria,[27,37] which together with inadequate organ perfusion lead to anaerobic metabolism and lactic acidosis. What causes patient death in sepsis is not always clear. Massive cell death is unlikely as organ dysfunction usually recovers over time in surviving patients and limited changes are visible in organs during autopsies of deceased patients.[22]

## 1.4 Sepsis definitions and severity of illness scoring

Previously, terms such as *septicaemia* and *blood poisoning* were used for severe infections with bacteria present in the bloodstream. However, the inflammatory response that causes sepsis often occurs without a bloodstream infection. There was a need of standardizing the terminology of the syndrome to aid diagnosis and research. A consensus conference took place in 1991 between the *American College of Chest Physicians* (ACCP) and the *Society of Critical Care Medicine* (SCCM), after which the first set of definitions for sepsis were published.[38]

The term *systemic inflammatory response syndrome* (SIRS) was proposed for the inflammatory response seen with various insults (infection, trauma, surgery), that manifests with fever, leukocytosis, tachycardia and tachypnea. *Sepsis* was defined as this systemic response caused by an infection, *severe sepsis* as sepsis with organ failure and *septic shock* as sepsis with hypotension requiring vasoactive support. These definitions were slightly refined in 2001[39] and have later been referred to as the Sepsis-2 criteria.

These definitions have been criticized for focusing on sensitivity, at the expence of severely reduced specificity, and in 2016 new definitions were

proposed (Sepsis-3).[40] *Sepsis* is defined as a life threatening organ dysfunction caused by a dysregulated host reponse to an infection, where organ dysfunction is represented by an increase of two or more points on the SOFA scoring system (see next paragraph). *Septic shock* is the subset of patients with vasopressor requirement as well as an elevated serum lactate (**Table 1)**. To date (2022), the Sepsis-2 criteria have been the most widely used in epidemiological and clinical research.

**Table 1:** The Sepsis-2 and 3 criteria differ in the definitions of sepsis and septic shock and the term severe sepsis was abandoned in Sepsis-3.

| **Comparison of Sepsis 2 and 3 criteria** | | |
|---|---|---|
| | **Sepsis-2** | **Sepsis-3** |
| ***Sepsis*** | *Infection and two or more systemic inflammatory response syndrome (SIRS) symptoms.* | *Infection induced organ failure (increase ≥ 2 points on SOFA)* |
| ***Severe sepsis*** | *Sepsis associated with organ failure* | *Not used* |
| ***Septic shock*** | *Vasopressor requirement despite adequate fluid resuscitation* | *Vasopressor requirement **and** a serum lactate > 2 mmol/L* |

Some grading of the severity of illness in patient cohorts is essential to interpret research findings and predict outcome. Several scoring systems are in use in critical care medicine. One of the oldest and most frequently used is the *Acute Physiology and Chronic Health Evaluation II* (APACHE II) which quantifies the degree of abnormality of various physiological variables during the first 24 hours of intensive care. It includes some severe comorbidities as well.[41] The *Sequential Organ Failure Assessment (*SOFA*)* score was later developed to objectively define the degree of organ dysfunction and follow their evolution over time.[42] The Charlson *Comorbidity Index* (CI) was initally developed to predict risk of death within one year of hospitalization for patients with specific conditions but remains widely used in research for quantifying chronic comorbidities.[43] Other widely used scoring systems include the *Kidney Disease: Improving Global Outcomes* (KDIGO) for staging of acute kidney injury[44] and the EuroScore II for calculating the risk of death with open-heart surgery.[45]

## 1.5 Epidemiology of sepsis

### 1.5.1 Incidence

Two methods have been primarily used for investigating the population incidence of sepsis: Diagnosis code search and chart review. In research based on code search, large databases of hospital discharge records are searched retrospectively for diagnosis codes for sepsis, usually *International Statistical Classification of Diseases* (ICD) - 9 or 10. As there is no single diagnosis code for sepsis, researchers need to include a variety of codes pertaining to infections of different origin as well as codes for organ failure. Code based studies tend to have very large patient cohorts and extended study periods, allowing for trend analysis. They are, however, deficient in data on some aspects, such as physiological variables and long-term outcome. The validity of the diagnosis codes can also be difficult to confirm, as their primary purpose is not research. A variation of code based research is the use of data from ICU admission databases, which have been established in some countries for audit and research purposes.[46-48]

Studies based on chart review have almost exclusively been based on the clinical diagnosis of sepsis by Sepsis-2 or 3 criteria by reviewing hospital charts. They are usually limited to patients admitted to intensive care units. Collecting data by chart review is labour intensive and study cohorts are accordingly small, but with more comprehensive data than code based studied. A summary of recent epidemiological studies and their methodology is presented in **Table 2.**

The published incidence rates of sepsis vary considerably. In studies applying the Sepsis-2 or 3 criteria on ICU patients, the reported population incidence ranges from 0.18 to 2.9 per 1000 inhabitants per year,[3,6,49-57] with the majority of studies reporting rates between 0.46-0.81 per 1000.[3,6,52-55] Code-based studies tend to show higher incidence rates of up to 3.0 1000 but they usually also include less severely ill patients not admitted to the ICU. Admission policies and the numbers of ICU and high-dependency unit beds vary between countries and regions, which likely explains these large variations in incidence.

### 1.5.2 Risk factors for sepsis

Apart from the neonatal period, the incidence rates of sepsis increase steeply with age (**Figure 4**). The median or mean age of patients in epidemiological studies is almost exclusively 61-69 years,[3,5,6,49,50,53-63] with a slight majority of males (54-67%)[3,5,6,49-51,53,55,56,58,60-63] in the patient cohorts.

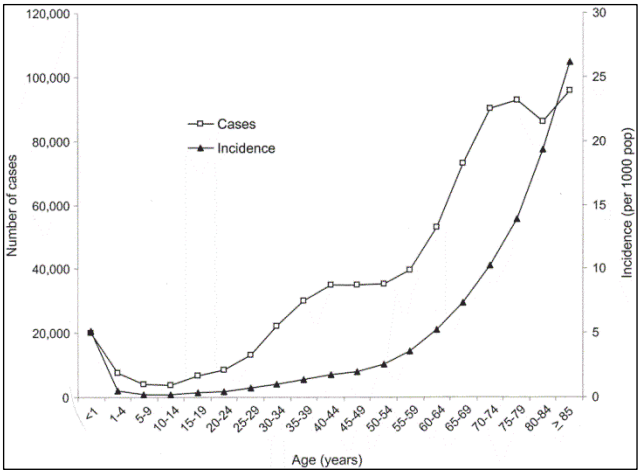


**Figure 4:** The age-specific number of cases and incidence of severe sepsis in the United states, reproduced with permission from Angus et al,[64] Copyright Wolters Kluwer Health, Inc.

Chronic disease is another important risk factor for developing sepsis. This has been studied carefully in patients with cancer, where incidence rates of sepsis are nearly ten times those in the non-cancer population.[65] A recent large, case-control study on community-acquired sepsis in Sweden found that 69% of sepsis patients had one or more comorbidities but only 31% of the matched community cohort.[66] All co-morbid conditions studied were correlated with an increased risk of ICU admission for sepsis, with the strongest associations observed for end-stage renal disease, liver disease, metastatic malignancy, substance abuse and congestive heart failure.

Medical care can also contribute to the development of sepsis. Immunosuppressive therapy is now widely used in various conditions such as cancer and rheumatological disease and every surgical procedure or insertion of catheters/devices involves some breach of the body‘s natural defence lines against pathogens. Hospital-acquired infections are reported to cause 34-57% of sepsis cases.[4,5,67]

**Table 2**: A summary of epidemiological studies on sepsis published between 2004 and 2022. Data shown include the country of origin, inclusion criteria and the number of patients included. Where reported, the annual incidence per 1000 inhabitants, severity of illness in the patient cohort (APACHE II and SOFA score) and mortality rates are included.

| Epidemiological studies on sepsis | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Author** | **Year of publication** | **Country** | **Inclusion criteria** | **Patients** | **ICU only** | **Incidence per 1000** | **APACHE II** | **SOFA** | **28/30 d mort.** | **Hosp. mort.** |
| *Vesteinsdottir et al[68a]* | 2022 | *Iceland* | *Sepsis-2* | *971* | *Yes* | *0.55-0.75[b]* | *21* | *8* | *25%* | *30%* |
| *Flaatten et al[69]* | *2004* | *Norway* | *ICD-9* | *6685* | *No* | *1.49* | | | | *27/29%[b]* |
| *Jacobson et al[70]* | *2004* | *Sweden* | *Sepsis-2* | *81* | *Yes* | *-* | *22* | *-* | *30%* | *-* |
| *Strandberg et al[71]* | *2020* | *Sweden* | *ICD-10* | *28,886* | *Yes* | *-* | *-* | *-* | *32-33%[b]* | *31-33%[b]* |
| *Lengquist et al[6]* | *2020* | *Sweden* | *Sepsis-3* | *1654* | *Yes* | *0.81* | *-* | *7* | *24%* | *26%* |
| *Karlsson et al[51]* | *2007* | *Finland* | *Sepsis-2* | *470* | *Yes* | *0.38* | *24.1* | *-* | *-* | *28%* |
| *Poukkanen et al[55]* | *2013* | *Finland* | *Sepsis-2* | *691* | *Yes* | *0.6* | *-* | *-* | *-* | *24%* |
| *Vincent et al[62]* | *2006* | *Europe* | *Sepsis-2* | *1177* | *Yes* | *-* | *-* | *6.5* | *-* | *36%* |
| *Padkin et al[53]* | *2003* | *UK* | *Sepsis-2[d]* | *15,362* | *Yes* | *0.51* | *-* | *-* | *42%* | *47%* |
| *Harrison et al[52]* | *2006* | *UK* | *Sepsis-2[d]* | *92,672* | *Yes* | *0.46-0.66[b]* | *-* | *-* | *-* | *45-48%[b]* |
| *Shankar-Hari et al.[63]* | *2016* | *UK* | *Sepsis-3[d]* | *248,864* | *Yes* | | *19-20[b]* | | | *32-45%[b]* |
| *van Gestel et al[54]* | *2004* | *NL* | *Sepsis-2* | *134* | *Yes* | *0.54* | *-* | *-* | *-* | *-* |
| *Engel et al[72]* | *2007* | *Germany* | *Sepsis-2* | *415* | *Yes* | *0.76-1.1* | *18/21[c]* | *6/10[c]* | *-* | *55%* |
| *Sepnet[4]* | *2016* | *Germany* | *Sepsis-1* | *1503* | *Yes* | *-* | *-* | *-* | *-* | *40%* |
| *Brun-Buisson et al[56]* | *2004* | *France* | *Sepsis-1* | *546* | *Yes* | *0.95* | *-* | *9* | *35%* | *42%* |
| *Sakr et al[50]* | *2013* | *Italy* | *Sepsis-2* | *446* | *Yes* | *0.18* | *-* | *7.7* | *-* | *49%* |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| *Blanco et al[49]* | *2008* | *Spain* | *Sepsis-2* | *311* | *Yes* | *0.25* | *25* | *9.6* | *48%* | *54%* |
| *Bouza et al[73]* | *2014* | *Spain* | *ICD-9* | *240,939* | *No* | *0.64-1.06[b]* | *-* | *-* | *-* | *43%* |
| *Uvizl et al[61]* | *2016* | *Czech R.* | *Sepsis-2* | *897* | *Yes* | *-* | *25* | *10* | *-* | *41%* |
| *Záhorec et al[74]* | *2005* | *Slovak R.* | *Sepsis-2* | *121* | *Yes* | *-* | *-* | *-* | *-* | *51%* |
| *Baykara et al[58]* | *2018* | *Turkey* | *Sepsis-2* | *463* | *Yes* | *-* | *21.5/25[c]* | *8/10[c]* | *62%* | *-* |
| *Angus et al[64]* | *2001* | *USA* | *ICD-9* | *192,980* | *No* | *3* | *-* | *-* | *-* | *29%* |
| *Martin G et al[75]* | *2003* | *USA* | *ICD-9* | *10,319,418* | *No* | *0.82-2.4[b]* | *-* | *-* | *-* | *18-28%[b]* |
| *Dombrovskiy et al[76]* | *2007* | *USA* | *ICD-9* | *8,403,766* | *No* | *0.65-1.35[b]* | *-* | *-* | *-* | *38-45%[b]* |
| *Martin C et al[59]* | *2009* | *Canada* | *Sepsis-2* | *1238* | *Yes* | *-* | *24.9* | *-* | *-* | *38%* |
| *Dreiher et al[77]* | *2012* | *Israel* | *ICD-9* | *27,516* | *Yes* | *-* | *-* | *-* | *-* | *53-55%[b]* |
| *Finfer et al[3]* | *2004* | *ANZ* | *Sepsis-2* | *691* | *Yes* | *0.77* | *21* | *-* | *32%* | *38%* |
| *Ogura et al[60]* | *2014* | *Japan* | *Sepsis-2* | *624* | *Yes* | *-* | *23.4* | *8.6* | *23%* | *30%* |
| *Xie et al[5]* | *2020* | *China* | *Sepsis-2* | *2322* | *Yes* | *-* | *18* | *7.8* | *-* | *32%* |
| *Machado et al[57]* | *2017* | *Brazil* | *Sepsis-2/3* | *795* | *Yes* | *-* | | *8* | *-* | *56%* |
| *Mulatu[78]* | *2021* | *Ethiopia* | *Sepsis-3* | *275* | *Yes* | - | *-* | *-* | *51%* | - |

ANZ: Australia and New Zealand, Czech R.: The Czech Republic, NL: The Netherlands, Slovak R.: The Slovak Republic, UK: The United Kingdom, USA: The United States of America. 28/30 d mort: 28/30 day mortality rate, Hosp.mort: In-hospital mortality rate.

[a]*Data from the study presented later in this thesis (**Study I**) is shown here for comparison.*

[b]*A study analyzing trends – the results in the table are the range of values reported from the period studied.*

[c]*Results reported separately for severe sepsis / septic shock.*

[d]*The study is based on data from a national ICU admission database*

### 1.5.3 Microbiology

Three sites of infection account for the majority of sepsis cases. The lungs are most common, causing 45-61% of the infections in the majority of epidemiological studies.[3,4,6,49,50,54-59,78] Infections of the abdomen are noted in 14-29%[3-6,55-57,62,70,72,78] of cases and in the urinary tract in 6-13%.[3-6,49,50,55,57,58,60,64,70,72]

Both an epidemiological study of long duration[75] and a meta-analysis[79] have found that gram-positive bacteria have become proportionately more common in the last 20-30 years (**Figure 5**). Gram-negative bacteria dominated earlier, causing over 90% of cases in 1958-1979.[79] This may be related to more advances in the development of antimicrobial therapy against gram-negative bacteria, or the increasing use of indwelling catheters and devices that are prone to colonization and infection by gram-positive bacteria.

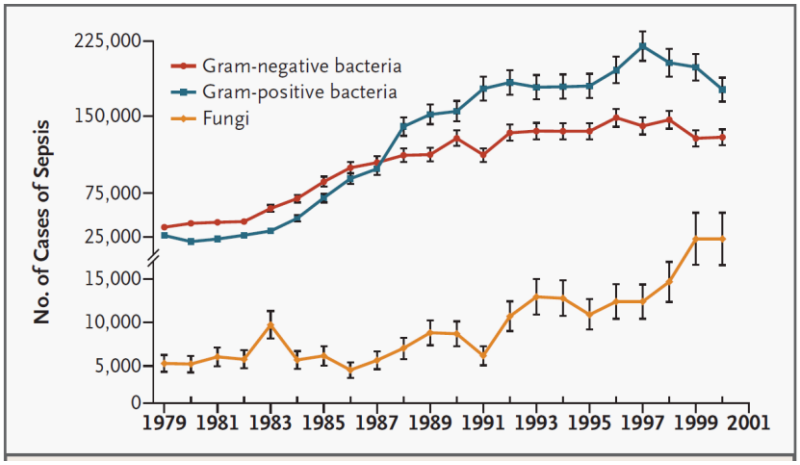


**Figure 5:** The number of sepsis cases caused by gram-positive-, gram-negative bacteria and fungi in the United States 1979-2001. Reproduced with permission from Martin et al,[75] Copyright Massachusetts Medical Society

### 1.5.4 Severity of illness and death in sepsis

Although some framework for defining organ dysfunction was provided in the Sepsis-2 definitions,[39] individual researchers have used variable criteria in their studies, with a resulting wide range of reported incidence. The rates of organ failure reported from clinically defined ICU populations are: Circulatory (51-81%),[49,51,55-57,59,60,63] respiratory (50-78%),[4,49,51,55,57-60,62,63,72] renal (20-52%),[4,49,51,55-60,62,63,72] coagulation system (12-40%),[49,55-60,62,72]

hepatic (2-29%),[49,51,55-58,60,62] metabolic (18-49%)[4,57-59,63,72] and *central nervous system* (CNS) (12-49%).[4,49,56,58,60,62,72]

An alternative way of describing the degree of organ dysfunction in a cohort is to examine the frequency of organ support provided. This too, varies considerably between study cohorts and may reflect variability in admission policies and hospital organisation. A clinic with high-dependency beds available outside the ICU, where some organ support can be provided, will likely have a higher severity of illness in the ICU than a clinic with no high-dependency beds.

The frequency of mechanical ventilation in ICU cohorts of sepsis patients ranges from 52 to 87%,[5,6,50,51,55,62,72] vasopressor use from 65-79%[55,72] and renal replacement therapy from 13-20%.[5,51,55,62,72] The hospital mortality rate for sepsis patients requiring intensive care ranges from 24 to 56%[3-6,49-53,55-57,59-62,72,74] with the lowest rates of 24-30% reported from the Nordic Countries and Japan (**Table 2**).

Although most epidemiological studies report mortality rates, few address the timing and exact cause of death. Some patients die from refractory circulatory shock in the initial phase of sepsis but this is rare. More often, the combination of age, severe comorbidities and sequelae of the ICU treatment contribute to a situation where recovery to a meaningful life for that patient becomes highly unlikely and decisions to forgo further invasive treatments are made. The hospital mortality from sepsis in younger patients, without comorbidities, has been reported to be only 4.6%,[80] highlighting the importance of patients' health status before the onset of sepsis. A study looking specifically at causes of death in sepsis found that only a third of deaths happened early (within three days of ICU admission). Late deaths were most often preceded by decisions to forgo life-sustaining therapy or new ICU complications such as infections or mesenteric ischemia.[81]

### 1.5.5 Trends in sepsis epidemiology

The aging population, a rising prevalence of comorbid disease and an increase in the use of invasive devices and procedures could all explain a growing population incidence of sepsis. This might be balanced by factors such as a more targeted chemotherapy for cancer and increased use of minimally invasive surgical procedures. Several studies have shown an increase in the incidence of sepsis in the past three decades, with an annual increase of 8-16% per year.[73,75,76,82] At the same time, studies have found an annual decrease in the mortality of sepsis of 1.4-7% per year.[73,76,83-85] These

studies are based on diagnosis coding from hospital discharge records and there is concern that they might be subject to bias. Increased awareness of sepsis and financial reimbursements systems could have the effect that more, and less severely ill patients, are labelled as sepsis cases. This would reduce the observed mortality rate. Studies that have used clinical patient data from electronic health systems to estimate sepsis frequency have found a stable or a substantially lower annual increase in incidence (0.6-4.9%/year),[83,85] as well as a more limited decrease in mortality (0-3.3%/year).[71,80,83-85]

## 1.6 Sepsis management

### 1.6.1 Influential research papers in the early 2000s

The mortality rate of sepsis remains high despite the availability of effective antimicrobial therapy and advances in diagnostic modalities. This likely reflects the complex nature of the syndrome. Progress in organ support may be an important element in reducing mortality from sepsis. Numerous landmark papers on sepsis and general intensive care were published in the early 2000s.

The study by Rivers et al. in 2001 on *early goal-directed therapy* (EGDT)[86] showed that outcome was better in patients receiving protocol-directed initial management with the goal of reaching pre-defined values for *central venous pressure* (CVP), *mean arterial pressure* (MAP) and *central venous oxygen saturation* ($S_{cv}O_2$). This resulted in more, and earlier, administration of blood, fluid and inotropic therapy in the treatment arm of the study compared with the standard arm. The mortality benefit with EGDT over usual care (30.5% versus 46.5%) is the largest reported in any sepsis trial to date.

A few years later (2006), Kumar et al. showed that a delay in the initiation of effective antimicrobial therapy was a critical variable associated with mortality (**Figure 6)**.[87] These two studies are frequently cited in the context of the perceived “golden hour” in sepsis management, where, as in severe traumatic injury, there might be a period of time immediately after the insult where prompt treatment may prevent death.

Among other influential papers from this era (2000) is the ARDS Network trial that showed reduced mortality rates with the use of lower tidal volumes during mechanical ventilation (6 ml/kg) than those that were traditionally used at the time (10-15 ml/kg).[31] Around 60% of the patients in the study had sepsis or pneumonia. In the same year, a mortality benefit was found for

strict glucose control in ICU patients.[88] Hyperglycemia had previously not been regarded as an important modifiable risk factor.

After an array of negative trials on agents to modulate certain parts of the inflammatory response syndrome in sepsis,[89-93] the infusion of *drotrecogin alfa (activated)* showed a small, but statistically significant reduction in mortality from sepsis in 2001.[94] *Drotrecogin alfa (activated)* is a recombinant human activated protein C which has anticoagulant activity. The use of high-dose corticosteroids to modulate the inflammatory response in sepsis has not been proven useful,[95] but in 2002 a low-dose regimen showed a mortality reduction in a (large) subset of patients with a relative adrenal insufficiency.[96]

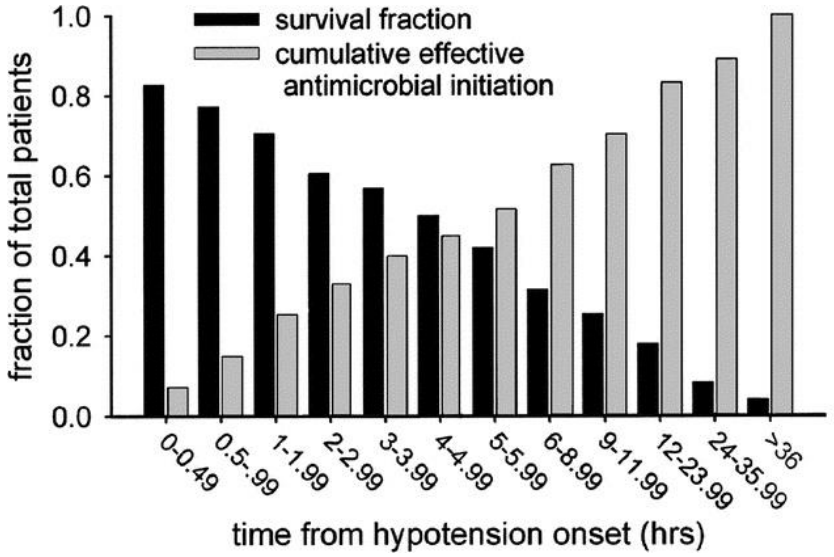


**Figure 6:** The cumulative effective antimicrobial initiation following the onset of septic shock-associated hypotension and associated survival. Reproduced with permission from Kumar et al,[87] copyright Wolters Kluwer Health, Inc.

### 1.6.2 The Surviving Sepsis Campaign Guidelines

The high death rates in sepsis and the publication of these trials showing a mortality reduction, were the impetus for the *Surviving Sepsis Campaign (SSC)*. This was a joint venture of 11 critical care and infectious disease organizations. A set of guidelines, the *Surviving Sepsis Campaign Guidelines*, were published in 2004,[97] with the aim of facilitating the use of evidence-based medicine and thus reducing mortality from sepsis. These guidelines were widely publicized and summarized into simple care "bundles" to be completed within a certain time after the diagnosis of sepsis. The

guidelines, and the bundles, have since been revised every fourth year in light of new evidence that has emerged.[98-101]

The campaign contributed to a greatly increased awareness and interest of sepsis, highlighting it as a medical emergency. The bundles were implemented into performance improvement programs by many hospitals. Compliance with the bundles has been linked to reduced mortality in sepsis,[102] although studies have been inconsistent and often performed in the setting of special educational efforts.

The initial version of the Surviving Sepsis Campaign was met with some criticism, especially regarding the role of the pharmaceutical company Eli-Lilly, the manufacturer of *drotrecogin alfa (activated),* in funding of the campaign.[103] Later studies did not confirm a mortality benefit with the agent[104-107] which was withdrawn from market in 2011. The mortality benefit of intensive glucose control[108] and steroids was also not confirmed in later trials,[109-111] although steroids have been found to accelerate resolution of shock[112] and their use is suggested in the latest SSC guidelines.[101]

The early goal-directed therapy met with a similar fate in 2014-2015 when three large, prospective, randomized trials did not find a benefit over usual care.[113-115] The mortality rates in the standard therapy arms of those trials were much lower (18.8-29.2%) than in Rivers‘ trial (46.5%). The reasons for this may be that important aspects of goal-directed therapy, such as early fluids, had already become the standard of care in sepsis, or, there might have been a lack of care in the control arm of Rivers‘ trial.

The latest version of the Surviving Sepsis Campaign Guidelines is a comprehensive document with a summary of relevant research articles on all aspects of sepsis care, from diagnosis and resuscitation to supportive care and treatment goals in the ICU.[101] The current bundle for initial care is shown in **Figure 7**. The cornerstone of sepsis management is early recognition and immediate fluid resuscitation. A prompt measurement of serum lactate is suggested and also a frequent reassessment of fluid therapy to avoid fluid overload. Crystalloids are recommended as the main fluid with the possible addition of albumin if large volumes are needed. The use of starch solutions is not recommended. Antibiotics should be administered within one hour of recognition, although in patients with an uncertain diagnosis and without shock up to three hours are allowed for assessment of the condition.

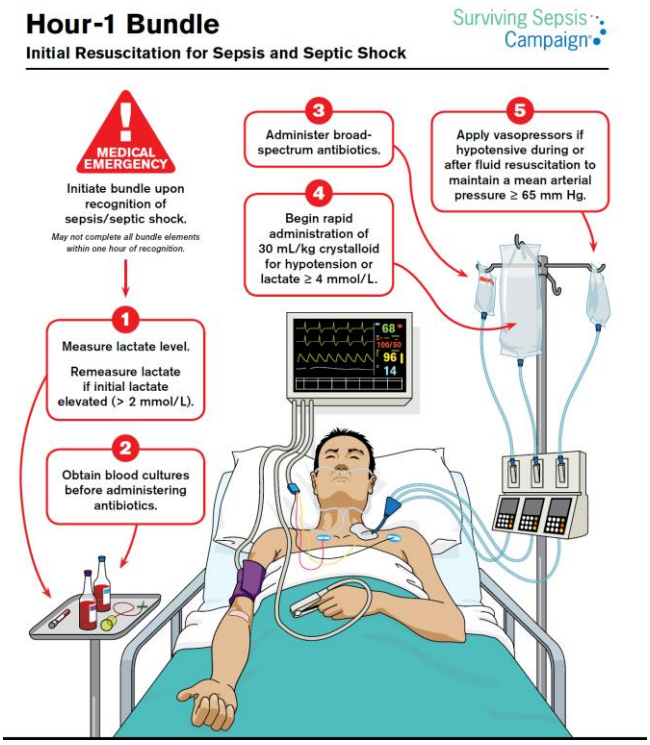


**Figure 7:** The initial 1-hour bundle of care from the Surviving Sepsis Campaign Guidelines. Reproduced from the campaign‘s website.[116]

## 1.7 Special patient groups

### 1.7.1 Cancer patients

Cancer patients are especially vulnerable with regard to sepsis.They frequently undergo major surgical procedures and receive radiotherapy and/or chemotherapy with subsequent immunosuppression. Although the age-standardized incidence rates of cancer may have started to decrease in recent years,[117,118] the prevalence of cancer in the community is increasing due to falling mortality rates[117,118] and changing age-distribution (**Figure 8)**. This has the effect that a rising number of cancer patients may be subject to intensive care, often for sepsis, which is a leading cause of ICU admission for cancer patients.[119]

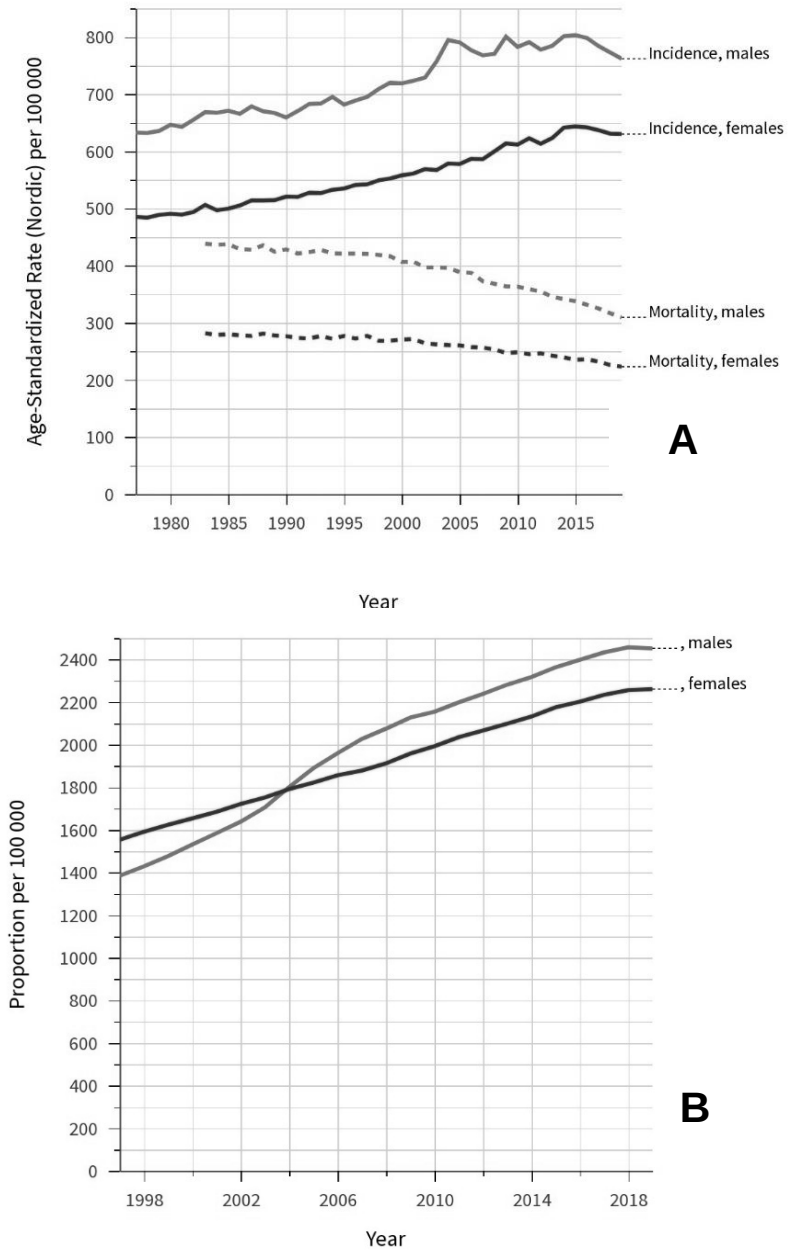


**Figure 8:** Figure A shows the trends in age-standardized (20-85 years) incidence and mortality rates of cancer (all sites but non-melanoma skin cancer) in the Nordic Countries 1977-2019. Figure B shows the trends in population prevalence of cancer 1997-2019. Figures generated with Nordcan‘s data visualisation.[118]

Historically, very high hospital mortality rates (74-77%) have been reported for some groups of cancer patients admitted to the ICU.[120-122] This may inevitably have caused some reluctance to admit these patients, as the invasive ICU treatment would probably be futile. Survival has, however, been steadily improving for cancer patients in the ICU in recent years,[123,124] including admissions for sepsis[125] and attitudes may be changing towards admitting patients with advanced cancer to the ICU.[126,127]

It has been argued that it is the acute organ dysfunction that drives short-term mortality in cancer patients in the ICU, and not the nature and stage of the malignancy.[119,128] Performance status may also be a better predictor of mortality than the cancer itself.[129,130] It has been suggested that critically ill cancer patients with uncertain prognosis receive a time-limited trial (three-to-four days) in the ICU without any limitations of care, before decisions to forgo life-sustaining therapy are made.[122,131] In a recent consensus conference, it was however stated that cancer patients no longer eligible to cancer treatments, or with a very short life expectancy would probably not benefit from an ICU admission.[132] Many of the studies on cancer patients in the ICU come from large cancer centres[121,133-135] and may not be generalizable to general hospitals.

### 1.7.2 Postoperative sepsis

Sepsis is an important cause of morbidity and mortality after surgical procedures. Postoperative patients are 24-37% of the study cohorts in epidemiological studies in the ICU setting.[3,5,51,56] The types of surgical procedures are usually not specified in these studies, but it is likely that many of these patients have had emergency surgery for conditions of infectious nature, e.g. perforated bowel or infective endocarditis. Sepsis after elective surgery is less common, or only 4-7% of cohorts.[51,56] Elective surgery is an operation that is scheduled in advance and usually performed during daytime hours. It includes most cancer surgery.

Several risk factors for developing postoperative sepsis have been identifed and include: Age,[136] male sex,[137,138] smoking,[139] cardiopulmonary,[137,140] and cerebrovascular comorbidities[141] and pre-operative anemia.[141] Few of these risk factors are modifiable. Postoperative sepsis is associated with considerable morbidity, such as a threefold increase in the length of stay,[136,142] and a hospital mortality of 26-39%.[136,137,140,143]

Epidemiological data on sepsis after elective surgery have been published in a few large, code-based studies.[136,137,142,143] The incidence is reported to

be 0.9-1.6% in mixed surgical cohorts,[136,137,142] with slightly higher rates (1.9-4.3%) after oncological procedures,[141,143] which often involve the gastrointestinal tract. Anastomotic insufficiency remains common despite advances in surgical techniques.[144]

The rates have been rising in the past decades with a declining case-fatality rate.[137,142] As for this category of studies, a bias from increased awareness of sepsis cannot be excluded. These studies lack data on the types of infections causing sepsis and the timeframe in which it developes.[137,142,143] Studies based on clinical patient data are often single centre, or from centres of excellence, focusing on patient outcomes after specific types of procedures.[145,146] The rates of sepsis in these kind of studies can be difficult to ascertain, as definitions vary and patients with sepsis may be masked by related or overlapping conditions, e.g. anastomotic leakage, pneumonia and need for mechanical ventilation.[145-148]

Diagnosing sepsis in postoperative patients can be challenging. The vast majority of patients who have undergone major surgery have signs of the systemic inflammatory response syndrome postoperatively.[149] Inadequate pain control, hypovolemia, pulmonary embolism and postoperative delirium may all mimic sepsis. The most utilized biomarker for infection detection, *C-reactive protein* (CRP), is also invariably raised after surgery. The persistence of SIRS and elevated CRP levels after postoperative day three to four have however been linked to the development of infectious complications.[149-151]

### 1.7.3 Cardiac surgery and infection outbreaks

The rates of sepsis after cardiac surgery (0.7-1%) are relatively low compared with gastrointestinal surgery (1-4%) in code-based studies.[136,137] A recent prospective study applying the Sepsis-3 criteria found however a considerably higher incidence of 9.5% after cardiac surgery.[152] These patients frequently receive invasive mechanical ventilation in the immediate postoperative period, possibly contributing to the development of pneumonia which is the most common site of infection after cardiac procedures.[153,154] It has been reported in 2-11% of cases,[153-158] followed by surgical site infections (5-8%)[155,159] and urinary tract infections (3-6%).[155,156] Bloodstream infections (1-2%)[153,160] and endocarditis (0.06%) are rare.[153]

The discovery of pathogens and aseptic technique revolutionized surgery, but contamination of wound and implants can still occur, with serious implications for patients. Perforations in instrument wraps,[161] glove

contamination[162] and inadequate cleaning and sterilization of equipment[163] are frequently implicated.

Gastrointestinal endoscopes do not under normal circumstances break the barriers between sterile and non-sterile areas of the body and a high-level disinfection by immersion in a disinfectant solution has been the commonly accepted practice.[164] Endoscopes do not tolerate sterilization in autoclaves which are used for surgical instruments. They have been implicated in pathogen transmission between patients, usually related to procedural errors in cleaning.[165] *Transoesophageal echocardiography* (TEE) probes are similar devices as gastrointestinal endoscopes, although they do not contain the long and narrow working channels frequently implicated in cleaning failures of gastrointestinal endoscopes (**Figure 9**).

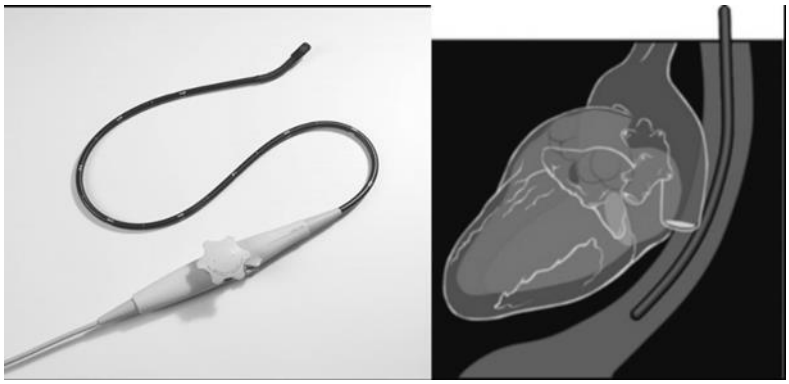

**Figure 9:** A photo of a transoesophageal echocardiography probe (left) and a schematic picture of its position in the oesophagus during use (right). Photo and illustration reproduced from Wikipedia (illustration by Patric J. Lynch)[166]

The use of TEE is standard practice in cardiac surgery to evaluate cardiac function and detect complications intraoperatively. After induction of anaesthesia, the probe is inserted into the oesophagus and left in place for the duration of surgery (**Figure 10**). A few case reports have been published linking TEE probes with respiratory infections[167-169] but its role as a possible risk factor for sepsis after cardiac surgery was not common knowledge when an outbreak of infections occurred at the ICU at Landspitali in Reykjavik in 2014, as described in Paper IV. In two separate outbreaks, minute surface damage of the TEE probes caused disinfection failure and transmission of pathogens to several patients.

A common denominator in infections related to re-usable devices are failures to sufficiently remove all organic matter before disinfection or sterilization. The wear and tear of normal use inevitably causes small cracks

and scrapes on devices which accumulate over time, impeding the cleaning process.

An outbreak may be defined as the occurrence of disease cases in excess of what would normally be expected in a certain environment. They are frequently reported in intensive care units and transmission of pathogens is suspected to occur by contaminated hands or frequently touched equipment such as infusion pumps and monitors. ICU-acquired infections have also been linked to bacterial growth in water reservoirs such as sink traps and heater-cooler units.[170] Many ICU outbreaks are caused by multi-drug resistant bacteria, or they may simply have been discovered due to their resistance. Resistant strains are frequently under special surveillance by infection control in hospitals, while clusters of infections caused by common bacteria may go under the radar.

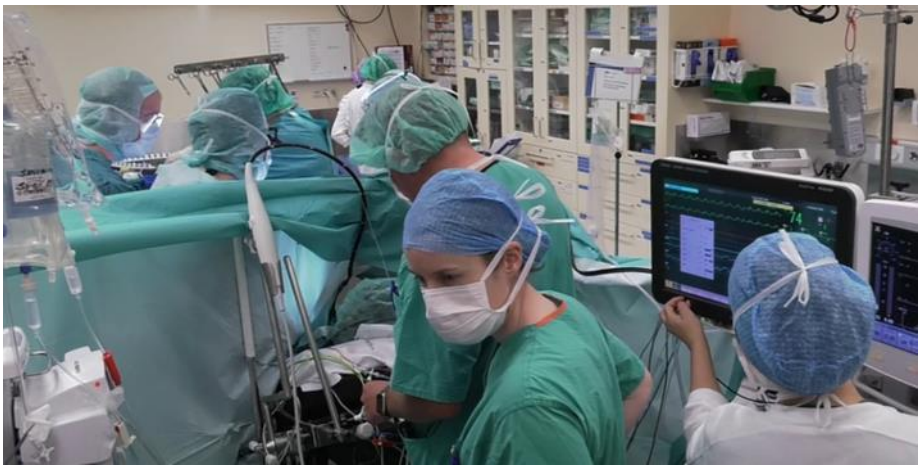

**Figure 10:** Cardiac surgery at Landspitali in Reykjavik. A TEE probe is in use. A screenshot from a newsreel published by Landspitali in 2016.[171] Captured and edited by author.

## 1.8 A few current topics and the present study

Several treatments for sepsis have shown promise in smaller studies,[88,94,172] but failed to do so in larger, randomized controlled trials.[104,108,113] One aspect of sepsis research is the vast heterogeneity of the patients. A 23 year old with fulminant meningococcal meningitis, a 65 year old man with multiple comorbidites and anastomotic leak after surgery and a frail 85 year old female with chronic lung disease and pneumonia. All three patients have sepsis, but the clinical presentation and response to treatment measures will be different.

This heterogeneity has led to studies aiming to identify different phenotypes of sepsis,[173,174] which might pave the way for a more individiualized therapy in the future. The universal administration of large fluid boluses is a debated topic in the SSC Guidelines and may not be tolerated well in all patients.[175] Fluid overload has been correlated with increased mortality[176] and currently there are several trials ongoing regarding the initial fluid management of sepsis. The CLOVERS study investigates liberal crystalloid fluids versus early vasopressors[177] and the CLASSIC trial a restrictive versus liberal fluid regime.[178]

The use of veno-venous *extracorporeal membrane oxygenation* (ECMO) for severe respiratory failure in sepsis is becoming an increasingly used rescue strategy, with a possible mortality reduction.[179,180] The role of veno-arterial ECMO in severe septic shock is less clear. Utility is probably limited in patients with a predominantly vasodilatory shock but a recent retrospective cohort study found improved survival in patients with profound septic myocardial depression.[181] However, only a very small minority of sepsis patients will ever be eligible for this invasive treatment. Advances in the detection of sepsis[182] and early pathogen identification[183] may have the potential to save more lives.

The island nation of Iceland is well suited to epidemiological research. Every person has a unique personal identification number that is used for all healthcare and administrative purposes. The population is small enough for detailed data acquisition to be possible, on a nationwide level, without having to rely on databases of variable quality. The scientific value of the research presented in this thesis are the accurate clinical data collected by chart review, used to describe topics such as trends over time and sepsis after surgery which have almost exclusively been studied with database research before.

# 2 Aims

The general aim of this project was to create a broad overview of sepsis requiring intensive care in a nationwide cohort in Iceland, with a focus on several subgroups of patients:

**Study I:** To describe the trends in the incidence and mortality of sepsis requiring intensive care over an 11-year study period. Additionally to assess developments in sepsis management in the years following the Surviving Sepsis Campaign guidelines.

**Study II:** To descibe the incidence of underlying cancer in patients admitted to intensive care units with sepsis and compare the aetiology of sepsis, outcome and decisions on life-sustaining therapy with sepsis patients without cancer.

**Study III:** To examine the incidence, aetiology and outcome of patients admitted to intensive care with sepsis following elective procedures. Additionally to find the incidence of sepsis per subtype of surgery performed at Landspitali.

**Study IV:** To describe the incidence of infections after cardiac surgery in Iceland and how it related to nosocomial infection clusters caused by surface-damaged transoesophageal echocardiography probes. Additionally, to describe risk factors for developing an infection and the associated outcome of cardiac surgery in Iceland.

# 3 Materials and methods

## 3.1 Study design and setting

All four studies were retrospective, observational, nationwide cohort studies conducted in Iceland. Study centres were Landspitali – The National University Hospital of Iceland in Reykjavik, which has two separate locations (Hringbraut and Fossvogur) and Akureyri Hospital in Akureyri. Organization of healthcare in Iceland is similar to other Nordic Countries, i.e. funded by taxes with equal access to care for every citizen.

Landspitali is a 650 bed tertiary care centre that has 14 ICU beds and Akureyri Regional Hospital has 110 beds and three ICU beds. They are the only hospitals providing ICU care in the country. All units are multidisciplinary with a specialist in intensive care medicine available in house 24 hours a day. Around 80% of the population of Iceland lives within one hour driving distance from these hospitals.[184] Transport of critically ill patients from smaller regional clinics around the country is mainly by ground transport or a fixed-wing aircraft based in Akureyri. Neither hospital has high-dependency units. All patients needing invasive monitoring, vasoactive support or invasive mechanical ventilation are referred to the ICUs, although low-dose vasopressors may occasionally be started in *emergency departments* (ED) in wait of an ICU bed. The EDs are staffed with specialists in emergency medicine 24 hours a day at Landspitali but during daytime at Akureyri, with specialist back-up at home nighttime. Rapid response teams were initiated in selected wards at Landspitali in 2007 and hospital wide in 2008. Akureyri Hospital has no formal rapid response team.

Landspitali is the sole provider of cardiac surgery in Iceland, as well as major oncological surgery. Only a small minority of patients in Iceland are referred abroad for highly specialized care, this includes solid organ transplant (other than kidney), allogenic stem cell transplant and mechanical circulatory assist other than ECMO and *intra-aortic balloon pump* (IABP).

**Studies I-III** were approved by the National Bioethics Committee of Iceland (Case number 16-088 with additions 16-088V1 and 16-088V2) and **Study IV** was approved by the Institutional review board of Landspitali (Case number 28/2018). The need for informed patient consent was waived given the observational nature of the studies. A summary of study populations and outcome variables is shown in **Table 3.**

**Table 3:** A summary of the patient populations studied in this thesis and the main outcome measures.

| | **Study I** | **Study II** | **Study III** | **Study IV** |
|---|---|---|---|---|
| Included patients | *All admitted to ICU because of severe sepsis or septic shock* | *All admitted to ICU because of severe sepsis or septic shock* | *All admitted to ICU because of severe sepsis or septic shock* | *All patients who underwent open-heart surgery at Landspitali* |
| Additional material | | | *Number and type of all elective surgical procedures at Landspitali* | |
| Nr. of patients | *971* | *971* | *971* | *973* |
| Study period | *2006, 2008, 2010, 2012, 2014 and 2016* | *2006, 2008, 2010, 2012, 2014 and 2016* | *2006, 2008, 2010, 2012, 2014 and 2016* | *2013-2017* |
| Study design | *Retrospective observational cohort study* | *Retrospective observational cohort study* | *Retrospective observational cohort study* | *Retrospective observational cohort study* |
| Outcome measures: | *Trends in incidence and mortality of sepsis requiring intensive care*<br><br>*Compliance with treatment guidelines* | *Incidence of cancer in patients admitted to ICU with sepsis*<br><br>*Aetiology and mortality of sepsis in patients with various types of cancer* | *Incidence of sepsis after elective surgery in Iceland*<br><br>*Aetiology and mortality of sepsis after elective surgery at Landspitali* | *Incidence of infections after cardiac surgery, complications rates and mortality*<br><br>*Description of two outbreaks traced to damaged esophageal probes* |

## 3.2 Patient selection and definitions

For **Studies I-III** all adult (≥18 years) intensive care unit admissions in Iceland in the calendar years 2006, 2008, 2010, 2012, 2014 and 2016 were screened for the presence of severe sepsis or septic shock on admission by chart review. This 11-year period was chosen to assess trends over time but data was collected every other year to reduce data collection resources. Patients who developed sepsis in the ICU while admitted for another reason were not included. Sepsis, severe sepsis and septic shock were defined according to the Sepsis-2 criteria[39] (**Figure 11)**. Work on these studies had started before the publication of the latest Sepsis-3 criteria,[40] but their fulfillment was assessed post-hoc. Additionally, for patients admitted to the ICUs at Landspitali, the patients' hospital dishcarge records were screened for ICD-10 diagnostic codes for sepsis or concurrent infection and organ failure.

In **Study I**, for analysis of the timing of interventions, time zero was defined as the time of triage at emergency departments for patients admitted to the ICU from the ED. For patients admitted from hospital wards, time zero was defined as the first documentation in the patients' chart of deteriorating vital signs or the time of request for an ICU evaluation, whichever was available. Compliance with four goals from the Surviving Sepsis Campaign Guidelines 1-hour bundle were assessed (emergency department patients only): I: A measurement of serum lactate, II: Blood cultures drawn before antibiotics, III Antibiotics administered, IV: Start of a fluid bolus (30 ml/kg) to be completed within three hours. Patients without hypotension were excluded from analysis of this goal. Patients admitted to the ICU from hospital wards were only analyzed regarding timing of cultures, antibiotics and ICU admission, since detailed data on variables such as fluid administration was not available in patient charts for patients admitted from hospital wards.

For **Study II,** patiens already included into **Study I,** who had an active cancer diagnosis were divided into three groups: (I) Solid tumour without metastasis, other than non-melanoma malignant neoplasm of skin, diagnosed within the past five years, (II) Metastatic solid tumour and (III) Haematological malignancies, which included acute and chronic myelogenous leukemia, acute and chronic lymphocytic leukemia, Hodgkin lymphoma, other lymphomas, lymphosarcoma, myeloma and Waldenström's macroglobulinemia. Treatment limitations were defined as all decisions to forgo life-sustaining therapy that were documented in patients' charts before or during ICU admission and included: No cardiopulmonary resuscitation, no

mechanical ventilation, no dialysis, no vasoactive therapy, no return to the ICU after discharge and transition to comfort care. A discharge home was a defined as a discharge from the hospital ward direct to the patient's previous residence. Patients not discharged home either died in hospital or were transferred to care homes or inpatient rehabilitation facilities.

***Sepsis:*** Documented or suspected infection along with a systemic inflammatory response syndrome (SIRS) manifested by two or more of the following conditions:

Temperature ≥38.3 or <36.0 C
Heart rate ≥90 beats/min
Respiratory rate ≥20 breaths/min or $Pa_{CO2}$ ≤32 mmHg
White blood cells >12,000 cells/$mm^3$, <4,000 cells/$mm^3$, or >10% band forms

***Severe Sepsis:*** Sepsis associated with organ dysfunction, hypoperfusion, or hypotension. Organ failure must be of acute onset and at least one failure must be present in the first 24 hours of intensive care. Organ failure variables:

| | |
|---|---|
| *Circulatory:* | Hypotension (SBP <90 mmHg or MAP <70 mmHg) |
| *Renal:* | Oliguria (urine output <0.5 ml/kg/hr for at least two hours) or acute creatinine increase (≥44 μmol/L) within two days |
| *Respiratory:* | Arterial hypoxemia ($PaO_2/FiO_2$ <250) |
| *Liver:* | Hyperbilirubinemia (>34 μmol/L), AST/ALT ≥ 2x over normal range |
| *CNS:* | Altered mental status |
| *Coagulation:* | Thrombocytopenia (platelet count <100,000/$mm^3$) or, aPTT >60 sec or INR >1.5 |
| *Metabolic acidosis:* | Metabolic acidosis (pH <7.30) or, elevated lactate (>2.0 mmol/L) |

***Septic Shock:*** Sepsis with hypotension, despite adequate fluid resuscitation. Patients who need vasopressor or inotropic agents to maintain SBP ≥ 90 mmHg.

**Figure 11:** The inclusion criteria for patient selection into studies I-III, adapted from the Sepsis-2 definitions.[39] SBP: Systolic blood pressure, PaO2/FiO2: The ratio of arterial oxygen partial pressure to the fraction of inspired oxygen. AST: Aspartate aminotransferase. ALT: Alanine aminotransferase, aPTT: activated Partial Thromboplastin Time, INR: International Normalized Ratio.

For **Study III** the number of all elective operations performed at Landspitali during the study years (2006, 2008, 2010, 2012, 2014 and 2016) was acquired from the operation room management system (Orbit) and

administrative data. The number of operations performed at other hospitals and private clinics could not be acquired. Elective surgery was defined as a planned procedure that was performed either on an outpatient basis or during a scheduled admission to the hospital. Sepsis after elective surgery was defined as an ICU admission because of severe sepsis or septic shock during the same hospital stay as the elective procedure, or an ICU admission for sepsis in an emergency hospital admission within 30 days of elective surgery, which was considered directly related to the procedure.

For **Study IV** all consecutive patients (≥18 years) that underwent open-heart surgery at Landspitali during calendar years 2013-2017 were included. Operation urgency was defined as follows: Elective: Routine admission for operation, Urgent: Patients who have not been electively admitted for operation but who require intervention or surgery during an admission for a cardiac event (such as acute coronary syndrome), Emergency: Operation before the beginning of the next working day after the decision to operate, Salvage: Patients requiring cardiopulmonary resuscitation en route to the operating theatre or prior to induction of anaesthesia. A critical preoperative state was defined as: Ventricular tachycardia, ventricular fibrillation or aborted sudden death, preoperative cardiac massage, preoperative ventilation before surgical theatre, preoperative inotropes or IABP or preoperative acute renal failure (anuria or oliguria <10 ml/hour).

## 3.3 Data collection

**For Studies I-III:** Data on patient demographics, physiological variables, laboratory results, microbiological cultures and treatment received were collected from the patients‘ medical charts on to pre-printed study forms which subsequentally were entered into a Microsoft Excel database. Severity of illness on admission was assessed with the APACHE II[41] and SOFA[42] scoring systems, burden of underlying comorbidites with Charlson comorbidity index[43] and acute kidney injury was classified according to the KDIGO guidelines.[44]

For **Study IV,** patient characteristics, surgery variables and the occurrence of postoperative complications were entered into a Microsoft Excel database. The EuroScore II was used to assess preoperative and surgical risk factors.[45] Two periods were defined when a contaminated TEE probe was in use in the main cardiac surgery theatre at Landspitali, from October 30$^{th}$ 2013 to November 12$^{th}$ 2014 and from September 15$^{th}$ 2016 to April 12$^{th}$ 2017. These are the periods from the first to the last patient diagnosed with outbreak pathogens in the two separate outbreaks.

## 3.4 Microbiology

For **Studies I-III**, only microbiological samples taken immediately before ICU admission or within the first 48 hour of intensive care were analyzed in the study. Infections were confirmed by cultures or other forms of pathogen detection (e.g. urine antigens, *polymerase chain reactions* (PCR)), diagnostic imaging (e.g. pulmonary infiltrates on chest X-ray) or visualisation (e.g. skin infections, heart valve vegetations on TEE). Hospital-acquired infection was defined as an infection that manifested after more than 48 hours following admission to hospital.

The initial empirical antimicrobial therapy was considered insufficient if the detected, clinically relevant, pathogens were resistant to the agents used, as determined by standard in-vitro susceptibility testing. A positive culture of *Candida spp*. was not considered pathogenic in respiratory or urine samples alone. Skin commensal bacteria (e.g. coagulase-negative staphylococci) in blood cultures were not considered pathogens unless found in repeated sets. The presence of *Enterococcus spp.* in polymicrobial abdominal infections was not considered to require anti-enterococcal therapy if adequate source control had been achieved. Multi-drug resistant pathogens were defined as pathogens resistant to three or more classes of antibiotics. A consultant in infectious diseases (MG) reviewed information on sources of infections, culture results and adequacy of antimicrobial therapy when needed.

For **Study IV** infections were defined and classified as in the European Center for Disease Prevention and Control Point prevalence survey of healthcare-associated infections.[185] Microbiology results were reviewed in all patients for 30 days after surgery, or up to 90 days for deep surgical infections and endocarditis.

## 3.5 Outcome variables

**Study I:** The primary outcome was the incidence of severe sepsis or septic shock requiring intensive care in Iceland over an 11-year study period. Secondary outcomes included analysis of severity of illness, compliance with treatment goals from the Surviving Sepsis Campaign and short- and long-term mortality.

**Study II:** The primary outcome was the incidence of underlying cancer in patients admitted to Icelandic ICUs because of severe sepsis or septic shock. Patient characteristics, aetiology of sepsis, limitations of treatment and mortality were compared with sepsis patients without malignancy.

**Study III:** The primary outcome was the incidence of sepsis requiring intensive care after elective surgery at Landspitali University Hospital. Patient characteristics, aetiology of sepsis, treatment received and mortality was compared with patients with sepsis after emergency surgery and sepsis without previous surgery.

**Study IV:** The main outcome was the diagnosis of a new infection within 30 days after cardiac surgery in Iceland (or 90 days for deep surgical site infections and endocarditis). Secondary outcomes included the incidence of other complications and mortality after cardiac surgery.

## 3.6 Missing values

In **Studies I-III**, missing values were most common for the timing of deterioration in hospital wards for patients admitted there from (47%), body mass index (39%), respiratory rate (19%), timing of interventions in the emergency departments (13-16%) and serum lactate (13%). Other parameters had less than 10% of values missing, most under 5%. In **Study IV**, missing values were most common for preoperative pulmonary artery pressure (67%), time on ventilation (17%) and preoperative left ventricular ejection fraction (11%). Other parameters had less than 1% of values missing.

When calculating the severity of illness scoring systems, missing values were presumed to have been within the normal range, adding no points to the score. Patients with missing values for a variable, or not applicable for analysis (e.g. due to pre-existing organ failure) were omitted from analysis of that particular variable. For the multivariable logistic regression in **Study I**, missing values were replaced with the variable mean for continuous variables and variable mode for categorical variables. For the multivariable logistic regression in **Study IV**, pulmonary artery pressure was not included.

## 3.7 Statistical analysis

For all **Studies**, continuous data are presented as medians and *interquartile range* [IQR] or means with *standard deviation* (SD) and proportions are presented as percentages, with 95% *confidence intervals* (CI) on incidence rates. All *p*-values are two sided and a level of ≤ 0.05 was considered significant. Statistical analysis was performed with SPSS by IBM (version 27.0.1) with the exception of **Figure 18** which was generated with R (R Foundation for Statistical Computing).

In **Study I,** trends over time were analyzed with generalized linear models: linear regression for normally distributed scale variables, logistic regression for binary variables and quantile regression for non-normally distributed variables. Age-adjusted incidence rates were calculated by direct methods based on the population of Northern Europe in 2020.[186] Survival was presented with a Kaplan-Meier graph. Survival of the sepsis population was also contrasted against the general population of Iceland by calculating an expected survival of an age, gender- and admission year-matched reference population. For analysis of risk factors for mortality, patient characteristics and treatment variables were entered into a univariate logistic regression with 28-day mortality as the dependent variable. Factors associated with mortality individually ($p \leq 0.05$) were entered into a multivariable logistic model after analyzing for collinearity and a forward, stepwise regression performed.

For **study II** Pearson‘s Chi-squared test was used for categorical variables to assess differences between the four groups of patients and a Kruskal-Wallis test with Bonferroni correction for multiple comparisons for continuous variables. Survival was presented with Kaplan-Meier curves.

In **study III,** comparisons between the three groups of patients was performed using Pearson‘s Chi-squared test for categorical variables or a Kruskal-Wallis test for continuous variables.

In **study IV** Mann-Whitney U test was used for comparing length of stay between infected and non-infected patients after cardiac surgery. For an analysis of risk factors for postoperative infections, patient and surgical characteristics were entered into a univariate logistic regression as infection as the dependent variable. Factors associated with the development of an infection individually ($p \leq 0.05$) were entered into a multivariable logistic model after analyzing for collinearity and a forward, stepwise regression performed

.

# 4 Results

## 4.1 Study I

### 4.1.1 Incidence of sepsis requiring ICU admission

During the six study years, 9166 patients were admitted to Icelandic ICUs, 971 (10.6%, 95% CI 10.0-11.2) of them because of severe sepsis or septic shock. The crude population incidence (≥18 years) ranged between 0.55-0.75 per 1000 inhabitants per year (95% CI 0.46-0.66 to 0.65-0.87) over the study years and the age-adjusted rates against the Northern-European population in 2020 ranged from 0.74 to 0.93 per 1000 (95% CI 0.62-0.89 to 0.78-1.09). The trends over time are shown in **Figure 12**. Neither the crude nor age-adjusted incidence showed a significant temporal trend (*p = 0.51* and *p = 0.81* respectively). The age-adjusted incidence rate was highest between 81 and 90 years for men but between 71 and 80 years for women (**Figure 13).**

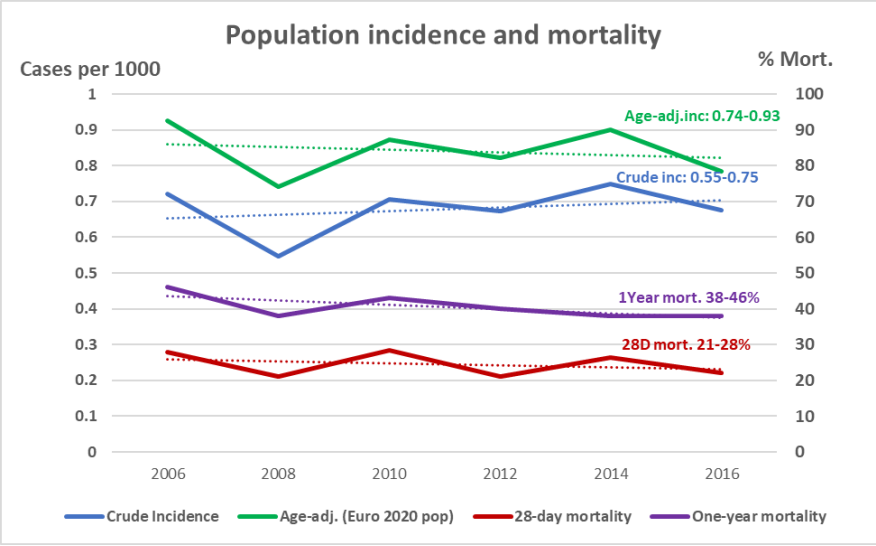


**Figure 12:** Trends over time in crude and age-adjusted incidence rates for sepsis requiring intensive care in Iceland 2006-2016 (left axis) and the 28-day and one year mortality rate trends (right axis).

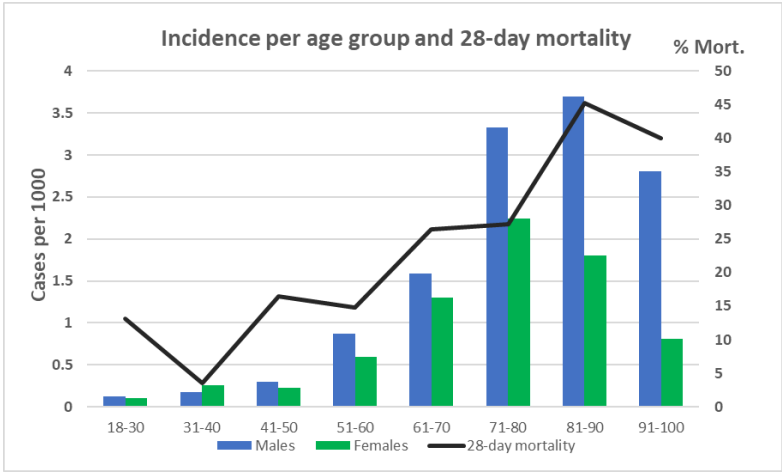


**Figure 13:** On the left axis are the age specific incidence rates of sepsis requiring intensive care for males (blue columns) and women (green columns). On the right axis is the 28-day mortality rate per age group (all patients) shown with a black line.

Of the 971 patients included in the study by Sepsis-2 criteria for severe sepsis or septic shock, 99.5% (966/971), also met the Sepsis-3 criteria for sepsis. The criteria for septic shock were fulfilled by 77% (747/971) by the Sepsis-2 criteria but 42% (374/901) by the Sepsis-3 criteria. Post-hoc code search in discharge summaries from patients admitted to the ICUs at Landspitali revealed that appropriate ICD-10 diagnostic codes for sepsis or concurrent infection and organ failure were found in 48% (407/853) of the cases.

### 4.1.2 The patient cohort

The median age of the patient cohort was 67 years [IQR 56-76] and 56% (548/971) were male (**Table 4**). Circulatory failure was the most common organ failure (94%), followed by respiratory failure (81%), metabolic acidosis (55%) and acute kidney injury (54%). For patients with AKI (513), the KDIGO stages were: I: 37% (192/513) patients, II: 24% (125/513) patients, III: 38% (196/513) patients. There was no observed change over time in the severity of illness on admission, measured by APACHE II score (median 21, $p = 0.29$), SOFA score (median 8, $p = 0.15$) and the number of organ failures (median 4, $p = 0.89$). There was no change over time in the degree of comorbidities measured by Charlson CI over time (median 4, $p = 0.42$) (**Figure 14**). Two changes were observed over time in the rates of organ failures in the patient cohort. Acute kidney injury decreased from 57% (88/154) in 2006 to 46% (76/167) in 2016 ($p = 0.027$) and the frequency of metabolic acidosis increased from 47% (75/159) in 2006 to 60% (101/168) in 2016 ($p = 0.003$).

**Table 4:** The characteristics and severity of illness of the 971 patients admitted to Icelandic ICUs with severe sepsis or septic shock. Variables are presented as proportions. If a variable contained missing data, the number of patients divided by patients with available data is shown.

| **Patient characteristics (*N = 971*)** | | | |
|---|---|---|---|
| **Age** | *67 years [56-76]* | **Comorbid illness:** | |
| **Males** | *56% (548)* | Ischaemic heart disease | *21% (208)* |
| **Charlson CI** | *4 [2-6]* | Chronic pulmonary disease | *21% (206)* |
| **APACHE II** | *21 [16-26]* | Diabetes mellitus | *14% (134)* |
| **SOFA score** | *8 [6-10]* | Congestive heart failure | *10% (101)* |
| **Admitted from:** | | Solid tumor | *10% (100)* |
| Emergency room | *49% (477)* | Connective tissue disease | *9% (89)* |
| Medical ward | *31% (304)* | Cerebrovascular disease | *8% (79)* |
| Surgical ward | *20% (190)* | Chronic kidney disease | *8% (76)* |
| **Admission year:** | | Metastatic solid tumor | *7% (69)* |
| 2006 | *16% (159)* | Peripheral vascular disease | *7% (66)* |
| 2008 | *13% (129)* | Haematological malignancy | *7% (66)* |
| 2010 | *17% (167)* | **Intensive care unit:** | |
| 2012 | *17% (161)* | Fossvogur | *50% (484)* |
| 2014 | *19% (184)* | Hringbraut | *39% (374)* |
| 2016 | *18% (171)* | Akureyri | *12% (113)* |
| **SIRS criteria:**[a] | | **Organ failure:**[a] | |
| Temperature | *68% (645/945)*[b] | Circulatory | *94% (907/971)* |
| Tachycardia | *96% (917/955)* | Respiratory | *81% (773/960)* |
| Tachypnea | *91% (846/931)* | Metabolic acidosis | *55% (532/962)* |
| White blood cells | *85% (785/922)*[c] | Acute kidney injury | *54% (513/945)* |
| Four SIRS | *44% (422/958)* | Central nervous system | *41% (397/967)* |
| Three SIRS | *42% (406/958)* | Coagulation system | *25% (232/917)* |
| Two SIRS | *14% (130/958)* | Hepatic | *16% (145/932)* |

[a]*See **Figure 11** for detailed definitions*
[b]*Of these 645 patients, 550 had fever and 95 had hypothermia.*
[c]*Of these 785 patients, 602 had leukocytosis and 183 had leukopenia*

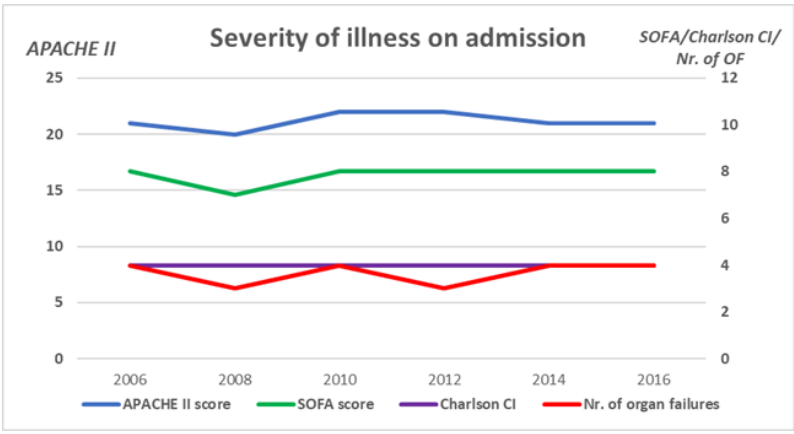


**Figure 14:** Trends over time in the severity of illness in the first 24 hour of ICU care (APACHE II, SOFA, number of organ failures) and in the burden of comorbidities (Charlson CI).

### 4.1.3 Treatment in the emergency department

Sepsis patients were admitted to the ICU directly from the emergency department in 49% (477/971) of cases. For all ED patients, the median *length of stay* (LOS) in the ED was 3.7 hours [IQR 2.1-6.3]. It increased with time from 2.9 hours [IQR 1.9-4.6] in 2006 to 4.9 hours [IQR 2.2-8.2] in 2016 ($p<0.001$). The time from triage to drawing of blood cultures was median 1.0 hour [IQR 0.5-2.3] with a slight increase in time from 0.7 hours [IQR 0.3-2.7] in 2008 to 1.4 hours [IQR 0.6-2.3] in 2016 ($p<0.001$). The time to administration of antibiotics was 1.8 hours [IQR 0.8-3.2] and did not change with time ($p = 0.629$). Lactate was measured at a median of 2.5 hours [IQR 0.5-5.8] after triage with a decrease in time from 4.1 hours [IQR 2.1-8.2] in 2006 to 1.2 hours [IQR 0.2-4.1] in 2016 ($p<0.001$) (**Figure 15)**.

The compliance with the 1-hour goals of the Surviving Sepsis Campaign in the emergency departments was as follows: Lactate measured: 34% (138/412), blood cultures drawn (*and* before antibiotics): 41% (161/396), antibiotics administered: 33% (131/402), fluid bolus 30 ml/kg started: 60% (212/354). The median number of goals achieved in each patient was two [IQR 1-3] without a trend over time ($p=0.97$). Neither the achievement of any single goal or the total number of goals completed was associated with increased 28-day survival ($p = 0.60$).

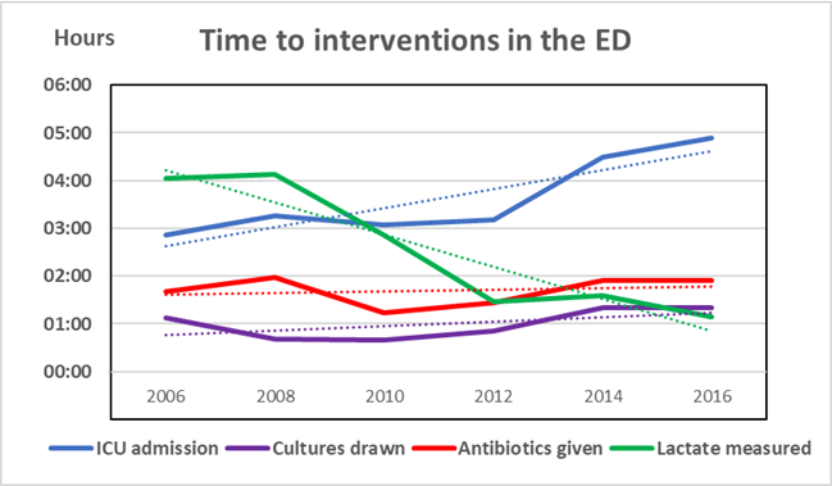


**Figure 15:** Temporal trends in the timing of interventions in the emergency departments for 477 patients admitted to Icelandic ICUs with severe sepsis or septic shock in 2006-2016.

### 4.1.4 Treatment in the hospital ward before ICU admission

Patients were admitted to the ICU from medical wards in 31% (304/971) of cases and surgical wards in 20% (190/971) of cases. The median length of stay for medical patients before ICU admission was three days [IQR 1-11], but five days [IQR 1-13] for surgical patients. Approximate time point for deterioration could only be determined for 264 patients (53%) and the following data is based on those patients only. The time from deterioration to arrival of the patient in the ICU decreased during the study period from 2.8 hours [IQR 1.5-4.3] in 2006 to 1.5 hours [IQR 0.7-2.6] in 2016 ($p<0.001$) (**Figure 16)**. The time to drawing of blood cultures was median 1.7 hours [IQR 0.7-4.6] and to administration of antibiotics 1.9 hours [IQR 1.0-3.8], with both goals achieved earlier in medical wards compared with surgical wards (1.4 hours [IQR 0.6-3.7] versus 2.4 hours [IQR 1.0-5.1], $p = 0.013$) for blood cultures and (1.7 hours [IQR 0.9-3.1] versus 2.8 hours [IQR 1.4-5.0], $p = 0.024$) for antibiotics.

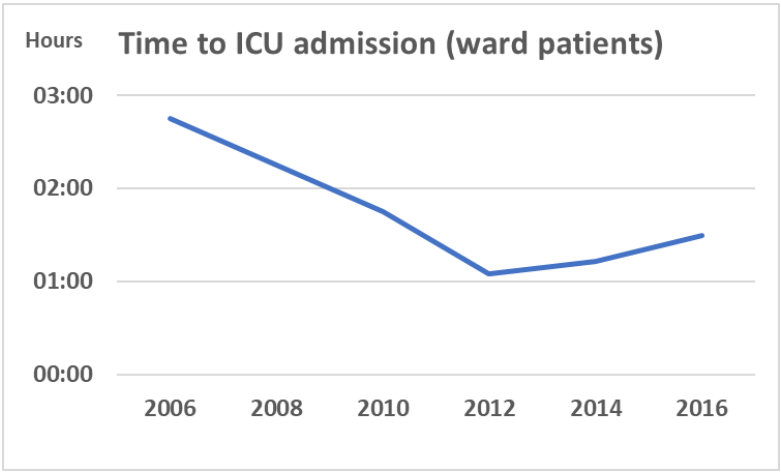


**Figure 16:** Duration of time from documented worsening of vital signs to the arrival of the patient in the intensive care units, 2006-2016. Rapid response teams were implemented at Landspitali in steps during 2007-2008.

### 4.1.5 Treatment in the intensive care department

The median length of stay in the ICU was four days [IQR 2-9] (**Table 5)**. Vasoactive medications were used in 77% (749/971) of patients. The most common agent was noradrenaline (670 patients), followed by dobutamine (372), vasopressin (123), dopamine (41), phenylephrine (32), adrenaline (23) and milrinone (10). Of the 740 patients receiving vasoactive therapy, 413 received only one agent, 231 received two and 106 patients three or more. Invasive mechanical ventilation was used in 50% (482/971) of patients and was started in the first 24 hours of ICU care in 85% (409/482) of those cases. The reintubation rate after extubation was 8% (39/482). The frequency of new-onset renal replacement therapy was 6% (62/959), it was started at a median of ICU day two [IQR 1-3] and the median duration of treatment was five days [IQR 3-9]. There was a decreasing trend in the use of synthetic colloids ($p<0.001$), red-cell- ($p<0.001$) and plasma- ($p<0.001$) transfusion during the study period, with an increase in the use of albumin ($p<0.001$). The total volume of fluid administered was stable ($p = 0.71$) (**Figure 17).**

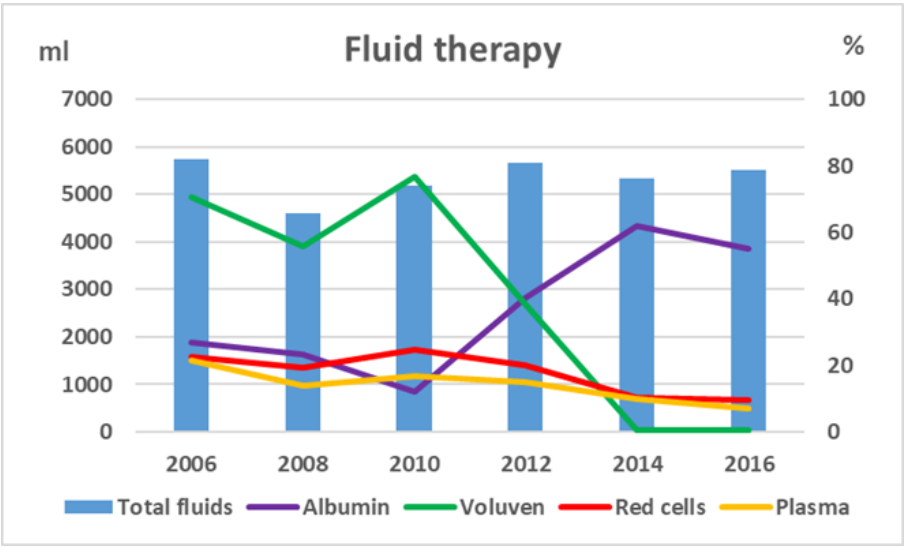


**Figure 17:** Trends in fluid therapy in the ICU over the 11 year period studied. On the left axis is the total fluid (ml) administered the first 24 hours, shown with blue colums. On the right axis are the proportions of patients (percentages) that received albumin, hydroxyethyl starch (Voluven), red cell or plasma transfusion (coloured lines) in the first 24 hours of care.

**Table 5:** Treatment administered in the intensive care unit and outcome for patients admitted because of sepsis. Categorical variables are are presented as proportions and continuous variables as medians [IQR]. If a variable contained missing data, the number of patients divided by patients with available data is shown.

| **Treatment and outcome in the ICU (N = 971)** | |
|---|---|
| Vasoactive medicines | *77% (749)* |
| Invasive mechanical ventilation (IMV) | *50% (482)* |
| Days on ventilator | *5 [2-11]* |
| Non-invasive ventilation (NIV) | *41% (393/965)* |
| Conversion to IMV[a] | *55% (205/371)* |
| New onset *renal replacement therapy* (RRT) | *6% (62/959)* |
| Corticosteroids | *47% (431/926)* |
| Fluid volume (*milliliters* (ml))[b] | *5348 [3978-7064]* |
| Fluid balance (ml)[b] | *3140 [1716-5065]* |
| Red cell transfusion[b] | *17% (169)* |
| Volume (Units)[c] | *2 [1-2]* |
| Plasma transfusion[b] | *14% (134)* |
| Volume (Units)[c] | *2 [2-4]* |
| Hydroxyethyl starch solution[d] | *39% (376)* |
| Volume (ml)[c] | *750 [500-1000]* |
| Albumin | *38% (366)* |
| Volume (ml)[c] | *250 [100-500]* |
| ICU length of stay (days) | *4 [2-9]* |
| Hospital length of stay (days) | *15 [8-31]* |
| **Mortality:** | |
| ICU | *15% (148/961)* |
| Hospital | *30% (285/956)* |
| 28-day | *25% (236/957)* |
| 90-day | *33% (315/957)* |
| One year | *41% (388/955)* |

*[a]Patients who started with NIV but needed subsequentially IMV. Patients only receiving NIV after extubation from IMV excluded.*
*[b]Fluid therapy in the first 24 hours of intensive care.*
*[c]Median number of units or ml given in those patients receiving the fluid in the first 24 hours of intensive care.*
*[d]Voluven© (6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride) was the predominant synthetic colloid in use in Iceland during the study period.*

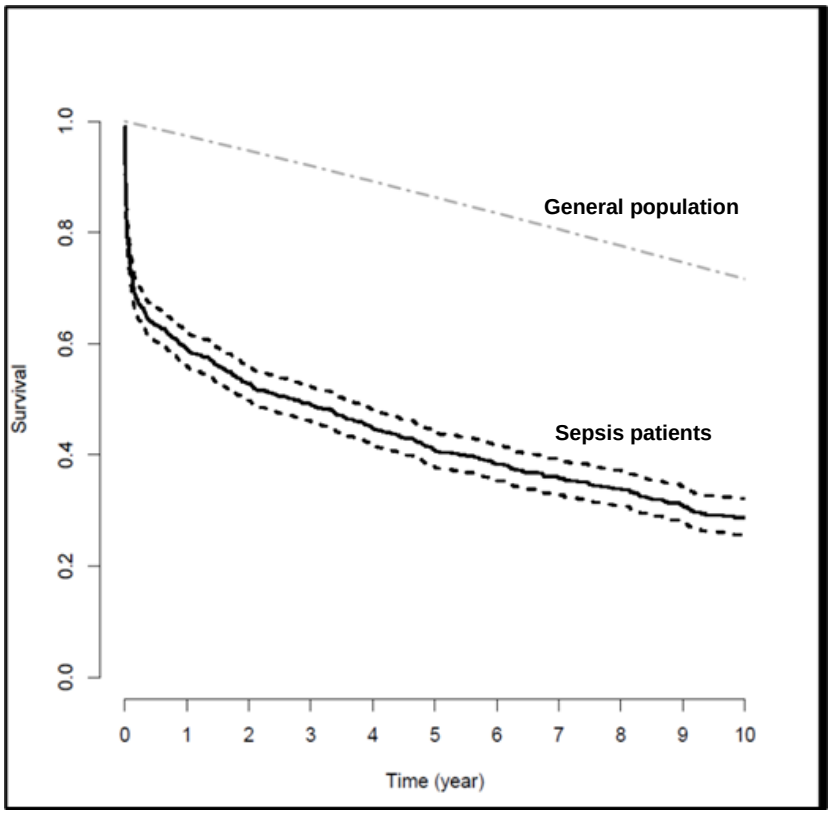


**Figure 18:** Long-term survival rates of sepsis patients admitted to intensive care (solid line with 95% CI) compared to a reference group (dotdashed line) using survival data from the Icelandic population matched by age, gender and year of admission.

### 4.1.6 Outcome

The 28-day mortality was 25% and the one-year mortality 41% with no significant reduction over time (*p = 0.45* and *0.17* respectively) (**Table 5** and **Figure 12)**. The median follow-up time in the study was 2.4 years [IQR 0.1 to 6.8]. Long-term survival compared with the survival of the Icelandic population of same age, sex and year is shown in **Figure 18.**

In a multivariable logistic regression, age, APACHE II score, medical admissions and metastatic cancer were among factors independently associated with 28-day mortality. Higher *body mass index* (BMI) and an increasing number of SIRS symptoms were associated with less risk of death (**Table 6**).

**Table 6:** Independent risk factors for 28-day mortality found in a multivariable logistic regression.

| **Risk factors for 28-day mortality *(n = 951)*** | | |
|---|---|---|
| | **Adjusted OR (95% CI)** | **p-value** |
| Age (years) | *1.04 (1.03-1.06)* | *<0.001* |
| APACHE II score | *1.07 (1.04-1.10)* | *<0.001* |
| **Admission category:** | | |
| Emergency department | Reference | |
| Surgical ward | *1.08 (0.64-1.84)* | *0.77* |
| Medical ward | *2.02 (1.37-2.98)* | *<0.001* |
| Metastatic solid tumour | *6.96 (3.88-12.47)* | *<0.001* |
| Body Mass Index (BMI) | *0.96 (0.93-1.00)* | *0.023* |
| Number of SIRS symptoms | *0.70 (0.55-0.89)* | *0.004* |
| PaO2/FiO2 ratio | *1.00 (0.99-1.00)* | *<0.001* |
| **Acute kidney injury:** | | |
| None | Reference | |
| KDIGO stage 1 | *0.92 (0.57-1.49)* | *0.92* |
| KDIGO stage 2 | *0.73 (0.42-1.36)* | *0.35* |
| KDIGO stage 3 | *1.82 (1.13-2.92)* | *0.013* |
| Number of vasopressors | *1.46 (1.20-1.78)* | *<0.001* |
| Insufficient empirical therapy | *2.11 (1.20-3.71)* | *0.01* |

**Table 7:** The sites of infection, pathogen detection, adequacy of antimicrobial therapy and hospital mortality for each infection site. In addition, the largest group of infections (pulmonary) is divided into community- and hospital-acquired infections. Values are presented as proportions.

| Sites of infection (N = 971) | | | | | |
|---|---|---|---|---|---|
| **Infection site** | **n** | **Pathogen identified** | **Positive blood cultures** | **Insufficient empirical therapy** | **Hospital mortality** |
| **Pulmonary** | *45% (436)* | *58% (252/436)* | *16% (68/436)* | *15% (32/218)* | *35% (149/431)* |
| *Community-acquired* | *350* | *57% (199/350)* | *15% (52/350)* | *11% (19/169)* | *32% (111/347)* |
| *Hospital-acquired* | *86* | *62% (53/86)* | *19% (16/86)* | *27% (13/49)* | *45% (38/84)* |
| **Abdomen** | *24% (230)* | *69% (159/230)* | *28% (65/230)* | *42% (65/153)* | *31% (70/224)* |
| **Urinary** | *10% (97)* | *100% (97/97)* | *54% (52/97)* | *8% (7/93)* | *18% (17/96)* |
| **Blood/endovascular** | *7% (67)* | *99% (66/67)* | *96% (64/67)* | *16% (10/64)* | *30% (20/67)* |
| **Skin and soft tissue** | *6% (59)* | *75% (44/59)* | *41% (24/59)* | *5% (2/44)* | *19% (11/58)* |
| **Central nervous system** | *3% (28)* | *93% (26/28)* | *64% (18/28)* | *4% (1/24)* | *36% (10/28)* |
| **Musculoskeletal** | *2% (23)* | *87% (20/23)* | *61% (14/23)* | *0% (0/23)* | *18% (4/22)* |
| **Others/unknown** | *3% (31)* | - | - | - | - |

### 4.1.7 Microbiology

The lungs and the abdomen were the most common sites of infection in the study (**Table 7**). In the overall cohort, 69% (670/971) had pathogens identified and 32% (307/971) had positive blood cultures. Infections were community-acquired in 74% (718/971) of cases. Gram positive infections were most common, 38% (252/670), followed by gram-negative (32% (214/670)) and mixed polymicrobial (22% (145/670)). A minority of infections were caused by viruses (5% (32/670)) or fungi only (3% (20/670)).

Identification of viral pathogens (with or without a concurrent bacterial infection) increased over the study period from 1% (1/159) in 2006 to 9% (15/171) in 2016, *p<0.001.* There was a significant decline in the frequency of sepsis caused by *S. pneumonia,* from 11% (18/159) in 2006 to 5% (8/171) in 2016, *p = 0.018*. Of the 623 patients with available antimicrobial susceptibility results, 19% (118) received insufficient empirical antimicrobial therapy. It was most frequent in abdominal infections (42%(65/153)) and more common in hospital-acquired (36% (61/169)) than community-acquired (13% (57/454)) infections, *p<0.001.* The pathogens most frequently associated with insufficient therapy were: *Enterococcus spp*. (46), *Candida spp*. (35), Enterobacteriaceae with some antimicrobial resistance (e.g. extended spectrum beta-lactamase producing) (20) and *Pseudomonas aeruginosa* (17). The frequency of multi-drug resistant pathogens was low (2% (13/670)).

## 4.2 Study II

### 4.2.1 Cancer patients with sepsis

In the study cohort of 971 patients admitted to Icelandic ICUs with sepsis, 235 had underlying malignant disease (24.2%, 95% CI 21.5-27.0). Cancer was more frequent in the latter half of the study period (2012-2016), 27.1% of patients (95% CI 23.3-31.2) compared with 20.8% (95% CI 17.3-24.9) in the first half (2006-2010), *p = 0.023*. There was also a slight increase in the proportion of cancer patients alive (5-year prevalence of all sites but non-melanoma skin cancer) that was admitted to the ICU with sepsis during the study period, from 0.79% (95% CI 0.64-0.96) in first half to 1.04% (95%CI 0.88-1.23) in the latter (*p = 0.031*). Cancer patients had most often a solid tumour (10% (100)), followed by metastatic solid tumour (7% (69)) and haematologic malignancies (7% (66)).

The characteristics of cancer patients with sepsis are shown in **Table 8**. Admission categories varied, haematological patients were most likely to be

admitted from medical wards (64%), patients with solid tumour from surgical wards (58%) and sepsis patients without cancer from emergency departments (55%). On a modified Charlson CI (points for the malignant disease itself removed), patients with metastatic disease had a lower burden of comorbidity (2 [1-3]) than patients without cancer (3 [2-5]) or only solid tumour (3 [2-5]). The severity of acute illness was highest in haematological patients (APACHE II score 26 versus 20-21 in other groups and SOFA score 10 versus 7-8). The rates of organ failure were similar in all patient groups, apart from a higher frequency of coagulopathy in haematological patients than other groups (58% versus 21-39%).

Patients with solid tumours and metastases were most likely to have an abdominal site of infection (46% and 36% respectively) while pulmonary infections were the most common site in haematological and other sepsis patients (both 47%). Bloodstream infections were more common in haematological patients than other groups (21% versus 2-6%). Overall, patients with cancer were more likely to have hospital-acquired infections than other sepsis patients, 52% versus 18%.

**Table 8:** The patient characteristics and severity of illness in sepsis patients with cancer admitted to the ICU, compared with data from sepsis patients without cancer. Values are medians [IQR] or proportions and p-values refer to Kruskal-Wallis or Chi-squared tests between the four group of patients. If a variable contained missing data, the number of patients divided by patients with available data is shown.

| Patient characteristics | | | | | |
|---|---|---|---|---|---|
| | **Comparison group without cancer (n = 736)** | **Solid tumour (n = 100)** | **Metastatic solid tumour (n = 69)** | **Haematological malignancies (n = 66)** | **p-value** |
| Age (years) | *67 [54-77]* | *70 [63-78]* | *65 [55-74]* | *69 [61-75]* | *0.014* |
| Males | *55% (403)* | *64% (64)* | *51% (35)* | *70% (46)* | *0.032* |
| Modified Charlson CI[a] | 3 [2-5] | 3 [2-5] | 2 [1-3] | 3 [2-5] | *0.001* |
| APACHE II score | 21 [15-26] | 20 [15-25] | 21 [17-27] | 26 [23-32] | *<0.001* |
| SOFA score | 8 [6-10] | 8 [6-9] | 7 [6-10] | 10 [8-12] | *<0.001* |
| **Admission category:** | | | | | |
| Emergency department | 55% (405) | 25% (25) | 39% (27) | 30% (20) | *<0.001* |
| Medical ward | 30% (219) | 17% (17) | 38% (26) | 64% (42) | *<0.001* |
| Surgical ward | 15% (112) | 58% (58) | 23% (16) | 6% (4) | *<0.001* |
| Recent surgery | 15% (109) | 56% (56) | 20% (14) | 6% (4) | *<0.001* |
| **Organ failure:** | | | | | |
| Circulatory | 93% (683/735) | 95% (95/100) | 94% (65/69) | 97% (64/66) | 0.55 |
| Respiratory | 91% (644/708) | 88% (79/90) | 91% (63/69) | 93% (60/64) | 0.64 |

| | | | | | |
|---|---|---|---|---|---|
| Renal | 54% (387/713) | 58% (57/99) | 51% (35/69) | 53% (34/64) | 0.85 |
| Central nervous system | 42% (310/732) | 43% (43/100) | 38% (26/69) | 27% (18/66) | 0.10 |
| Hepatic | 16% (112/711) | 14% (13/96) | 15% (9/61) | 17% (11/64) | 0.92 |
| Coagulation | 23% (166/714) | 21% (21/99) | 39% (24/62) | 58% (15/26)[b] | *<0.001* |
| Metabolic acidosis | 54% (391/729) | 58% (57/99) | 69% (47/68) | 56% (37/66) | 0.10 |
| Nr. of organ failures | 4 [3-5] | 3 [3-5] | 4 [3-5] | 3 [3-5] | 0.75 |
| Neutropenia | 0.6% (4/725) | 0.2% (2/99) | 10% (7/67) | 48% (32/66) | *<0.001* |
| **Infection site** | | | | | |
| Pulmonary | 47% (348) | 34% (34) | 33% (23) | 47% (31) | *0.016* |
| Abdomen | 20% (149) | 46% (46) | 36% (25) | 15% (10) | *<0.001* |
| Urinary | 10% (76) | 10% (10) | 12% (8) | 5% (3) | *0.48* |
| Blood/endovascular | 6% (47) | 2% (2) | 6% (4) | 21% (14) | *<0.001* |
| Others | 16% (116) | 8% (8) | 13% (9) | 12% (8) | *0.62* |
| Pathogens identified | 68% (499) | 74% (74) | 67% (46) | 77% (51) | *0.27* |
| Positive blood cultures | 31% (230) | 33% (33) | 33% (23) | 45% (30) | *0.13* |
| Hospital-acquired infections | 18% (131) | 61% (61) | 42% (29) | 48% (32) | *<0.001* |
| Insufficient empirical therapy | 16% (74/465) | 33% (23/69) | 27% (12/44) | 20% (9/45) | *0.003* |

[a]*Modified Charlson CI is the Charlson CI without points for the malignancy itself.*
[b]*Patients with pre-existing coagulopathy before the onset of sepsis are excluded*

### 4.2.2 ICU treatment and outcome in cancer patients

Vasopressor use was similar in all four groups of patients studied but the use of invasive mechanical ventilation differed. Patients with metastatic disease were less likely to receive mechanical ventilation than sepsis patients without cancer (36% versus 51%, *p = 0.023*) and the duration of ventilation was shorter than for other groups of patients (median two days versus 4-6.5 days) (**Table 9**). Furthermore, their ICU length of stay was shorter than for other groups (median two days versus three to five days).

Cancer patients were more likely than other sepsis patients to have treatment limitations registered before ICU admission (6% versus 2%, *p = 0.006*) and they were also more likely to receive limitations during the ICU stay (30% versus 17%, *p<0.001*). The decisions were made after a median of one day [IQR 1-3] in cancer patients but two days [IQR 1-6] in other sepsis patients, *p = 0.14* (**Figure 19**). For all patients combined, the hospital mortality for patients with treatment limitations was 82% (186/226). The most common treatment limitations registered were (a patient could have more than one): No cardiopulmonary resuscitation (141), transition to comfort care (87), no mechanical ventilation (75), no return to the ICU after discharge (27), no renal replacement therapy (23) and no vasopressors (2).

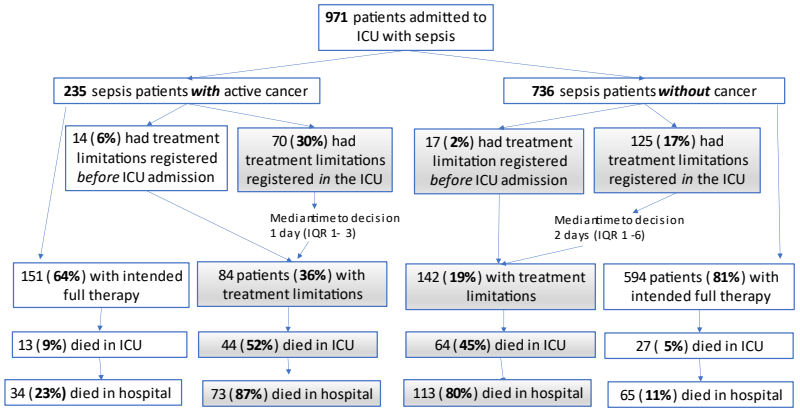


**Figure 19:** A flow-chart over decisions to limit treatment in the group of 971 patients admitted to Icelandic ICUs because of severe sepsis or septic shock.

For all cancer patients with sepsis combined, the ICU, hospital and one-year mortality rates were 24% (57/234), 46% (107/233) and 67% (157/235) respectively. Survival of individual groups of patients are depicted in **Figure 20**.

**Table 9** Treatment received in the ICU and outcome of cancer patients with sepsis. Categorical variables are presented as proportions and continuous variables as medians with [IQR]. Values are medians [IQR] or proportions and p-values refer to Kruskal-Wallis or Chi-squared tests between the four group of patients. If a variable contained missing data, the number of patients divided by patients with available data is shown.

| ICU treatment and outcome | | | | | |
|---|---|---|---|---|---|
| | **Comparison group without cancer (n = 736)** | **Solid tumour (n = 100)** | **Metastatic solid tumour (n = 69)** | **Haematological malignancies (n = 66)** | **p-value** |
| Vasopressors | 76% (557/735) | 85% (84/99) | 75% (52/69) | 85% (56/66) | *0.09* |
| Mechanical ventilation (IMV) | 51% (373/736) | 58% (58/100) | 36% (25/69) | 39% (26/66) | *0.013* |
| Duration of IMV (days) | 5 [2-12] | 4 [2-12.5] | 2 [1-7.5] | 6.5 [2-14.25] | *0.019* |
| New-onset RRT | 6% (47/725) | 6% (7/100) | 1% (1/69) | 12% (8/65) | *0.087* |
| ICU LOS (days) | 4 [2-9] | 5 [2-10.75] | 2 [1-4] | 3 [1-9] | *<0.001* |
| Hospital LOS (days) | 15 [8-31] | 18 [10.3-33.8] | 12 [4.5-25] | 13.5 [5-25.3] | *0.004* |
| Limitations of treatment[a] | 19% (143/736) | 23% (23/100) | 52% (36/69) | 39% (26/66) | *<0.001* |
| Discharged home | 48% (348/730) | 37% (37/100) | 29% (20/69) | 41% (27/66) | *0.006* |
| **Mortality:** | | | | | |
| 28-day | 20% (146/722) | 25% (25/100) | 55% (38/69) | 41% (27/66) | *<0.001* |
| One-year | 32% (231/720) | 50% (50/100) | 88% (61/69) | 70% (46/66) | *<0.001* |
| ICU | 13% (91/727) | 21% (21/99) | 26% (18/69) | 27% (18/66) | *<0.001* |
| Hospital | 25% (178/723) | 35% (34/98) | 59% (41/69) | 48% (32/66) | *<0.001* |

[a]*Decisions on limitations of treatment made before or during the ICU stay*

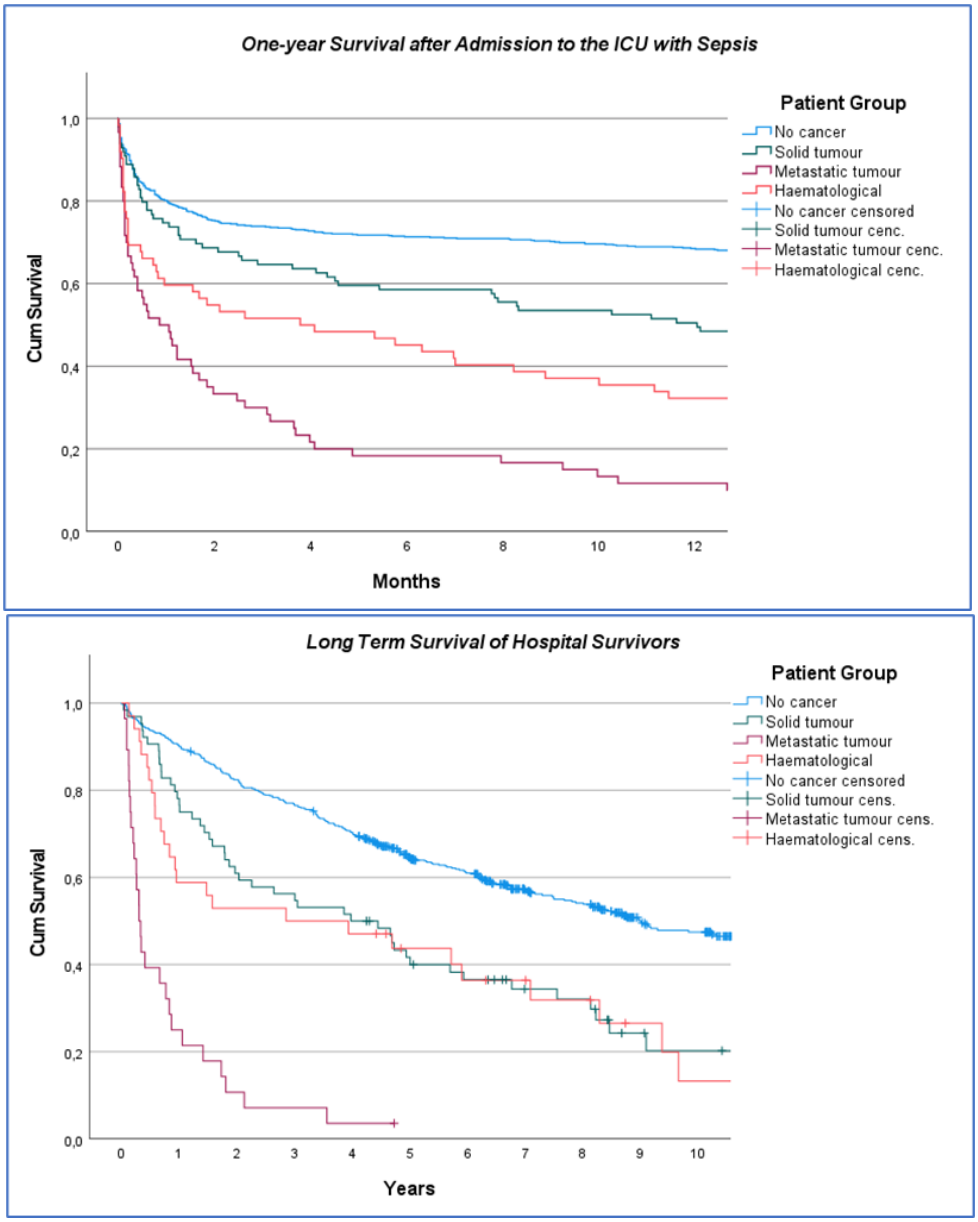


**Figure 20:** Kaplan-Meier curves for one-year survival (A) and long-term survival after hospital discharge (B) for the four groups of sepsis patients studied.

The 28-day mortality rate was similar for patiens with solid tumour and no cancer (25% versus 20%, $p = 0.27$) but haematological patients (41% versus 20%, $p<0.001$) and patients with metatastic disease (55% versus 20%, $p<0.001$) had higher rates. The median survival from ICU admission for

sepsis was 363 days (CI 74-632) for solid tumour patients, 19 days (CI 4-23) for metastatic disease, 64 days (CI 0-194) for haematological patients and 4.7 years (CI 3.7-5.7) for sepsis patients without cancer (*p<0.001).* The median survival for patients who were discharged from hospital was 3.9 years (CI 1.7-6.2) for patients with solid tumours, 91 days (CI 60-122) for metastatic disease, 2.5 years (CI 0-6.9) for haematological malignancies and 9.0 years (CI 7.2-10.7) for sepsis patients without cancer.

## 4.3 Study III

### 4.3.1 Characteristics of patients with sepsis after surgery

Of the patient cohort of 971 patients admitted to Icelandic ICUs because of severe sepsis or septic shock, 88 (9.1%, 95% CI 7.3-11.1) had developed sepsis after an elective procedure, 95 (9.8%, 95% CI 8.0-11.8) following acute surgery and 788 (81.2%, 95% CI 78.6-83.6) had sepsis unrelated to surgery. Patient characteristics are shown in **Table 10**. A solid tumour was a common comorbidity in elective surgery patients (51%) while patients without prior surgeries were more likely to have chronic pulmonary disease and haematological malignancies.

The severity of acute illness was lower in patients with sepsis after elective surgery than other sepsis patients, measured with the APACHE II score (17.5 versus 22, *p<0.001)* and the number of organ failures (median three versus four, *p=0.046*). Pulmonary infections were the most common source of sepsis (50%) in patients without prior surgery but abdominal infections dominated (65%) in patients who had undergone surgery. For patients with positive cultures and available susceptibility test results, the initial antimicrobial therapy was insufficient in 50% (30/60) of cases after elective surgery. This was higher than in patients after emergency surgery (37%, *p = 0.14*) and no prior surgery (13%, *p<0.001).*

**Table 10:** The characteristics of patients with sepsis after surgery compared with patients with sepsis unrelated to surgery. Values are medians with [IQR] or percentages and p-values refer to Kruskal-Wallis or Chi-squared tests between the three groups of patients.

| **Patient characteristics** | | | | |
|---|---|---|---|---|
| | **Sepsis after elective surgery (n = 88)** | **Sepsis after emergency surgery (n = 95)** | **Sepsis without prior surgery (n = 788)** | **p-value** |
| Age | *67.5 [58-75]* | *69 [58-79]* | *67 [55.3-76]* | *0.23* |
| Males | *65% (57)* | *56% (53)* | *56% (438)* | *0.26* |
| Charlson CI | *5 [3-7]* | *4 [3-6]* | *4 [2-6]* | *0.032* |
| APACHE II score | *17.5 [13-23]* | *19 [14-23]* | *22 [16-27]* | *<0.001* |
| SOFA score | *7 [6-9]* | *7 [6-9]* | *8 [6-10]* | *0.021* |
| **Comorbidities:** | | | | |
| Ischemic heart disease | *28% (25)* | *22% (21)* | *21% (162)* | *0.23* |
| Chronic pulmonary disease | *9% (8)* | *16% (15)* | *23% (183)* | *0.003* |
| Diabetes mellitus | *16% (14)* | *11% (10)* | *14% (100)* | *0.55* |
| Congestive heart failure | *8% (7)* | *6% (6)* | *11% (88)* | *0.25* |
| Solid tumor | *51% (45)* | *13% (12)* | *5% (43)* | *<0.001* |
| Metastatic solid tumor | *6% (5)* | *11% (10)* | *7% (54)* | *0.36* |
| Haematological malignancy | *0% (0)* | *4% (4)* | *7% (52)* | *0.01* |
| **Organ failures:** | | | | |
| Circulatory | *91% (80/88)* | *93% (87/94)* | *94% (740/788)* | *0.52* |
| Respiratory | *85% (75/88)* | *76% (71/93)* | *80% (627/779)* | *0.32* |
| Acute kidney injury[a] | *46% (39/85)* | *45% (41/91)* | *56% (433/769)* | *0.03* |
| Coagulation | *20% (17/87)* | *27% (25/93)* | *25% (184/731)* | *0.46* |
| Central nervous system | *34% (30/88)* | *31% (29/94)* | *43% (338/785)* | *0.03* |
| Hepatic | *16% (13/83)* | *14% (12/87)* | *16% (120/762)* | *0.89* |
| Metabolic | *52% (46/88)* | *49% (46/94)* | *56% (440/780)* | *0.32* |
| Nr. of organ failures | *3 [2-4]* | *3 [2-4]* | *4 [3-5]* | *0.01* |

[a]*Any KDIGO score. Acute kidney injury was defined according to the criteria presented in Figure 11 and not KDIGO in paper III. Numbers in this table vary slightly from the printed article because of this.*

### 4.3.2 ICU treatment and outcomes of surgical patients

A larger proportion of patients with sepsis after elective surgery received invasive mechanical ventilation than patients with sepsis unrelated to surgery, 72% versus 45%, *p<0.001* (**Table 11)**. However, the frequency of respiratory failure (85% versus 80%, *p = 0.28)* and the lowest PaO2/FiO2 values were similar (183 versus 170, *p = 0.1*3) in the two groups. Both the median ICU length of stay (5.5 days versus four days) and hospital length of stay (26 days versus 13 days) was longer in elective surgery patients compared with other sepsis patients. Patients admitted to the ICU with sepsis after elective surgery were less likely to receive limitations of treatment than sepsis patients without prior surgery (11% versus 25%, *p = 0.004).* The 28-day mortality for patients with sepsis after elective surgery was 16% and one-year mortality was 41%. The mortality rates did not differ significantly between the three groups of patients.

### 4.3.3 The incidence of sepsis after elective surgery

Of the 88 patients with sepsis after elective surgery, the majority (80) had been operated at Landspitali University Hospital. Three were operated at Akureyri Hospitals, two in small local hospitals, one in a private clinic and two patients had sepsis after an endoscopic procedure. Seven patients (8%) had been discharged home on the day of surgery but were readmitted later because of sepsis. In the study years of 2006, 2008, 2010, 2012, 2014 and 2016, a total of 42,649 elective operations were performed at Landspitali, giving an average incidence of sepsis requiring intensive care of 0.19% per procedure (95% CI 0.15-0.23). The incidence was highest in general surgery (0.60%) and the individual procedures associated with the highest rates where pancreaticoduodenectomy (Whipple procedure) (14%), oesophageal resections (13%) and cystectomy (6%) (**Table 12)**. The greatest number of patients (all clinics included) developed sepsis after a colorectal resection, 30% (26/88). Overall, 66% (58/88) developed sepsis after an abdominal procedure, followed by cardiothoracic (9% (8/88)) and urologic (9% (8/88)). Patients were admitted to the ICU with sepsis at a median of the fifth postoperative day [IQR 3-11].

**Table 11**: Microbiology data and outcomes in patients admitted to the ICU with sepsis after surgery. Categorical variables are presented as proportions and continuous variables as medians with [IQR].

| Infection sites and outcome | | | | |
|---|---|---|---|---|
| | **Sepsis after elective surgery (n = 88)** | **Sepsis after emergency surgery (n = 95)** | **Sepsis without prior surgery (n = 788)** | **p-value** |
| **Infection site:** | | | | |
| Pulmonary | *22% (19)* | *22% (21)* | *50% (397)* | *<0.001* |
| Abdomen | *65% (57)* | *65% (62)* | *14% (112)* | *<0.001* |
| Urinary | *5% (4)* | *4% (4)* | *11% (89)* | *0.02* |
| Blood/endovascular | *2% (2)* | *3% (3)* | *8% (61)* | *0.05* |
| Skin and soft tissue | *2% (2)* | *0% (0)* | *7% (57)* | *0.006* |
| Others | *5% (4)* | *5% (5)* | *5% (72)* | *0.18* |
| Pathogens identified | *70% (62/88)* | *67% (64/95)* | *69% (544/788)* | *0.91* |
| Insufficient empirical therapy | *50% (30/60)* | *37% (22/60)* | *13% (65/502)* | *<0.001* |
| Vasopressors | *83% (73)* | *81% (77)* | *76% (599)* | *0.22* |
| Mechanical ventilation (IMV) | *72% (63)* | *64% (61)* | *45% (358)* | *<0.001* |
| Duration of IMV (days) | *5 [2-10]* | *3 [1-6]* | *6 [2-12]* | *0.002* |
| New-onset RRT | *7% (6)* | *8% (8)* | *6% (48)* | *0.7* |
| ICU LOS (days) | *5.5 [2-14.5]* | *3 [1-8]* | *4 [2-8]* | *0.014* |
| Hospital LOS (days) | *26 [12.3-46]* | *18 [9-43]* | *13 [7-27]* | *0.007* |
| Limitations of treatment | *11% (10)* | *18% (17)* | *25% (199)* | *0.007* |
| Discharged home | *36% (32/88)* | *35% (33/93)* | *47% (367/784)* | *0.029* |
| **Mortality:** | | | | |
| 28-day | *16% (14/88)* | *26% (24/93)* | *26% (198/776)* | *0.14* |
| One-year | *41% (36/87)* | *42% (39/93)* | *40% (313/775)* | *0.95* |
| ICU | *14% (12/88)* | *12% (11/93)* | *16% (125/780)* | *0.51* |
| Hospital | *24% (21/86)* | *34% (32/93)* | *30% (232/777)* | *0.34* |

**Table 12:** The incidence of sepsis after elective surgery at Landspitali per surgical specialty (upper half) and per individual procedure (lower half).

| **Incidence of sepsis after elective surgery at Landspitali** | | | |
|---|---|---|---|
| **Surgical specialty** | **Sepsis cases** | **Number of procedures** | **Incidence (95% CI)** |
| General | *52* | *8,674* | *0.60 (0.45-0.79)* |
| Vascular | *4* | *1,018* | *0.39 (0.11-1.00)* |
| Cardiothoracic | *8* | *2,063* | *0.39 (0.17-0.76)* |
| Urologic | *8* | *4,669* | *0.17 (0.07-0.34)* |
| Plastic | *2* | *1,429* | *0.14 (0.02-0.50)* |
| Orthopaedic | *3* | *7,077* | *0.04 (0.01-0.12)* |
| Obstetric/gynaecology | *3* | *10,534* | *0.03 (0.01-0.08)* |
| Ear, nose and throat | *0* | *3,851* | - |
| Neurosurgery | *0* | *3,334* | - |
| **Procedure** | **Sepsis cases** | **Number of procedures** | **Incidence (95% CI)** |
| Whipple procedure | *7* | *51* | *14% (6-25)* |
| Oesophageal resection | *5* | *40* | *13% (4-27)* |
| Cystectomy | *4* | *67* | *6% (2-15)* |
| Gastric resection | *3* | *70* | *4% (1-12)* |
| Colorectal resection | *23* | *1041* | *2.2% (1.4-3.3)* |
| Lung resection | *4* | *322* | *1.2% (0.3-3.2)* |
| Liver resection | *1* | *107* | *0.9% (0.0-5.1)* |
| Nephrectomy | *2* | *302* | *0.7% (0.1-2.4)* |
| Cardiac surgery | *4* | *721* | *0.6% (0.2-1.4)* |
| Bariatric surgery | *1* | *303* | *0.3% (0.0-1.8%)* |
| Hernia surgery | *4* | *1,472* | *0.3% (0.1-0.7)* |
| Cholecystectomy | *4* | *1,683* | *0.2% (0.1-0.6)* |
| Hysterectomy | *2* | *1,208* | *0.2% (0.0-0.5)* |
| Joint replacement | *2* | *3,482* | *0.1% (0.0-0.6)* |

## 4.4 Study IV

### 4.4.1 The patient cohort and general outcome

In the study period of five years (2013-2017), 973 patients underwent open-heart surgery at Landspitali, patient characteristics are presented in **Table 13**. The most common operation was *coronary artery bypass grafting* (CABG) (50%), followed by *aortic valve replacement* (AVR) (16%). The median Euroscore II was 1.82.

**Table 13:** Patient characteristics and procedure types for patients that underwent open-heart surgery in Iceland 2013-2017. Categorical variables are presented as proportions and continuous variables as medians with [IQR].

| **Patient characteristics (N = 973)** | | | |
|---|---|---|---|
| Age (years) | *68 [60-75]* | **Procedure:**[c] | |
| Males | *76% (738)* | CABG | *50% (483)* |
| Weight (kilograms) | *84 [76-95]* | AVR | *16% (156)* |
| **Comorbidities:** | | CABG+valve | *12% (113)* |
| Recent myocardial infarction | *18% (178)* | Aortic surgery | *6% (61)* |
| Angina pectoris at rest | *14% (134)* | MVR | *3% (29)* |
| Chronic lung disease | *8% (77)* | OPCAB | *3% (26)* |
| Peripheral vascular disease | *6% (58)* | Others | *11% (105)* |
| Diabetes mellitus[a] | *5% (51)* | Duration (minutes) | *223 [185-273]* |
| Dialysis dependent | *1.3% (13)* | Re-do procedure | *3% (25)* |
| Critical preoperative condition | *5% (48)* | Active endocarditis | *2% (18)* |
| Ejection fraction | *55 [50-60]* | **Urgency:** | |
| **NYHA class:**[b] | | Elective | *53% (511)* |
| 0 | *10% (94)* | Urgent | *40% (386)* |
| I | *10% (97)* | Emergency | *7% (68)* |
| II | *37% (357)* | Salvage | *1% (8)* |
| III | *25% (238)* | Euroscore II (median) | *1.82 [1.1-3.8]* |
| IV | *19% (187)* | Euroscore II (mean) | *3.78 (SD 5.8)* |

[a] *Insulin dependent diabetes only*
[b] *NYHA: New York Heart Association*
[c] *MVR: Mitral Valve Replacement, OPCAB: Off-Pump Coronary Artery Bypass. Re-do: Reoperation in a patient with previous sternotomy*

The most common complication after surgery was a new-onset atrial fibrillation (32% (95% CI 29-35)), followed by infection (20% (CI 18-23)), pleurocentesis (10% (CI 8-12)), mechanical ventilation for > 48 hours (9% (CI 7-10)), re-operation for bleeding (7% (CI 5-8)), need of mechanical assist device (5% (CI 4-7)), re-intubation (4% (CI 3-5), pericardiocentesis (3% (CI 2-4)), cerebrovascular accident (2% (CI 1.4-3.4)), renal replacement therapy (2% (CI 1.0-2.9)) and reoperation for suspected graft failure (1% (CI 0.2-1.3)). The median length of stay in the ICU was one day [IQR 1-2] and in hospital median eight days [IQR 7-12]. For patients who were extubated within 24 hours of their surgery, the median time to extubation was 6.5 hours [IQR 4.5-8.9] post-procedure. There was a trend towards decreasing duration of ventilation over the study period, from 7.0 hours [IQR 4.9-9.3] in 2013 to 5.2 hours [IQR 4.0-8.5] in 2017, *p<0.001*. The 30-day mortality was 3.2% (95% CI 2.2-4.5) and the in-hospital mortality 3.5% (95% CI 2.4-4.9)). The causes of death were cardiovascular (13 patients), infectious (12), stroke (2) and unknown (4).

### 4.4.2 Infections after cardiac surgery

A total of 273 postoperative infections were diagnosed in 198 (20%) patients (**Table 14)**. The most common infection was pneumonia, with an overall frequency of 9% (95% CI 7.4-11.1). The rate was 14% (CI 10.5-17.8) in the periods where a damaged TEE probe was in use, but 7% (CI 5.0-8.9) in other periods, *p<0.001,* see **Figure 21** for the trends in pneumonia incidence over time. The majority of pulmonary infections were diagnosed while the patient was still in the intensive care unit (74% (67)) and the median time to diagnosis was postoperative day three [IQR 2-4]. Positive microbiological cultures were obtained in 69% (61) of pneumonia patients and the six most common pathogens were: *Klebsiella oxytoca* (23), *Pseudomonas aeruginosa* (10), *Serratia marcescens* (8), *Enterobacter cloacae* (8), *Klebsiella pneumoniae* (7) and *Escherichia coli* (5). The frequency of each pathogen over time is shown in **Figure 22**.

**Table 14:** The rate of infections developed postoperatively in a cohort of 973 patients who underwent open-heart surgery. Variables are presented as proportions.

| **Frequency of postoperative infections (N = 973)** | |
|---|---|
| **Infection site** | |
| Pneumonia | 9% (89) |
| *With positive cultures* | *6% (61)* |
| *Clinical diagnosis only* | *3% (28)* |
| Surgical site infection | 8% (73) |
| *Deep sternal* | *2% (17)* |
| *Superficial (sternum or vein harvest site)* | *6% (56)* |
| Urinary tract | 5% (52) |
| *Symptomatic* | *1% (14)* |
| *Asymptomatic bacteriuria* | *4% (38)* |
| Bloodstream infection | 3% (27) |
| Endocarditis | 0.5% (5) |
| Clostridium difficile enterocolitis | 0.3% (3) |
| Others | 2% (24) |

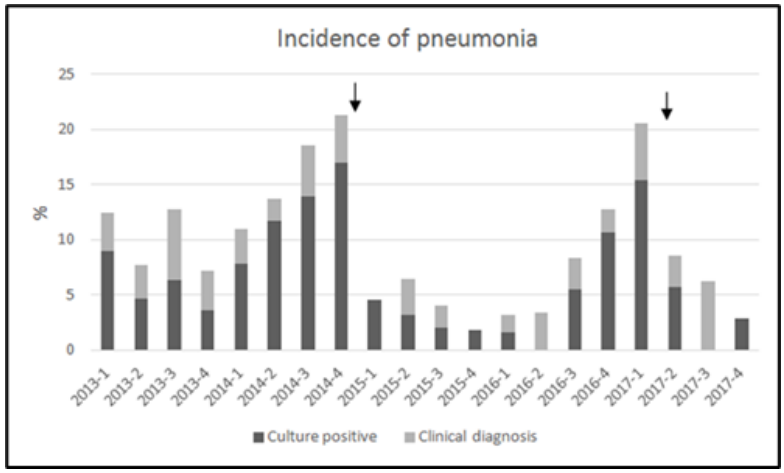


**Figure 21:** The incidence rate of postoperative pneumonia in 973 open-heart surgery patients. Each column represents a quarter year. The time points where damaged TEE probes were removed from the cardiac surgery theatre are marked with arrows.

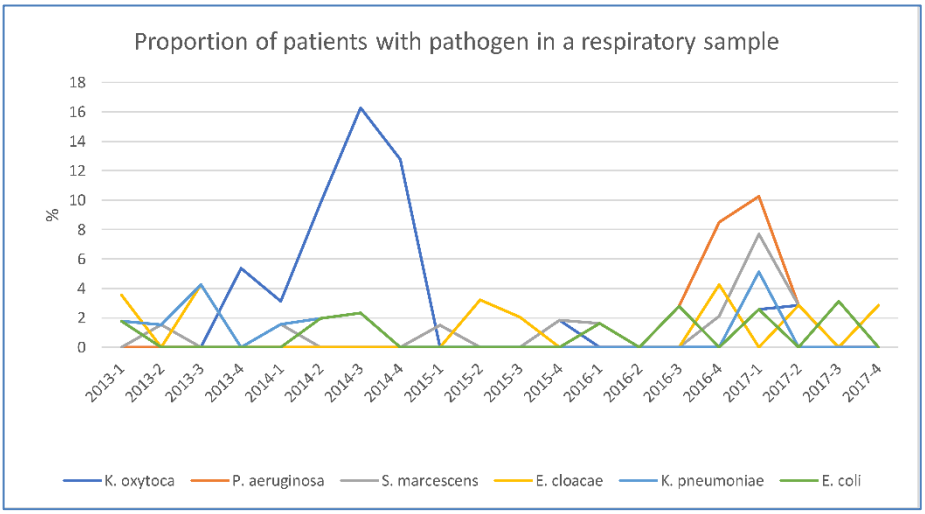


**Figure 22:** The figure shows the proportion of patients with each pathogen in a respiratory sample postoperatively after cardiac surgery.

### 4.4.3 Risk factors for and impact of infections

In a multivariable analysis, an operation within a time period where a damaged TEE probe was in use was independently associated with the development of a postoperative infection (**Table 15**). Patients with postoperative infections stayed longer in the ICU than patients without infections (median two days [IQR 1-6] versus one [IQR 1-1], *p<0.001* and the duration of hospital stay was also longer (median 14 days [IQR 9-28] versus eight [IQR 7-10], *p<0.001.* Infected patients had a higher 30-day mortality rate compared with non-infected patients (8% (16/198) versus 2% (15/775), *p<0.001)),* with the highest rates seen in patients with bloodstream infections (19% (5/27) and pneumonia (17% (16/98)).

**Table 15:** Risk factors independently associated with the development of a postoperative infection after cardiac surgery.

| Predictors of a postoperative infection | | |
|---|---|---|
| **Risk factor** | **Adjusted Odds Ratio (95% CI)** | **p-value** |
| Duration of procedure (minutes) | *1.01 (1.00-1.01)* | *<0.001* |
| Age (years) | *1.04 (1.02-1.05)* | *<0.001* |
| Diabetes mellitus (insulin dependent) | *3.17 (1.67-6.05)* | *<0.001* |
| EuroScore II | *1.05 (1.02-1.08)* | *0.03* |
| Reoperation for bleeding | *1.94 (1.05-3.57)* | *0.03* |
| Operation in a contaminated period | *1.56 (1.08-2.25)* | *0.02* |

### 4.4.4 Two infectious outbreaks

*Klebsiella oxytoca* with extensive beta-lactam resistance was cultured from the respiratory tract of 22 patients during the first period with a damaged probe (October 30th 2013 to November 12th 2014) There was one in-hospital death in those 22 patients but it was not considered to be directly related to the infection. In the latter period with a damaged probe (September 15th 2016 to April 12th 2017), 10 patients had *Pseudomonas aeruginosa* in their respiratory tract, of which three also had a bloodstream infection and septic shock. All three, and one additional patient with pneumonia, died while in hospital. During this period two patients were diagnosed with *Enterococcus faecalis* endocarditis in a new biologic valve prosthesis, one of whom died. These three pathogens (*K. oxytoca, P. aeruginosa and E. faecalis)* were all cultured from the TEE probe in use at respective timepoints, after a routine disinfection process. During mid-year 2014 (quarter 2-3), the multi-resistant strain of *K. oxytoca* was found in 60% (12/20) of all respiratory samples taken from cardiac surgery patients.

# 5 Discussion

In this long-term nationwide study of sepsis requiring intensive care in Iceland, the incidence, severity of illness and mortality rates remained stable over the 11-year study period. By using chart review and consistent clinical criteria for patient identification, sources of bias were kept to a minimum. Recent treatment campaigns did not have a substantial effect on the initial resuscitation of sepsis patients in the emergency departments, although a few developments in treatment were observed. Insufficient empirical antimicrobial therapy was frequent in intra-abdominal and hospital-acquired infections and was an independent predictor of mortality. Malignant disease was a common comorbidity in sepsis patients but cancer patients with sepsis were a heterogenous group with varying aetiology and outcome of sepsis. The incidence of sepsis after elective surgery at Landspitali was generally low, although high rates were seen after some major oncological procedures. The length of stay was long in this patient group but mortality similar as in other sepsis patients. The general incidence of postoperative infections after cardiac surgery in Iceland was in the higher end of previous reports, but two nosocomial clusters of infections associated with damaged TEE probes had a large effect on the rates.

## 5.1 The incidence of sepsis and severity of illness

The crude population incidence of sepsis requiring intensive care (0.55-0.75 / 1000 per year) found in this study falls within the range reported in similar studies (**Table 2**). The crude incidence was age-standardized against the Northern European population, as the age-composition of the Icelandic population is relatively young. The age-standardized rates (0.74-0.93 / 1000 per year) are in the higher range reported, which is not unexpected in a healthcare system without high-dependency units. ICU-acquired sepsis was not included in the present study but these patients have been 18-30% of cohorts when included.[3,56,58]

Previous studies on trends in sepsis incidence over time have been based on diagnostic codes[73,75-77,82,83] or data extraction from large digital databases.[52,80,83,85] In the present study, every case was identified by detailed chart review so any bias from variations in diagnosis codes or misclassifications in electronic databases should be limited. No evidence of

any increase in the incidence of sepsis requiring intensive care over the 11-year study period was found. This data thus supports the notion that the rapid increase observed in code-based studies[73,75,76] may not necessarily reflect actual trends.

Although only assessed unidirectionally in this study, the now abandoned term "*severe sepsis*" by the Sepsis-2 definitions identified the same population (99.5%) as the term "*sepsis*" in Sepsis-3. Considerably fewer patients (42% versus 77%) were however classified as *septic shock* with the more stringent Sepsis-3 criteria, that requires a lactate elevation.[40] Only 48% of this patient cohort would have been found by a commonly used methodology of ICD-10 diagnosis code search. The yield of code search may differ between healthcare systems. In Iceland, codes in discharge summaries are for informative purposes only. They are not linked to financial reimbursement and not subject to any regular formal audits.

Although the age-specific incidence of sepsis in hospitalized patients has been shown to increase consistently with age (**Figure 4**),[64] in the present study the incidence peaked before declining again in the oldest age groups. This most likely reflects ICU admission policies. The age-specific incidence rates peaked earlier in women (71-80 years) than men (81-90 years), which raises concerns of a gender bias regarding ICU admissions. The mean age of death in Icelandic women is higher (84 years) than in men (81 years).[184] Males have been shown to receive more invasive treatments than females,[187] even after adjusting for severity of illness.[188,189]

## 5.2 Treatment before ICU admission

No changes in patient severity of illness on admission to the intensive care units over time was observed. There were no major organizational changes in Icelandic hospitals over the study period, so any change in the population admitted to ICUs related to such factors would not be expected. There was, however, an increase in the length of stay in the emergency departments in the latter half of the study period. This might reflect a relative reduction in ICU bed availability, which remained the same throughout the study period despite population growth. Iceland lies below the European average in the number of ICU beds per capita.[190,191]

Another possible explanation for increased length of stay in the ED would be a change in the approach to sepsis management following the publication of the Surviving Sepsis Campaign Guidelines. The recommendations of a fluid bolus of a certain amount, serial lactate measurements and (in the most

recent version) peripheral vasopressors may have led to a tendency to complete these steps before evaluating the need for intensive care. An ICU admission within six hours is however recommended in the SSC Guidelines as prolonged stay in the emergency department has been associated with worse outcome.[192,193]

Achievement of individual goals of the 1-hour bundles ranged from 33% to 60% per goal in ED patients and completion of goals was not associated with better survival. Comparison with previous studies is difficult as they have been very heterogenous and the bundles have also evolved with time.[194,195] The median time from triage to antibiotics was 1.8 hours in the present study, which is in the lower range of previous reports using similar methodology (1.9-4.7 hours).[196-201] Still only 33% of patients received antibiotics within one hour of triage. The clinical presentation of sepsis is highly variable and sepsis may not have been suspected in the first hour of emergency care in all patients. A study that assessed the delay time to antibiotics found that in a cohort with a median of 3.4 hours delay to antibiotics, 2.7 hours were because of a recognition delay and only 0.6 hours because of delays in administration of antibiotics. Some studies have used the diagnosis of sepsis as time zero[202,203] but that time point is challenging to assess retrospectively.

Several studies have shown increased mortality with delays in antibiotic administration,[87,200,203-205] but others have, like the present study, not found any increased mortality with delays up to five or six hours.[196-198,206,207] There may be an inherent bias in these studies, as severely ill patients would be diagnosed with sepsis sooner than less ill patients and thus receive antibiotics sooner. The severity of illness has been reported to be higher in patients receiving antibiotics within one hour of arrival in the ED[200,204] and a J-curve relationship has been demonstrated with regard of mortality and antibiotic administration.[199]

We found a reduction in the time to lactate measurements in emergency department patients from 4.1 to 1.2 hours over the study period. This coincided in time with availability of point-of-care blood gas analysis at the largest emergency department at Landspitali. A venous blood gas analysis that includes lactate is now frequently performed parallel to routine blood work on arrival. This may explain the perceived increase in the frequency of metabolic acidosis observed over the study period, as it was presumably missed in the earlier study years where blood gas analysis was frequently not performed until after ICU admission

Studying the initial management of sepsis patients in hospital wards is difficult. The syndrome often presents with a slowly deteriorating patient where assigning a certain time point for the “onset” of sepsis retrospectively can be problematic. This is reflected in the large number of ward patients excluded from analysis of time variables in the present study due to missing values. The optimal way of monitoring ward patients for signs of sepsis to aid early detection is an area of active research. Implementation of electronic health records and tools to alert staff of abnormal values have the potential to decrease diagnostic delays, but the effect on outcome is not clear.[208]

## 5.3 ICU treatment and outcome

There were no significant changes in the total volume of fluid administered in the first 24 hours of intensive care during the study period, but the composition varied. There was a decrease in the use of blood products over time and a complete cessation of the use of hydroxyethyl starch solutions in mid-year 2012. This was following the publication of a multicentre trial where increased need for renal replacement therapy in sepsis was identified for patients who received hydroxyethyl starch.[209] The optimal fluid therapy in sepsis and critical illness in general has been widely studied, especially with regard of mortality and acute kidney injury. Balanced crystalloid fluids have been shown to be equal to, or marginally advantageous over normal saline.[210-213] Albumin may elevate blood pressure with a lower net fluid balance but a mortality benefit over crystalloids has not been demonstrated.[214-216]

The 28-day mortality rate in Icelandic sepsis patients was 25% and hospital mortality 30%, which is in line with recent rates from similar healthcare systems in the Nordic Countries.[6,55,71] The severity of illness in the cohort (APACHE II score 21 and SOFA score 8) was comparable to other ICU based studies which have reported APACHE II scores ranging from 18 to 25[3,5,49,51,58-60,63,72] and SOFA scores from 6-10.[5,6,49,50,57,58,60,62,72] As for the incidence of sepsis requiring intensive care, there was no significant trend in the mortality rate over time, which supports the theory that some of the reported reduction in mortality may be related to changes in code use. A large study based on 101,064 sepsis patients from an ICU database found an annual absolute decrease in mortality of 1.3% per year over 12 years, but a similar mortality reduction was found in other ICU patients as well.[80] Another study that pooled together data from 14,418 sepsis patients from the control arm of sepsis trials found an annual percent reduction of 3% over 19 years.[84]

The study cohort in this project may have been too small and the study period to short to detect real changes of this magnitude.

Like in previous studies, age,[60,62] medical admissions[62] and cardiovascular failure[60] were independent predictors of death in sepsis. Mortality was lower in patients exhibiting a greater number of SIRS symptoms. A strong inflammatory response is likely beneficial in sepsis and previous studies have found a correlation between fever and reduced mortality in infections.[217,218] The lack of a strong response may also be correlated to confounding comorbid disease and medicines (e.g. bone marrow suppression, beta-blockers). The absence of fever may also cause a delay in the recognition and start of treatment for sepsis. A higher BMI was independently associated with lower mortality in the present study, which has been described previously in sepsis.[219] This may be related to a greater reserve during catabolic states or that a low body weight represents some frailty not captured in the traditional severity of illness scoring systems. Only one risk factor for death identified in the multivariable analysis was potentially modifiable, the choice of initial antimicrobial therapy.

## 5.4 Microbiology

The rates of pathogen identification was high in the study (69%). Microbiological cultures have been positive in 45-65% of cases in previous publications.[3-6,49,50,56,58,59,62,70,72] The reasons for these seemingly low rates may include cultures taken after the onset of antimicrobial therapy, infection site difficult to access (e.g. pneumonia) or cultures not taken at all, which in low-income regions can be for financial reasons.[78] The detection of viral pathogens increased during the study period which is likely related to increased diagnostic capacity with PCR tests. The H1N1 influenza pandemic, which caused a surge in ICU admissions, peaked in 2009 in Iceland,[220] a year that was not included in the study. A reduction in the frequency of *S. pneumoniae* sepsis was observed over the study period, which coincided with the implementation of routine childhood vaccinations against the bacteria in 2011. A decline in hospitalization for pneumococcal pneumonia has been reported as well.[221]

The frequency of multi-drug resistant pathogens is low in Iceland[222] and they were not the most common cause of insufficient empirical antimicrobial therapy in the study cohort. In the overall patient group the rates of insufficient therapy was 19% which is within the previously reported range of 17-20%[223-225] in mixed cohorts. The rate varied considerably between

infections sites, with the highest frequency in abdominal infections (46%) and hospital-acquired pneumonias (27%). A common empirical antimicrobial therapy in abdominal sepsis in Iceland during the study period was a combination of a second- or third generation cephalosporins with metronidazole that has inadequate efficacy against *Enterococcus spp*., *Pseudomonas spp*. and *Candida spp*. Third generation cephalosporins and in some cases aminopenicillins were commonly prescribed for pulmonary infections, which in hospital-acquired cases may be caused by resistant Enterobacteriaceae or *Pseudomonas spp*.

The role of *Enterococcus spp*. in intra-abdominal infections has been debated[226] and the presence of enterococci in polymicrobial abdominal infections was not considered to warrant anti-enterococcal therapy in the present study if adequate source control had been achieved and the patient was clinically improving. Patients admitted to ICUs with abdominal sepsis may however frequently have complicated infections with abscess formation, where empirical therapy against enterococci should be considered.[226,227] There has been increased awareness of the role of *Candida spp*. is abdominal sepsis in recent years. In guidelines from 2016, the presence of yeast in normally sterile intra-abdominal specimens (e.g. operative room specimens) in clinically infected patients should be considered indicative of intra-abdominal candidiasis. Furthermore, empiric antifungal therapy should be considered in intra-abdominal infections in high-risk patients, which include recent surgery, anastomotic leaks and gastroduodenal perforations.[228] Prophylactic fluconazole in surgical patients[229] and empirical micafungin in Candida colonized ICU patients[230] has however not been shown to improve outcome.

## 5.5 Cancer patients with sepsis

Underlying cancer was a common comorbidity in sepsis patients requiring intensive care in Iceland (24%). The frequency was in the higher range reported from previous studies (13-24%).[5,6,60,85] The proportion of all sepsis patients with metastatic disease (7%) and haematological malignancies (7%) was also high, where rates of 3-7%[50,51,60,85,231] and 2-7%[5,6,50,231] have been reported respectively. The fraction of sepsis patients with cancer increased over the study period, most likely reflecting increased prevalence of cancer in the population, but the proportion of all cancer patients alive that were admitted to intensive care with sepsis also increased slightly. The cohort of sepsis patients with cancer was heterogenous and division into groups was considered to be appropriate to adequately describe the characteristics and clinical course of these patients.

Although elective ICU admissions for postoperative observation after cancer surgery were not included, 56% of solid tumour patients had undergone surgery in the same hospital stay as the subsequent ICU admission for sepsis. Major cancer surgery is associated with the highest rates of sepsis after surgery[136,141] and this may explain the high rates of abdominal infections in solid tumour patients. Similar findings have been described before in cohorts of cancer patients in the ICU, as well the frequent bloodstream infections observed in haematological patients.[232]

The severity of illness measured with the APACHE II and SOFA scoring systems was highest in haematological patients but the immunosuppression and/or thrombocytopenia frequently associated with haematological disease is captured in both scoring systems, irrespective of any sepsis-induced organ failure. Despite excluding patients with pre-existing organ failure, the rates of coagulopathy were highest in haematological patients. The pattern of organ failures was otherwise similar in all groups of patients despite different aetiology of sepsis.

The rates of organ support varied, however, with patients with metastatic disease less likely to receive invasive mechanical ventilation, they also had a shorter duration of stay in the ICU and were most likely to receive treatment limitations in the ICU. This group of patients was comparatively young and had a lower burden of comorbid disease than other groups of patients, indicating that there may be some selection in which patients with metastatic disease are admitted to the ICU.

## 5.6 Treatment limitations

The frequency and timeline of decisions to forgo further invasive treatments are not often reported in epidemiological studies. In the present study, 73% of all deaths in the ICU were preceded by decisions to limit therapy. Decisions to forgo life-sustaining therapy are usually made when death is considered imminent and further invasive treatment would only be burdensome for the patient. These decisions have, however, been shown to be an independent and strong predictor of hospital mortality, even after adjusting for severity of illness and chronic disease in a multivariable analysis.[233] This should not be interpreted as causative, but rather that treatment decisions are made with regard to factors not captured in traditional scoring systems. These include factors such as frailty, functional status and patient and family wishes.

Interestingly, the median time to first decisions on treatment limitations was only one day after ICU admission in cancer patients and median two

days in other sepsis patients. This is shorter than the three-to-four day long trial of unlimited ICU care for cancer patients that has been proposed in the literature.[122,131] The median length of ICU stay for cancer patients with metastatic disease was also short, or only two days. This may indicate that some of the ICU admissions for sepsis might have been inappropriate, as invasive treatment was considered futile already in the first day of care. In other cases, the acute deterioration caused by sepsis and the ICU admission may have been a trigger for a treatment goal discussion, with decisions made on partial treatment limitations (e.g. no cardiopulmonary resuscitation, but otherwise full ICU treatment). However, the hospital mortality was high (87% in cancer patients, 80% in other sepsis patients) in all patients where any decision to limit treatment was made, even only "no cardiopulmonary resuscitation."

For both cancer patients and other sepsis patients, the hospital mortality rate (46% and 25% respectively) was almost double the ICU mortality rate (24% and 13% respectively). This is a greater difference between ICU and hospital mortality rates than several others have reported,[3,5,59,62] but similar to data from Finland.[51] The reasons for this are unclear and likely multifactorial. Cancer patients may not have been eligible to further oncological therapy after the multiorgan dysfunction caused by sepsis. Also, for patients with multiple comorbidities, a severely reduced functional status after sepsis requiring ICU stay would make further ICU admissions in case of a new deterioration futile. Data on treatment decisions taken in hospital wards after ICU discharge was not collected in this study.

Patients with solid tumours had similar 28-day mortality rate as sepsis patients without cancer (25% versus 20%), but otherwise all groups of cancer patients had reduced survival at all time points. These findings do not support the notion that it is predominantly the severity of acute organ failure that predicts survival in cancer patients in the ICU, and not the characteristics of the underlying malignancy. The median survival from admission for patients with metastatic disease was only 19 days which may raise the question of futility. However, 29% of patients with metastatic disease could be discharged back home after the hospital stay for sepsis and they had a median survival of 91 days after discharge. On a case-by-case basis, even a short extension in survival allowing discharge to home might be a meaningful outcome for a patient with an otherwise incurable disease.

## 5.7 Sepsis after elective surgery

The aim of this study was to analyse the aetiology and outcome of sepsis after elective surgery with comparison to other sepsis patients. A third group of patients was included, patients with sepsis after emergency surgery, as those patients were likely to share many characteristics with the elective surgery ones and possibly confound the analysis if included in an "*other sepsis patients*" category.

Solid tumours were frequent (51%) in patients with sepsis after elective surgery, which likely explains the slightly higher Charlson comorbidity index in these patients compared with other sepsis patients. Many of the patients with sepsis after surgery developed it after major oncological surgery. The severity of acute illness on admission to the intensive care units was however lower in patient with sepsis after elective surgery than patient without prior surgery, which may be related to earlier admission to the ICU in ward patients compared with patients who deteriorate at home.

Abdominal infections predominated (65%) in this elective surgery patient group, which differentiates it from other groups of sepsis patients, e.g. those in randomized clinical trials of sepsis interventions where only 11-25% are reported to have an abdominal origin of infection.[94,110,114] Other sites of infections that have been the focus of many sepsis prevention studies, such as urinary[234] and bloodstream infections,[235] were rare causes of sepsis that required intensive care in surgical patients.

The high rate of invasive mechanical ventilation in elective surgery patients is likely related to the frequent need of re-operations for source control in this group. Ventilator treatment started in the surgical theatre is frequently continued for some time in the ICU, e.g. due to anticipated need of further operations within a day or two. The high rates of abdominal sepsis may also affect the length of stay in the ICU and hospital, as these patients frequently need multiple operations, vacuum-assisted closure therapy and may develop fistulas and other complications.[236]

Patients admitted for elective surgery will in most cases have undergone a pre-operative assessment, with the option of postponing the procedure for optimization of a comorbid disease if needed. Considering that, and a low severity of acute illness on admission to the intensive care in this group, a better outcome from sepsis would be expected. This was not the case, as mortality rates did not differ between groups of patients. The frequency of abdominal sepsis in the cohort may have affected this, as it has been

associated with worse outcome,[237] although this was not confirmed in the present study. There was a lower rate of decisions to limit treatment in elective surgery patients than other sepsis patients. It likely reflects that these patients are in most cases admitted from home for a curative procedure. In other patient groups, the sepsis may be one of several setbacks in the context of deteriorating functional status.

The incidence of sepsis after elective surgery at Landspitali in Reykjavik was 0.19% per procedure. This is lower than previous reports from mixed cohorts (0.9-1.6%).[136,137,142] These studies have focused on inpatient procedures while the cohort at Landspitali included outpatient procedures as well. As others have reported,[136,143] the highest incidence rates of sepsis after elective surgery were after pancreaticoduodenectomy, oesophagectomy, cystectomy and gastrectomy. These are major oncological procedures associated with considerable perioperative morbidity and mortality.[145,147,238-241] The rates of sepsis after pancreaticoduodenectomy and oesophagectomy in the present study (14% and 13% respectively) are at the higher range of previous reports.[136,241,242] Landspitali is a low-volume centre for these procedures which has been shown to affect outcome negatively.[143,243]

The 28-day mortality in patients with sepsis after elective surgery was 16% and the one-year mortality was 41%. No data was collected on the outcome of surgical patients without sepsis so the added morbidity and mortality caused by the sepsis cannot be estimated. For comparison, a prospective study on the outcome of all general surgery patients in 2014 at Landspitali found a 1.8% 30-day mortality and 5.6% one-year mortality.[244]

## 5.8 Infections after cardiac surgery

In this study detailed microbiological data on all cardiac surgery patients in Iceland for five years was collected. The aim was to provide contemporary data on infections and outcome after cardiac surgery in light of two outbreaks of TEE related infections. The latter outbreak, in 2016-2017, unfolded as work on **Study I** had begun and some patients from the 2014 outbreak are included in **Studies I** and **III**. In this part of the project, all infections after cardiac surgery were documented. Only a minority of them caused *sepsis* as defined in the previous studies. In **Study III**, low rates (0.6% per procedure) of sepsis requiring intensive care after elective cardiac surgery were reported, but only 53% of all cardiac surgery performed was elective. The rest of the patients had waited for surgery in-hospital or had emergency operations where sepsis rates per procedure may be higher. Since patients

with ICU-acquired sepsis were not included, patients who developed sepsis during a protracted ICU stay after cardiac surgery, will also have been missed in **Study III**.

This was a single centre study, but from nationwide cohort, with patient characteristics similar to those reported in the large Swedish database Swedeheart.[245] The Euroscore II (median 1.8) was identical with the Swedish median (1.8) but the 30-day mortality rate in Iceland, 3.2% was slightly higher than the comparative rate in Sweden, 2.1%.[245] Among registered complications, Iceland had higher rates of pleurocentesis (10% versus 6.4%), infections (20% versus 11%) and mechanical ventilation >48 hours (9% versus 4%) than the Swedish cohort.

The rates of pneumonia (9%) are in the higher end of previous reports (2-11%),[153-158,245] but the rate differed significantly between periods with a contaminated TEE probe in use (14%) and not (7%). The rates of other infections were similar to the rates reported in previous studies.[153,155,156,159,160,245] It is likely that the high rate of pneumonia contributed to a higher incidence of pleurocentesis and a longer duration of mechanical ventilation, as well as mortality. Postoperative infections were associated with an almost twofold length of stay in hospital and four times higher perioperative mortality. In line with previous research, factors such as such as age[157,158] and duration of procedure[153] were confirmed as risk factors for infections, but the use of a damaged TEE probe was also independently associated with postoperative infections.

The course of events from minute surface damage of a TEE probe to pneumonia, septic shock and endocarditis is not fully elucidated, but is likely as follows: Decontamination of organic material during cleaning may have been incomplete due to scratches on the probe surface and the pathogenic bacteria survived the standard disinfection process. The TEE probe is inserted orally and through to the oesophagus. These are non-sterile sites, but do not contain Enterobacteriaceae or *Pseudomonas spp*. under normal circumstances. The TEE probes inevitably touches the laryngeal inlet during insertion and may cause small lacerations on mucous membranes in the pharynx and oesophagus. Both the endotracheal intubation[246] and sedative/analgesic drugs[247] cause laryngeal dysfunction in the immediate postoperative period, so pathogens that have colonized the laryngopharynx may easily be transferred to the lungs. Postoperative atelectasis and reduced clearing of the airways (e.g. reduced coughing due to pain) will further promote the development of pneumonia.

It is not known how many patients were colonized by these pathogens, as respiratory samples are not taken from cardiac surgery patients unless an infection is suspected. During mid-year 2014, the outbreak strain of *Klebsiella oxytoca* could be cultured from 60% of all respiratory samples taken from cardiac surgery patients. This outbreak continued for 13 months and several factors may have contributed to that. Even though the bacteria showed antimicrobial resistance, it was not among the strains that were under surveillance by infection control at the time. Being a small centre, there is no independent cardiothoracic ICU at Landspitali. Cardiac surgery patients are cared for in a multidisciplinary ICU, which also cares for patients with hospital-acquired infections, frequently caused by Enterobacteriaceae. Initial efforts to find the source of these *K. oxytoca* infections were therefore focused on the ICU environment. *Pseudomonas spp*. is also common in ICU patients, but the occurrence of septic shock by the bacteria in two cardiac surgery patients within a short time was very unusual and led to the detection of the latter outbreak.

Multiple steps have been taken at Landspitali to hinder further infections from TEE probes. Routines for examining the probe for damage and cleaning have been updated and the use of single-use probe sheaths is now mandatory. Ultraviolet cabinets for sterilization of the probes were purchased and used, although it was later discovered that not all TEE probes are compatible with this sterilization technique. These infection clusters have highlighted the importance of continuous pathogen surveillance in hospitals. Unusual antimicrobial susceptibility patterns facilitated the detection of these clusters. Local outbreaks of common pathogens with traditional antimicrobial susceptibility will be harder to detect unless some genomic surveillance is applied.

## 5.9 Methodological considerations

All the studies presented in this thesis were retrospective observational studies with the goal of describing the epidemiology of sepsis requiring intensive care in Iceland and infections after cardiac surgery. As such, the aim was not to prove causation of any outcome, but rather to report the current situation and recent trends. Provision of such data can reveal areas where care might be improved and aid in determining future needs in the healthcare system. They can also help in interpreting data from clinical trials and assessing if they are applicable in the current institution.

An important aspect when evaluating observational studies is whether they actually measure what was intended, in this case sepsis. The definitions of sepsis (infection induced organ failure) are very sensitive and leave room for interpretation. Every patient in **Studies I-III** had an infection and one or more new-onset organ failures. It is, however, unlikely that every organ failure in the patient cohort was directly caused by an inflammatory response against infection. Factors such as hypovolemia, chronic pulmonary disease and congestive heart failure may all cause an acute organ dysfunction. In case of a minor concurrent infection, these patients will fulfill the criteria for sepsis, but they may not have been considered to have sepsis by the treating clinicians. Every effort was made by study authors in the present study to include only patients where an infection was the most likely cause of the organ dysfunction that led to ICU admission, but over- or under-inclusion of patients cannot be excluded.

Another aspect in observational studies is whether the data analysed is true. For **Studies I-III**, paper patient charts were retrieved, but this is a vanishing study method as the vast majority of all health data is now electronic. Electronic health records may facilitate observational studies by simplifying time-consuming chart reviews, but systems vary in how easily data can be extracted. There is always a risk of automatic registration of incorrect data in such systems. An example can be a pulsoxymeter probe that has fallen out of place and gives a false signal of hypoxemia. It registers in the system but is not a true measurement and can confound later studies. Paper charts are less prone to inaccurate data being recorded, but the frequency of missing data can be high. Reliable data on the severity of illness can only be extracted from electronic systems if the included scoring systems are consistently filled for every patient, which may not always be the case.

## 5.10 Strengths and limitations

An important strength of the present study is that the same authors assessed every patient, so if there is an inclusion bias, it would be consistent over the study period. Another strength is that all scoring systems for severity of illness were filled by study authors especially for these studies, although this was done retropectively. Further strengths of this work include the accurate population census of Iceland with personal identification numbers and accessible health records. All the studies are nationwide and should be generalizable to similar healthcare systems, although the Icelandic results on surgical patients may not be applicable to larger specialized centres.

An important limitation of the studies are the small patient cohorts, even though the total cohort of 971 sepsis patients is large in comparison with other chart-review studies. The small subgroups and natural fluctuations in incidence rates may have precluded the detection of small, but real, trends. One ethical aspect of the studies is the fact that study authors were the treating clinicians in many cases. It is however unlikely that this affected any of the results, as data was gathered retrospectively several months to years after the ICU admission.

## 5.11 Future perspectives

Due to the small population size, large clinical trials on sepsis are not feasible in Iceland, except in the setting of one study centre in larger, international, multicentre trials. Landspitali has previously participated in a few pragmatic ICU trials in collaboration with the other Nordic Countries.[209,248] The field were Iceland is most likely to be able to contribute new knowledge on sepsis internationally might be in genetics. A large genealogy database over the present day population of Iceland has been built by a private company (deCODE Genetics), which is active in research on several diseases.[249] The heterogeneity of sepsis patients is however likely to be an obstacle in this kind of research were distinct phenotypes are important. The present database of clinically defined sepsis cases might however be utilized to identify phenotypes for linking with genotypes.

At a more local level, several areas of concern were discovered, such as insufficient antimicrobial therapy, high infection rates after some surgical procedures and an increasing duration of stay in the emergency departments. These areas may warrant further studies. With the widespread implementation of electronic health records in the past few years, including in the ICUs, it is important to from early on establish some sort of quality control so that these data can be easily utilized in future studies.

# 6 Conclusions

The incidence, severity of illness and outcome of sepsis requiring intensive care did not change over an 11-year study period in this nationwide, clinically defined cohort. Both the incidence and outcome was similar to previous reports from comparable healthcare systems.

Recent treatment campaigns did not affect the management of sepsis in key areas such as the timing of antibiotics. Compliance with the one-hour goals of the Surviving sepsis guidelines was not associated with increased survival.

The choice of empirical antimicrobial therapy needs careful consideration, especially in hospital-acquired and intra-abdominal infections.

Cancer was a common comorbidity in sepsis patients but the aetiology and outcome of sepsis varied. The use of intensive care resources was limited in patients with metastatic disease, who also had reduced short- and long-term survival but an acceptable outcome after ICU admission may be reached on case-to-case bases.

Sepsis following elective surgery is a rare complication but associated with prolonged length of stay and similar mortality rates as in other sepsis patients. The majority of cases were intra-abdominal infections following major oncological procedures

Minor surface damage and contamination of TEE probes used intraoperatively caused a surge in pneumonia rates after cardiac surgery in Iceland. The frequency of postoperative infections and some minor complications was slightly higher than in similar cohorts as a result.

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# Original publications

# Paper I

# Paper II

# Paper III

# Paper IV