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Studies of incidence, risk factors and prognosis

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BY
VIGGO HOLTEN MORTENSEN

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AALBORG UNIVERSITY
DENMARK

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CURRICULUM VITAE

Viggo Holten Mortensen was born in Aalborg, Denmark on September 6th, 1991. He graduated from Aalborg Technical Gymnasium in 2011. He started his medical studies at Aalborg University in 2011 and graduated in 2017. During his studies, he worked as substitute medical doctor at the Department of Clinical Microbiology, Aalborg University Hospital. Following his graduation, he completed a one-year internship at Aalborg University Hospital. First, six months at the Department of Infectious Diseases followed by six months at the Department of Cardiothoracic Surgery.

His first scientific work was an informatics approach to handle the cumbersome challenges of incomplete data on antimicrobial resistance that is produced in the routine laboratory work. This work was presented at the ECCMID Congress in 2017. In the end of his internship at Aalborg University Hospital, he started the preparation for the current PhD study under guidance of Professor Henrik Carl Schønheyder. In January 2018, he then initiated the current PhD project on the epidemiology of hospital-acquired bacteraemia in the North Denmark Region. Initially, with Professor Henrik Carl Schønheyder as main supervisor followed by Associated Professor Lone Hagens Mygind.

He is married to Maiken Holten Mortensen and have a two-year-old son, Lukas, and a newly born daughter, Neel.

ENGLISH SUMMARY

Bacteraemia is considered a severe complication in hospitalised patients. Bacteraemia contracted during a hospital stay is often coined nosocomial or hospital-acquired and is associated with factors related specifically to hospitalisation, high mortality, and an economic burden. To distinguish hospital-acquired cases from others, a time window of 48 hours after admission to 48 hours after discharge is often applied. Although the literature of hospital-acquired infections and infection control is vast, studies often lack comparison groups or compare hospital-acquired to community acquired bacteraemia. Studies have traditionally reported incidence as a rate according to the background population, while it may be more reasonably reported as the rate among hospitalised patients at risk. Mortality and excess length of stay following hospital-acquired bacteraemia are often reported in absolute values without comparison to the non-infected patients or include limitations related to time-dependent bias. Furthermore, only few studies are population-based, and therefore estimates may suffer from selection bias or follow-up limited to the end of hospital stay (e.g., assess only in-hospital mortality).

The aim of this thesis is to 1) explore the treatment options, interventions, and surgery as risk-factors for developing bacteraemia during hospital stay, 2) investigate the incidence and 30-day mortality associated with hospital-acquired bacteraemia compared with hospitalised patients at-risk of developing hospital-acquired bacteraemia, and 3) investigate the excess length of stay following hospital-acquired bacteraemia compared with hospitalised patients at-risk, and to assess rates of readmission in patients, who had a hospital-acquired bacteraemia episode compared to patients who did not.

The thesis is based on an explorative case-control study of hospital interventions as risk factors comparing patients with hospital-acquired bacteraemia with matched incidence-density sampled controls, and two population-based cohorts studies including the entire North Denmark Region's adult population with a hospital stay for ≥ 48 hours from 2006 through 2018. Hospital-acquired bacteraemia was identified using The Department of Clinical Microbiology Laboratory Information System and the North Denmark Bacteraemia Research Database. Interventions were identified in electronic medical records. Complete follow-up was achieved through linkage of Danish registries (i.e., the Civil Registration System, and the National Patient Registry).

Study 1 revealed that central venous catheters (adjusted odds ratio of 3.46, 95% CI 1.92 – 6.23) and haemodialysis (adjusted odds ratio of 5.05, 95% CI 1.41 – 18.06) were the most likely intervention-related risk factors for hospital-acquired bacteraemia. While immunosuppression from medical treatment may play a role as well (adjusted odds ratio of 1.72, 95% CI 1.00 – 2.96). Study 2 showed a two percent

annual increase in the incidence rate of hospital-acquired bacteraemia through the study period. Mortality associated with hospital-acquired bacteraemia was 4-fold higher compared with patients at risk (adjusted hazard ratio of 4.32, 95% CI 3.95 – 4.72). Mortality was highest in patients with hospital-acquired bacteraemia of unknown source (adjusted hazard ratio of 6.42, 95% CI 5.67 – 7.26). Study 3 revealed that patients experience a decreased probability of discharge following hospital-acquired bacteraemia leading to an excess length of stay of 6.6 days (95% CI 6.2 – 7.1). Additionally, among patients discharged alive, patients who had experienced hospital-acquired bacteraemia were more likely to be readmitted to the hospital (adjusted hazard ratio of 1.42, 95% CI 1.42 – 1.53) than patients without bacteraemia.

The thesis highlights the challenges associated with hospital-acquired bacteraemia and extend the current literature by exploring hospital interventions as risk factors, and providing updated population-based estimates of incidence, associated mortality, excess length of stay, and rates of readmission using sophisticated statistical modelling to account the temporal dynamics surrounding this topic.

In conclusion, risk of infection should be considered in relation to interventions. The consequences of hospital-acquired bacteraemia can be severe and pose an economic burden. This thesis emphasises the need for more research to prevent hospital-acquired bacteraemia and infections in general.

DANSK RESUME

Bakteriæmi er en alvorlig komplikation under indlæggelse. Bakteriæmi, der er opstået på sygehuset, bliver ofte kaldet 'nosokomiel' eller 'hospitalserhvervet' og er associeret med faktorer relateret til indlæggelse, høj dødelighed, og udgør økonomisk byrde. Bakteriæmi klassificeres typisk som hospitalserhvervet, hvis den opstår inden for et tidsinterval fra 48 timer efter indlæggelse til 48 timer efter udskrivelse. Selvom der allerede er omfattende litteratur omkring hospitalserhvervet bakteriæmi, så er mange af studierne begrænset af mangel på sammenligningsgrupper eller ved at bruge samfundserhvervet bakteriæmi som sammenligning. Endvidere rapporterer mange studier incidensen som en rate i forhold til baggrundsbefolkningen, hvor det ville være mere meningsfyldt at beskrive raten af hospitalserhvervet bakteriæmi i forhold til indlagte patienter, der er i risiko for at få infektionen. Dødelighed og forlænget indlæggelse som følge af hospitalserhvervet bakteriæmi er ofte rapporteret i absolutte værdier uden sammenligning med ikkeinficerede patienter eller indeholder begrænsninger i form af 'tidsafhængig' bias. Kun få af de eksisterende studier er populationsbaserede, og studierne kan derfor være påvirket af selektionsbias og rapporterer ofte kun dødeligheden under indlæggelse.

Formålet med denne afhandling er 1) at undersøge avancerede behandlinger, interventioner, og kirurgi som risikofaktorer for at få hospitalserhvervet bakteriæmi under indlæggelse, 2) at undersøge incidensen og dødeligheden associeret med hospitalserhvervet bakteriæmi sammenlignet med indlagte patienter i risiko for at udvikle hospitalserhvervet bakteriæmi, og 3) at undersøge forlænget indlæggelse efter hospitalserhvervet bakteriæmi sammenlignet med indlagte patienter i risiko for at udvikle hospitalserhvervet bakteriæmi, og undersøge hvorvidt genindlæggelse er hyppigere blandt patienter, der udskrives i live efter en episode med hospitalserhvervet bakteriæmi sammenlignet med patienter, der ikke udviklede bakteriæmi.

Afhandlingen er baseret på et eksplorativt case-kontrolstudie af hospitalsinterventioner som risikofaktorer, hvor patienter med hospitalserhvervet bakteriæmi sammenlignes med matchede 'incidence-density' samplede kontroller, og to populationsbaserede kohortestudier af hele Region Nordjyllands voksne befolkning med en indlæggelse af ≥48 timers varighed i årene fra 2006 til 2018. Hospitalserhvervet bakteriæmi blev identificeret ved brug af laboratoriesystemet ved Klinisk Mikrobiologisk Afdeling og den Norddanske Bakteriæmi-database. Interventioner blev identificeret ved gennemgang af elektroniske patientjournaler. Komplet opfølgning var mulig ved hjælp af kobling til øvrige danske registre (herunder Det Centrale Personregister og Landspatientregisteret).

Studie 1 viste at centrale venekatetre (justeret odds ratio på 3,46, 95% konfidensinterval 1,92 – 6,23) og hæmodialyse var de mest oplagte

interventionsrelaterede risikofaktorer for hospitalserhvervet bakteriæmi. Immundæmpende effekt af medicin spiller muligvis en rolle (justeret odds ratio på 1,72, 95% konfidensinterval 1,00 – 2,96). Studie 2 viste en to procents årlig stigning i incidensen af hospitalserhvervet bakteriæmi i studieperioden. Dødeligheden blandt patienter med hospitalserhvervet bakteriæmi var 4 gange højere sammenlignet med indlagte patienter i risiko for hospitalserhvervet bakteriæmi (justeret hazard ratio på 4,32, 95% konfidensinterval 3,95 – 4,72). Dødeligheden var højest blandt patienter med hospitalserhvervet bakteriæmi uden kendt infektionskilde (justeret hazard ratio på 6,42, 95% konfidensinterval 5,67 – 7,26). Studie 3 viste, at sandsynligheden for udskrivelse var lavere blandt patienter med hospitalserhvervet bakteriæmi, hvilket resulterer i en 6,6 dages (95% konfidensinterval 6,2 – 7,1 dage) forlængelse af indlæggelsestiden, sammenlignet med patienter uden bakteriæmi. Blandt de patienter som blev udskrevet i live, havde patienter med hospitalserhvervet bakteriæmi højere risiko for at blive genindlagt på hospitalet (justeret hazard ratio på 1,42, 95% konfidensinterval 1,42 – 1,53).

Denne afhandling fremhæver udfordringer forbundet med hospitalserhvervet bakteriæmi og supplerer den eksisterende litteratur med ny viden om hospitalsrelaterede interventioner som risikofaktorer, og populationsbaserede mål for incidens, dødelighed, forlænget indlæggelse, og genindlæggelse ved brug af sofistikeret statistisk modellering, der tager højde for temporale dynamik forbundet med udviklingen af infektion under indlæggelse

Risiko for infektion bør overvejes ved brug af interventioner. Konsekvenserne af hospitalserhvervet bakteriæmi kan være alvorlige og øge den økonomiske byrde forbundet med hospitalsindlæggelser. Denne afhandling understreger behovet for yderligere forskning i forebyggelse af hospitalserhvervet bakteriæmi og infektioner generelt.

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The studies presented in this thesis were carried out from 2019 to 2022 during my employment at the Department of Clinical Microbiology at Aalborg University Hospital.

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I am grateful to all my colleagues and friends at the Aalborg University Research Group for great advice and stimulating discussions and an encouraging environment.

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Viggo Holten Mortensen
Aalborg, February 2022

Studies included in this thesis

Study I

Mortensen VH, Søgaard M, Kristensen B, Mygind LH, Schønheyder HC. Risk factors for hospital-acquired bacteraemia – an explorative case–control study of hospital interventions. *Infect Dis (Lond)*. 2022;54(3):178-185.

Study II

Mortensen VH, Søgaard M, Mygind LH, Wolkewitz M, Kristensen B, Schønheyder HC. Incidence and mortality of hospital-acquired bacteraemia: A population-based cohort study applying a multi-state model approach. *Clin Microbiol Infect*. Published online 17 December 2021.

Study III

Mortensen VH, Mygind LH, Schønheyder HC, Staus P, Wolkewitz M, Kristensen B, Søgaard M. Extended length of stay and readmission following hospital-acquired bacteraemia: A population-based cohort study. Submitted.

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CHAPTER 1. INTRODUCTION

1.1. BACTERAEMIA

The detection of bacteria was first described in 1850 by the French physician Casimir-Joseph Davaine. Twenty-two years later in 1872, the term bacteraemia (bactériémie) was coined by Edmé Vulpain in recognition of the pathogenic role of bacteria found in the blood. Since then, other terms have been used indiscriminately to refer to this entity e.g., pyaemia and septicaemia. By convention, fungemia (presences of fungi in the blood stream) have been included, as the distinction between these two kingdoms had not been discovered at the time, and bacteria were classified as a subdivision of fungi (Schizomycetes).[1]

In 1898, the blood culture technique was featured in the 2nd edition of William Osler's Textbook of Medicine, and in the early days of the twentieth century, it gained in popularity by clinicians as a valued diagnostic tool. Early studies on bacteraemia and positive blood cultures were often focused on specific pathogens or groups hereof (e.g., pneumococci,[2,3] *Staphylococcus aureus*,[4,5] and gram-negative rods[6,7]). With the introduction of antimicrobial chemotherapy, the interest shifted slightly towards studies of bacteraemia as an entity.[8] However, to this day, many studies still centre around a very specific population or aetiology. The severity of mortality linked with bacteraemia was underlined in studies by McCabe and Jackson and the first population-based studies from Carolina, US.[9–12] With the contemporary advances in clinical epidemiology, Weinstein and colleagues followed with two seminal papers that laid the foundation for future studies of bacteraemia.[13,14]

Bacteraemia is often considered a severe complication and a sign of disseminated infection of an underlying localised infection. However, microorganisms can also be introduced transiently to the bloodstream.[13,15] Transient presence of bacteria has been seen in relation to routine procedures such as toothbrushing and dental appointments, without leading to infection.[15,16] Therefore, Weinstein and colleagues introduced the concept of *true septicaemia* in which each positive blood culture was evaluated to determine whether it more likely represented true infection or contamination based on "history of the patient, physical body temperature, peripheral leukocyte count and differential, clinical course, result of cultures from other body sites, and percentage of blood cultures".[13] The North Denmark Research Database have in part adopted this definition as "Bacteraemia is a clinical entity associated with detection of one or more micro-organisms in the blood, usually by culturing techniques"[17] in which isolates likely to be contaminants are ruled out in accordance with the criteria proposed by Weinstein et al.[13] This definition has been used throughout this thesis.

The alternative term blood stream infection was popularised during the nineteen-eighties and have been used extensively in the infection control literature. It is often

used to denote cases without a definitive underlying infection,[18] but is also used to emphasise that the researcher included both bacteraemia and fungaemia.

The presence of microorganisms in the blood of a patient with an underlying infection implies a failure in the patient's defence mechanisms against infections.[19] The human defences against infection are complex and includes physical barriers, innate immune defence, adaptive immune response, and filtration in liver and spleen. Bacteraemia may lead to a severe and life-threatening condition often known as sepsis. The term sepsis has often been confused with bacteraemia due to the similarities with the term septicaemia. In 1991, to avoid further confusion, a definition was proposed by American College of Chest Physicians and the Society of Critical Care Medicine. This definition was revised in 2001 with the introduction of the term systemic inflammatory response syndrome (SIRS).[20] SIRS were characterised by two of the following: tachycardia, fever, hypothermia, tachypnoea, leucocytosis, or leukopenia. However, these characteristics can often be found in patients with non-infectious conditions including trauma, burns, or sterile inflammatory processes. In 2016, a third international consensus definition for sepsis and septic shock were proposed to address limitations of the previous definition.[21] The task force behind the new recommendation highlighted the following limitations of the SIRS-criteria: an excessive focus on inflammation, a misleading model that sepsis follows a continuum through severe sepsis to shock, and inadequate specificity and sensitivity. The current recommendations rely on the Sequential Organ Failure Assessment (SOFA)-criteria in which clinicians score their patients according the degree of organ-dysfunction in the following categories: Respiration, coagulation, liver, cardiovascular, central nervous system, and renal.[21]

Defining the length of an episode of bacteraemia is difficult as it may vary from case to case depending on various clinical factors and treatment. There is no consensus for the length of an episode in the current bacteraemia research. For the sake of register research and surveillance, several algorithms to differentiate one episode from the next have been proposed including time-fixed definitions ranging from 48 hours to 6 months,[13,22–25] or calendar-based distinction (first isolate each year or month).[26–28] Others base the distinction on available clinical data; end of antibiotic treatment[29] or change in aetiology.[28] For the studies included in the current thesis, I adopted the algorithm used in the North Denmark Research Database: "1) a blood culture isolate that differs from the previous with regard to species and/or antibiogram, 2) a different focus of infection, or 3) an interval of at least 30 days between two positive blood cultures".[17]

Bacteraemia can be categorised in multiple ways. A natural classification is based on the underlying source of bacteraemia i.e., the underlying localised infection. This is often referred to as the primary focus or the source. However, some bacteraemia episodes may not be a result of an underlying infection but stem from colonisation of a foreign object or a hospital procedure. This is often referred to as the 'site of entry'

or ‘portal of entry’. To include both scenarios and avoid confusion with secondary foci (i.e., haematologic spread to another focus than the primary) I have used *source* in all the current studies. Despite thorough clinical examination, the source of bacteraemia remains unknown in about one fifth of episodes.[30]

An alternative categorisation is based on the causative pathogen, which is highly correlated with the source of infection. However, it may be far more relevant to centre a study around aetiology in studies of choice of antimicrobial chemotherapy.[31]

The place of acquisition is another important way to distinguish episodes of bacteraemia. In the early literature, an episode was classified as either community-acquired (i.e., arising in the community) or hospital-acquired (i.e., arising during hospital stay). Later, a third category was proposed by Friedmann et al; health care-associated bacteraemia.[32] The distinction between hospital-acquired episodes and others may be very relevant as source, aetiology, risk factors and prognosis, while overlapping, may not be the same.

1.2. HOSPITAL-ACQUIRED BACTERAEMIA

In the literature, hospital-acquired infections are often referred to as nosocomial infections derived from Greek (nosos: disease, komein: to take care of, nosokomein: hospital). The U.S. National Library of Medicine uses the term “Cross Infection” to index articles about hospital-acquired infections.[33] However, this indexation does not differentiate between hospital-acquired and health care-associated infections.

In 1975, McGowan et at. was the first to study hospital-acquired bacteraemia defined as clinically significant positive blood cultures drawn after more than 48 hours of hospitalization.[34] While citing definitions provided by the Centers for Disease Control and Prevention (CDC) in 1988, many studies have adopted this time-based definition of hospital-acquired bacteraemia. However, the actual definition provided by the CDC emphasises use of all clinical data and not to rely on time of blood draw. This is in line with the work of Leibovici et al. who found a linear increase in infections caused by pathogens commonly associated with hospital-acquired infections and no threshold effect.[35] This was further emphasised by Gradel et al. as no time point could unanimously distinguish hospital-acquired infections with regard to sex, comorbidity, aetiology, or mortality.[36] However, regardless of the time window used, prognosis deteriorated from community-acquired to health care-associated and furthermore to hospital-acquired.[36]

The time point at 48 hours of hospitalisation is still widely applied due to its ease of use, transparency, and reproducibility. A defined time point makes it possible to utilise routinely collected data in surveillance and register studies. Hence, the current studies in this thesis are conducted using this definition.

1.3. INCIDENCE

The incidence of hospital-acquired bacteraemia remains unclear. Population-based studies of the incidence of bacteraemia primarily reports estimates as episodes pr. 100,000 person-years of the background population. I carried out a literature review in PubMed using the search words presented in Table 1 (one word from each section joined with AND). I searched for population-based studies that reported incidence of hospital-acquired bacteraemia overall or caused by specific pathogens. According to these studies, the incidence ranged from 29.5 to 77.2 episodes pr. person-year. In two Canadian studies, the incidence of severe or intensive care unit-related episodes ranged from 3.1 to 5.2 episodes pr. 100,000 person-years. The habit of presenting incidence pr. 100,000 person-years may stem from reporting of community-acquired infections. However, for hospital-acquired infections it may be more appropriate to estimate the incidence pr. hospitalisation or hospital patient-days, as this more accurately addresses the population at risk. However, only few studies have reported this measure with incidences ranging from 1.3 to 3.7 episodes pr. 1,000 hospitalisations and from 4.5 to 8.0 episodes pr. 10,000 hospital patient-days. The incidence varies between countries (Table 2) and, especially according to aetiology (Table 3).

Table 1: Search words used in PubMed for a systematic search of population-based studies on incidence of hospital-acquired bacteraemia.

MeSH-term	**Free text**
Cross-infection	Nosocomial Hospital-acquired
Bacteremia	Bacteremia Bacteraemia Bloodstream infection*
Incidence	Incidence Burden
No MeSH-term	Population-based

In 2013, Goto and Al-Hasan extrapolated on current population-based studies and estimated an annual number of 242,692 to 414,477 episodes of hospital-acquired bacteraemia in Europe and 3,196 episodes in Denmark alone.[37] In recent years, automated surveillance of hospital-acquired infection have become more common and may provide valid and up to date estimates.[38] In 2005, the Danish hospital-acquired infections data launched a national surveillance of hospital-acquired infections including bacteraemia. From 2010 through 2014, the national incidence of hospital-acquired bacteraemia was 7.4 pr. 10,000 days at risk. The incidence was lower in the North Denmark Region (6.7 pr. 10,000 days at risk), but with a slight annual increase.

Table 2: Population-based incidence studies of hospital-acquired bacteraemia across all aetiologies

Author	Country	Study period	Setting	Number of episodes	Definition	Incidence (pr. 100,000 person-years)
Laupland 2002[39]	Canada	1999 – 2000	Calgary Health Region Intensive Care Units	51	≥48 h admission to 48 h after discharge	5.2 / 100,000 person-years
Lauland 2004[40]	Canada	2000 – 2002	Calgary Health Region Intensive Care Units	69	Severe cases (need of intensive care) ≥48 h into admission	3.1 / 100,000 person-years
Søgaard 2011[30]	Denmark	1992 – 2006	North Denmark Region	4,619	Citing CDC[41]	77.2 / 100,000 person-years 4.5 to 7.8 / 10,000 hospital patient-days
Nielsen 2014[42]	Denmark	2000 – 2008	Funen County	2,415	≥48 h admission to 48 h after discharge	66.7 / 100,000 person-years
Lyytikäinen 2002[43]	Finland	1999 – 2000	Nationwide	1,477	≥48 h admission to 48 h after discharge	8.0 / 10,000 hospital patient-days 2.7 / 1,000 discharges
Mehl 2017[44]	Norway	2002 – 2013	Nord-Trøndelag County	274	Citing Friedman et. al[32]	29.5 / 100,000 person-years
Holmbom 2016[45]	Sweden	2000 – 2013	Östergötland	3,788	≥48 h admission	3.7 / 1,000 admissions
Rhodes 2019[46]	Thailand	2007 – 2014	Sa Kae & Nakhon Phanom	1,109	≥48 h admission	1.3 / 1,000 hospitalisations
Uslan 2007[47]	USA	2003 - 2005	Olmsted County	124	Citing Friedman et. al[32]	33.3 / 100,000 person-years

Table 3: Population-based incidence studies of hospital-acquired bacteraemia of a specific aetiology

Author	Country	Study period	Setting	Number of episodes	Definition	Aetiology	Incidence
Laupland 2008[48]	Canada	2000 – 2006	Calgary Health Region	599	≥48 h admission to 48 h after discharge	*S. aureus*	7.7 / 100,000 person-years
El Atrouni 2009[49]	USA	1998 – 2005	Olmsted County	58	≥48 h into admission	*S. aureus*	9.0 / 100,000 person-years
Huggan 2010[50]	New Zealand	1998 – 2006	Canterbury District Health Board	277	≥48 h admission or 48 hr admission within 7 days	*S. aureus*	7.7 / 100,000 person-years
Jokinen 2017[51]	Finland	2005 – 2015	Nationwide	835	Symptoms ≥48 h admission, surgery within 30 days, or invasive procedure within 7 days	*S. aureus*	11.5 to 20.8 /100,000 person-years
Lam 2019[52]	Canada	2012 – 2014	Calgary Health Region	Not reported	≥48 h admission to 48 h after discharge	*S. aureus*	Approx. 7 / 100,000 person-years (read from bar chart)
Laupland 2012[53]	Australia, Canada, Denmark, Finland, Sweden	2000 – 2008	Multiple regions and nationwide Finland	Not reported	≥48 h admission to 48 h after discharge	Methicillin susceptible and resistant *S. aureus*	9.2 / 100,000 person-years 0.8 / 100,000 person-years
Lessa 2009[54]	England	2006 – 2007	Nationwide	2,743	≥48 h into admission	Methicillin resistant *S. aureus*	7.8 / 100,000 person-years
Lessa 2009[54]	USA	2006 – 2007	Surveillance in 8 metropolitan areas and 1 state	6.434	≥48 h into admission	Methicillin resistant *S. aureus*	7.2 / 100,000 person-years
Lyytikäinen 2007[55]	Finland	1995 – 2002	Nationwide	387	≥48 h admission to 48 h after discharge	*S. pneumoniae*	0.9 / 100,000 person-years 0.6 / 100,000 hospital patient-days

Table 3 (cont.): Population-based incidence studies of hospital-acquired bacteraemia of specific aetiology

Author	Country	Study period	Setting	Number of episodes	Definition	Aetiology	Incidence
Pinholt 2013[56]	Denmark	2006 – 2009	The North Denmark Region and the Capital Region of Denmark	416	≥48 h admission to 48 h after discharge	*Enterococcus sp.* (Monomicrobial)	11.6 / 100,000 person-years
Billington 2014[57]	Canada	2000 – 2008	Calgary Health Region	338	≥48 h admission to 48 h after discharge	*Enterococcus sp.*	3.3 / 100,000 person-years
Badri 2019[58]	Sweden	2012 – 2016	Region of Skåne	38	≥48 h into admission	Gram- positive anaerobic cocci	0.6 / 100,000 person-years
Leal 2008[59]	Canada	2000 – 2006	Calgary Health Region	45	≥48 h admission to 48 h after discharge	*Clostridium sp.*	0.6 / 100,000 person-years
Laupland 2008[60]	Canada	2000 – 2006	Calgary Health Region	355	≥48 h admission to 48 h after discharge	*E. coli*	4.5 /100,000 person-years
Williamson 2013[61]	New Zealand	2005 – 2011	Auckland District Health Board	389	≥48 h admission to 48 h after discharge	*E. coli*	13.5 / 100,000 person-years
Bonnie 2009[62]	Canada	2000 – 2007	Calgary Health Region	174	≥48 h admission to 48 h after discharge	*Klebsiella sp.*	1.9 / 100,000 person-years
Al-Hasan 2010[63]	USA	1998 – 2007	Olmsted County	14	Citing CDC[41]	*Klebsiella sp.*	1.3 / 100,000 person-years
Al-Hasan 2008[64]	USA	1998 – 2007	Olmsted County	12	Citing CDC[41]	*P. aeruginosa*	1.1 / 100,000 person-years
Parkins 2010[65]	Canada	2000 – 2006	Calgary Health Region	128	≥48 h admission to 48 h after discharge	*P. aeruginosa*	1.6 / 100,000 person-years

Table 3 (cont.): Population-based incidence studies of hospital-acquired bacteraemia of specific aetiology

Author	Country	Study period	Setting	Number of episodes	Definition	Aetiology	Incidence
Al-Hasan 2010[66]	USA	1998 – 2007	Olmsted County	8	Citing CDC[41]	*Enterobacter sp.*	0.7 / 100,000 person-years
Engel 2009[67]	Australia	1998 – 2007	Canberra area	599	≥48 h admission or 48 hr admission within 7 days	*Serratia sp.*	0.5 / 100,000 person-years
Ngo 2013[68]	Canada	2000 – 2008	Calgary Health Region	300	≥48 h admission to 48 h after discharge	Anaerobic bacteria	2.9 / 100,000 person-years

1.4. RISK FACTORS

Hospital-acquired bacteraemia shares many risk factors with community-acquired bacteraemia, especially, when it comes to comorbidities. Hospital-acquired bacteraemia have been associated with age, male sex, urban residence, diabetes mellitus, alcoholism, cancer, and lung disease.[40] However, hospitalised patients are exposed to a different environment compared with patients infected outside the hospital. Factors related to the hospital and the staff have been associated with hospital-acquired bacteraemia (e.g., understaffing[69] and size of the hospital[70]).

Other types of risk factors associated with hospitalisation, which are more directly affecting the individual patient, relate to interventions experienced by the patient during hospitalisation. I conducted a literature review of intervention-related risk factors for hospital-acquired bacteraemia in adult patients based on studies identified in PubMed using the search terms provided in Table 4.

Table 4: Search words used in PubMed to search the literature for studies on intervention-related risk factors for hospital-acquired bacteraemia in adult patients

MeSH-term	Free text
Adult	
Cross-infection	Nosocomial Hospital-acquired
Bacteremia	Bacteremia Bacteraemia Bloodstream infection*
Risk factor	Risk factor*
Anesthesia	Anesth*
Biological Therapy	Biological therap*
Catheters	Catheter*
Catheterization	Vascular access
Drainage	Drainage
Intubation	Intubation
Renal Replacement Therapy	Renal Replacement Therapy
Surgical Procedures	Dialysis
Ventilator, Mechanical	Surg*
	Ventilat*

Selected studies are presented in Table 5. It is clear from the literature that risk factors for hospital-acquired bacteraemia have been of interest for many years. Many intervention-related risk factors have been examined, and hospital-acquired bacteraemia have been associated with urinary catheters, venous catheters, indwelling devices, haemodialysis, invasive procedures, surgery, stay in the intensive care unit, contaminated blood products and intravenous medicine, parenteral nutrition, length of stay, and being bedridden. Vascular access with arterial cannulation, peripheral- or

central venous catheters, or implantable access ports have been studied extensively with regard to the effect of type and coatings, placement and technic, timing and changing intervals.[71–79] Despite high interest and many studies, few studies have examined intervention-related risk factors of hospital-acquired bacteraemia in the general hospital population, and even fewer studies have applied confounder correction based on current recommendations. One database-based study carried out in the US using a case-control design compared hospitalised patients with bacteraemia with patients without bacteraemia and found an adjusted association between nosocomial blood stream infection and central venous catheters, mechanical ventilation, and haemodialysis.[80] A study conducted in Nagano, Japan, found a statistically significant association between urinary catheters and indwelling femoral central venous catheters and risk of hospital-acquired bacteraemia using culture negative patients as controls.[81] However, this comparator represents a special group of patients who may have a culture negative infection.

Table 5: Selected studies on intervention-related risk factors of hospital-acquired bacteraemia in adult patients

Author	Design	Population	Proposed risk factor	Comparator	Analytical limitation (assessed by VHM)
Jepsen, 1982[82]	Case-control	Urinary tract infection patients	Indwelling catheters	Noncatheter patients	Unadjusted association
Trilla, 1991[72]	Case-control	Non-neutropenic bacteraemia patients	Indwelling urethral catheter (>3days), intravenous central lines or peripheral venous lines (>4 days), high-risk surgery (i.e., lower abdominal, cardiac, or thoracic), and admission to an intensive care unit	Nonmatched controls	Unadjusted association
Zaza, 1994[83]	Case report	Patients receiving blood products	Contaminated blood products (thrombocytes transfusion)	Not applicable	No comparison
Jamulitrat, 1994[84]	Case-control	Bacteraemia hospital patients	Duration of immunosuppressive drugs and indwelling intravenous catheter	Diagnosis matched controls	Uncertain adjustment (matched case-control does not correct confounding)
Wenzel, 1995[85]	Case-control	Non-leukaemia bacteraemia patients	Prior Hickman catheter and haemodialysis	Underlying condition matched controls	Adjustment variables not reported
Bennett, 1995[86]	Investigation of epidemic	Surgical patients	Contaminated intravenous medicine (propofol)	Noninfected surgical patients	Investigation of epidemic thus no adjustment.
Ibrahim, 1996[87]	Case-control	Urological surgery patients	Bacteriuria prior to prostatectomy	Non-bacteriuria controls	Noncolonised patients
Velasco, 1998[88]	Case-control	Bacteraemia hospital patients	Central venous catheters	Age and date matched controls	Only statistically significant univariate variables included in multivariate model

Table 5 (cont.): Selected studies on intervention-related risk factors of hospital-acquired bacteraemia in adults

Author	Design	Population	Proposed risk factor	Comparator	Analytical limitation (assessed by VHM)
Legras, 1998[89]	Cohort	Bacteraemia in intensive care patients	Length of stay, mechanical ventilation, and central venous catheter	Nonexposed patients	Stepwise model selection, time-dependent bias
Rojo, 1998[90]	Case-control	Patients with hospital-acquired bacteraemia	Intravascular catheterization, invasive procedures, indwelling devices, intensive care unit or surgical department stay	Community-acquired infections	Stepwise model selection, control group are very unlikely to be exposed
Marena, 2001[91]	Cohort	Haematopoietic stem cell transplantation patients	Allograft from matched unrelated or partially matched family donor, graft-versus-host disease prophylaxis (non-methotrexate), type and duration of central venous catheters, and parenteral nutrition	Nonexposed patients	Stepwise model selection, time-dependent bias
Laupland, 2004[40]	Cohort	Population-based hospital patients	Haemodialysis	Nonexposed patients	Stepwise model selection, time-dependent bias
Yoshida, 2005[81]	Case-control	Bacteraemia hospital patients	Urinary catheters and indwelling femoral central venous catheters	Nonmatched blood culture negative controls	Only statistically significant univariate variables included in multivariate model
Al-Rawajfah, 2009[80]	Case-control	Bacteraemia hospital patients	Central venous catheters, mechanical ventilation, and haemodialysis	Nonmatched controls	Lack of adjustment and time-dependent bias
Reunes 2011[92]	Case-control	Bacteraemia elderly hospital patients	Intravenous catheters and being bedridden	Length of stay matched controls	Stepwise model selection

1.5. PROGNOSIS

Prognosis, derived from Greek (pro and -gnosis: knowledge), means to foresee, predict, or estimate future outcomes. The prognosis of bacteraemia has been studied extensively, especially regarding community-acquired episodes. Mortality is the most commonly investigated outcome of bacteraemia, however, in studies by Dalager-Pedersen and colleagues alternative outcomes have been studied (i.e., thrombotic events,[93,94] delayed return to work,[95] and functional status[96]). Factors that influence the probability of an outcome are often coined prognostic factors. Associations between mortality following bacteraemia and severity of underlying illness, various comorbidities,[40] socioeconomic status,[97] and appropriateness of empirical antibiotic treatment[98] have been reported.

In the review by Goto and Al-Hasan, estimates for the burden of hospital-acquired bacteraemia based on available population-based studies were made for Europa and North America.[37] It was estimated that the annual number of deaths following hospital-acquired bacteraemia were 29,123 to 132,633 in Europe and 18,233 to 39,575 in North America while the case-fatality rate ranged from 12% to 32%. No studies included in the review reported attributable mortality specific to hospital-acquired episodes. One study presented an estimate of 12% in-hospital mortality attributable to all episodes bacteraemia, however, it was a non-population-based study.[99]

To find comparative studies of mortality and identify recent population-based studies of mortality, I carried out a literature review. I searched for estimates of the mortality associated with hospital-acquired bacteraemia in either absolute measures or relative to the background or hospital population not including studies with relative mortality compared to patients with bacteraemia of other origins. I used the search terms provided in Table 6.

Table 6: Search words used in PubMed for systematic search of population-based studies on mortality following hospital-acquired bacteraemia.

MeSH-term	**Free text**
Cross-infection	Nosocomial Hospital-acquired
Bacteremia	Bacteremia Bacteraemia Bloodstream infection*
Mortality	Mortalit* Death rate* Fatality
No MeSH-term	Population-based

I found one additional population-based study published since the review by Goto and Al-Hassan (Table 7). Additionally, I identified a study by Laupland and colleagues estimating a two-fold increase in intensive care unit-mortality following intensive care unit-acquired bacteraemia (odds ratio 2.03, 95% CI 1.03 – 4.00) along with a non-statistically significant increase in in-hospital mortality (estimate not reported).[39]

Comparative studies of mortality following hospital-acquired bacteraemia may be complicated as the timing between admission, onset of infection, discharge and mortality should be taken into consideration.[100] Comparing the mortality in hospitalised patients with and without hospital-acquired bacteraemia, counting the patient as infected since admission, or using a time-indifferent analysis (e.g., logistic regression) may underestimate the association between mortality and hospital-acquired bacteraemia. This bias stems from the fact patients with hospital-acquired bacteraemia would have to survive for a certain time to develop the infection. Thereby, eventually infected patients would appear immortal for the initial time of the analysis.

Various methods can be used to address this time-dependent bias. One way would be to address it in the selection of the reference group while properly considering the time of onset and hospital stay.[101] This method can be referred to as risk-set sampling or specifically: Exposure density sampling. However, matching and sampling of individuals introduces its own challenges of correct matching, reduction in the size of comparison group, and limitations in generalisability or availability of subgroup analyses.

Alternatively, a multi-state model approach could be considered.[100] In the multi-state model approach, one would consider the patient's stay as transitions through possible states. Transitions may be evaluated using various methods from survival analysis such as the Aalen-Johansen estimator and Cox regression while treating the infection as a time-dependent covariate. This allows for regression-based confounder adjustment without limiting the cohort while offering a dynamic way to handle the temporal dynamics.

Table 7: Population-based studies of hospital-acquired bacteraemia and mortality across all aetiologies

Author	Country	Study period	Setting	Number of episodes	Definition	Mortality estimates
Pittet, 1997[102]	USA	1986 – 1991	Uptake of the University of Iowa hospitals and clinics	1,745	Blood cultures drawn >72 hours after admission	28-day mortality: 17% In-hospital mortality: 44%
Laupland, 2002[39]	Canada	1999 – 2000	Intensive care units in Calgary Health Region	51	≥48 h admission to 48 h after discharge	Intensive care unit mortality: 27% Odds ratio 2.03 (95% CI 1.03-4.00)[1] In-hospital mortality: 37% Odds ratio for in-hospital mortality not significant, but not reported.[1]
Lyytikäinen, 2002[43]	Finland	1999 – 2000	Nationwide (voluntary hospital participation)	1,477	≥48 h admission to 48 h after discharge	7-day mortality: 9% 28 day-mortality: 16%
Laupland, 2004[40]	Canada	2000 – 2002	Calgary Health Region	342	Severe cases (need of intensive care) ≥48 h into admission	Intensive care unit mortality: 33% In-hospital mortality 42%
Søgaard, 2011[30]	Denmark	1992-2006	North Denmark Region	4,619	Citing CDC	30-day mortality: 27.6 - 29.1%
Wang, 2020[103]	Taiwan	2007-2015	Nationwide	14,234	Not reported	In-hospital mortality 44% Odds ratio: 1.67 (95% CI 1.59-175)[2] 14-day mortality 30% Odds ratio: 1.42 (95% CI 1.35-1.49)[2] 28-day mortality 39% Odds ratio: 1.41 (95% CI 1.34-1.47)[2]

[1]Comparison between patients with intensive care unit-acquired bacteraemia compared with patients staying >48 hours in the intensive care unit without intensive care unit-acquired bacteraemia.

[2] Comparison between patients with intensive care unit-acquired bacteraemia compared with propensity matched reference from the intensive care population that did not develop intensive care unit-acquired bacteraemia or any sepsis related diagnosis.

1.6. ECONOMIC BURDEN

Additional economic expenditures are another consequence of hospital-acquired bacteraemia and infections in general. Studies suggest that hospital-acquired bacteraemia is associated with an increased length of hospital stay. I conducted a literature search for comparative studies of length of stay following hospital-acquired bacteraemia using the search words in Table 8.

Table 8: Search words used in PubMed for a systematic search of comparative studies of length of stay following hospital-acquired bacteraemia across all aetiologies in adult patients.

MeSH-term	Free text
Cross-infection	Nosocomial Hospital-acquired
Bacteremia	Bacteremia Bacteraemia Bloodstream infection*
Length of stay	Length of stay Hospital stay* Stay length*

According to the literature, the prolongation of hospital stays following a hospital-acquired bacteraemia range from 5 to 29.8 days depending on the population and the estimands used (Table 9). Most studies used either the difference in mean or median total length of stay. Contrarily, one study suggests no difference based on a non-significant result of a log-rank test of cumulative end-of-stay curves.[104]

However, adapting the same mindset as with mortality, the temporal dynamics are of special importance when trying to estimate an increase in time following hospital-acquired infection. The literature review on risk factors revealed that long length of stay is associated with an increased risk of developing hospital-acquired bacteraemia. It is important not to allow this time to contribute to the estimate of excess length of stay following infection, as it would overestimate the length of stay contributed by the infection.[105] This would be the result of comparing total length of stay of the infected patients with those that did not develop an infection during hospital stay.

Alternative estimands for prolonged length of stay have been proposed along with a simplified description assuming time-constant hazards.[106] One approach is to estimate the residual length of stay of the infected versus those not infected. This effectively answers the following clinical question: How many additional days can a patient expect to be admitted following a hospital-acquired infection. A non-parametric approach that are not dependent of constant hazards assumption have been proposed[107] (see ‘statistical analysis’ in Chapter 3: Material and methods for details).

I found no studies that combined the investigation of excess length of stay with readmission rates. A possible increased risk of readmission may increase the number of days stayed in a way that is not captured in native length of stay analyses. This may lead to a further increase the economic burden following a hospital-acquired bacteraemia.

Table 9: Selected studies of excess length of stay following hospital-acquired bacteraemia.

Author	Comparison	Number of episodes	Estimands	Estimate
Spengler, 1978[108]	Nosocomial bacteraemia compared with diagnosis matched control	81	Difference in mean total length of stay	14 days
Pittet, 1994[109]	Nosocomial bloodstream infection compared with pair-wise matched controls (diagnosis, age, sex, length of stay before infection, and total number of discharge diagnoses)	108	Difference in median total length of stay	14 days (24 for survivors)
DiGiovine, 1999[110]	Primary intensive care unit-acquired bloodstream infection compared with matched controls (acute physiology score)	72	Difference in mean and median total length of stay	10 days (mean) 5 days (median)
Orsi, 2002[111]	Hospital-acquired, laboratory-confirmed bloodstream infection compared with matched controls using complex stepwise matching including prior length of stay	108	Difference in mean and median total length of stay	19.9 days (mean) 13-15 days (median)
Wisplinghoff, 2003[112]	Nosocomial bloodstream infections in neutropenic adults compared to matched controls	81	Difference in mean total length of stay	18 days
Hoste, 2004[104]	Nosocomial bloodstream infection in critically ill patients in acute renal failure compared to matched controls (age, gender, severity, vasoactive treatment and mechanical ventilation and length of stay prior to infection)	50	Log-rank test of cumulative end of stay curve	p = 0.539
Pirson, 2005[113]	Hospital-acquired bacteraemia compared with all non-bacteraemia patients with the same diagnosis-related group	46	Difference in mean total length of stay	21.1 days
Laupland, 2006[114]	Intensive care unit-acquired bloodstream infections compared with controls matched following a stepwise loosening of criteria (location, surgical/medical diagnosis, chronic renal dialysis, days in intensive care unit, age, sex, severity, and length of stay prior to intensive care)	144	Difference in median total length of stay	3.5 days
Shorr, 2006[115]	Hospital-acquired bacteraemia compared with all non-bacteraemia patients with the same diagnosis-related group	603	Difference in mean and median total length of stay	29.8 (mean) 25.1 (median)

Table 9 (cont.): Selected studies of excess length of stay following hospital-acquired bacteraemia.

Author	Comparison	Number of episodes	Estimands	Estimate
Kothari, 2008[116]	Hospital-acquired bacteraemia compared with controls matched on age, sex, and similarity in the procedures performed	24	Difference in mean total length of stay	22.9 days
Vrijens, 2010[117]	Hospital-acquired, laboratory-confirmed bloodstream infection compared with matched controls	1.839	Difference in mean total length of stay	9.9 days
Barnett, 2013[118]	Hospital-acquired bloodstream infections compared with incidence density sampled controls	5.847	Difference in residual length of stay	0-12.8 days
Kaye, 2014[119]	Nosocomial bloodstream infection in elderly compared with controls matched on at least same length of stay prior to infection	830	(Uninfected mean length of stay * inverse log of beta coefficient) - infected mean length of stay	10 days
Watson, 2019[120]	Hospital-acquired bloodstream infections compared with risk-set propensity score matched reference	374	Difference in mean total length of stay	12 days
Zhang, 2020[121]	Hospital-acquired bloodstream infections compared with risk-set propensity score matched reference	557	Difference in mean total length of stay	16.9 days
Wang, 2020[103]	Nationwide intensive care unit-acquired bloodstream infections compared with propensity score matched reference	14.234	Difference in residual length of stay	8 days

1.7. KNOWLEDGE GAPS

While the literature on hospital-acquired bacteraemia is abundant with many studies from all around the globe, population-based studies are limited to few countries. Most studies on the incidence of hospital-acquired bacteraemia follow methods or estimate the incidence in combination with community-acquired bacteraemia. This may have led to estimates being reported as a rate according to the background population. However, the incidence of hospital-acquired infections is influenced by the number of patients at actual risk i.e., the hospitalised patients. Therefore, it may be reasonable to report incidence as the rate of infection pr. patient bed-days.

Previous literature has focused on comorbidity as a risk factor of hospital-acquired bacteraemia, and while some studies suggest various hospital interventions, few studies report adjusted estimates following currently recommended confounder selection. Furthermore, studies are often limited to specific patient groups or make comparison to an arbitrary control group instead of the patients at-risk of hospital-acquired bacteraemia.

Few population-based studies have assessed mortality following hospital-acquired bacteraemia and most studies report mortality in absolute rates. This leaves the question of how much this mortality is associated with the infection *per se* and how much is associated with being critical ill and requiring hospital admission. Two studies limited to intensive care unit-acquired bacteraemia have reported estimates of association, but this does not capture the entire population of patients with hospital-acquired bacteraemia. While non-population-based studies have reported estimates of attributable mortality, they are often limited to specific patient groups, aetiology, and combinations hereof. Furthermore, most studies are limited to in-hospital mortality or have ignored the temporal dynamics of infection, discharge, and mortality entirely.

The excess length of stay following hospital-acquired bacteraemia has often been studied as the difference in either mean or median total length of stay. This may introduce time-dependent bias and effectively overestimate the association. Furthermore, I found no population-based studies reporting the excess length of stay of hospital-acquired bacteraemia.

CHAPTER 2. OBJECTIVES

The purpose of this thesis is to address knowledge gaps in the current literature on hospital-acquired bacteraemia. Specific objectives of the studies were as follows:

Study I: Risk factors for hospital-acquired bacteraemia. To explore the advancing treatment options, interventions, and surgery as risk-factors for developing bacteraemia during hospital stay.

Study II: Incidence and mortality of hospital-acquired bacteraemia. To investigate the incidence and 30-day mortality following hospital-acquired bacteraemia compared to hospitalised patients at-risk of developing hospital-acquired bacteraemia.

Study III: Excess length of stay and readmission following hospital-acquired bacteraemia. To investigate excess length of stay following hospital-acquired bacteraemia compared to hospitalised patients at-risk, and to assess the rate of readmission in patients, who had a hospital-acquired bacteraemia episode compared to patients who did not.

CHAPTER 3. MATERIALS & METHODS

3.1. DATA SOURCES

Study I

The Department of Clinical Microbiology Laboratory Information System (WWBakt, Autonik, Sköldinge, Sweden) is the computerised information system utilised at the Department of Clinical Microbiology at Aalborg University Hospital[122]. Since 1996, it contains routinely collected records on all microbiological specimens including blood cultures handled by the department.[122] The records are linked to the unique personal identifier known as CPR-number and contains results of pathogen identification and antimicrobial susceptibility tests.

Electronic medical records (Clinical Suite, DXC Technology, Ashburn VA, USA) at Aalborg University Hospital is used in routine care of patients.[123] It is used for clinical communication and legal documentation of the patients' course, symptoms, clinical findings, summary of laboratory findings, interventions, and medical prescriptions.

Studies II & III

The Civil Registration System was introduced in 1968 as a replacement of manual index card-based registration led by registration offices in the municipalities.[124] The national system was established primarily for administrative purposes, especially taxation, but has become an important research tool in epidemiological research.[125]

All individuals, who have taken permanent residence in Denmark, are registered and assigned a 10-digit personal unique identifier, a CPR-number.[124,126] The first 6 digits indicate the birthday, the following 3 digits is a serial number and additionally account for the century of birth. The last digit indicates the gender (odd for male, even for female). As the CPR-number is personal, it cannot be reused in the future. The register also contains information on vital status, family and spousal relations, place of birth, place of residence, emigration, immigration, and disappearance.[126]

The quality of the data is considered very high as registration is required by law and continuously validated by the use in all public institutions that interact with Danish residents.[124–126] The high quality and unique registration allow for unambiguous linkage between nearly 200 national databases including the Danish National Patient Registry.

The Danish National Patient Registry was first established in 1976 by collecting the data from the comity-level computerised patient administrative systems.[127,128] The

primary aim was to monitor hospital and health service utilization for the Danish Health and Medicines Authority. Since then, it has also been used to monitor disease occurrence including the incidence of hospital-acquired infections.[129] The Danish National Patient Registry collects information on contacts with the Danish health care system and is updated daily with data from the Danish Regions.[128] It contains information on administrative data, diagnoses, treatments, and examinations.[127] The current study utilised information based on the second version of the Danish National Patient Registry, which was replaced by third version in March 2019.[130] In the second version, each record contains a record-ID, which is unique and generated at each new contact with the healthcare system. All records are linked at the individual level by CPR-number. In addition to CPR-number, administrative data also include information on municipality and region of residence, admission type (acute or non-acute), contact type (in-patient or out-patient), specialty, department, referral information, contact reason, and dates of admission and discharge.[128]

Diagnoses were originally recorded using the International Classification of Diseases (ICD) 8th edition. From 1993 and onward, a modified danish version of ICD-10 have been used.[128] This modified version is more detailed than the regular ICD-10 and is available through the Danish Health Data Authority in the Danish Health Care Classification System.[131] Treatment such as surgeries and other procedures are recorded using Nordic Medico-Statistical Committee Classification of Surgical Procedures. For examinations including radiological procedures a similar coding scheme is applied.[128]

The registration of diagnosis codes in the Danish National Patient Registry has been validated in numerous studies.[128] The diagnosis codes used for calculation of the Charlson Comorbidity Index have shown very high validity with positive predictive values ranging from 82% to 100% when using record review as gold standard.[132] Unfortunately, the sensitivity remains undetermined.

Following the Danish version of ICD-10, bacteraemia may be registered as DA499A or by codes indicating the aetiology (e.g., DA401 Sepsis due to *Streptococcus pyrogenes*, DA410 Sepsis due to *Staphylococcus aureus*, and DA415A Sepsis due to *Escherichia coli*). However, from 2000 through 2011, the sensitivity of this coding was only 32.3%, and application of wider categorises of infections only captured 64.9% of the episodes of bacteraemia.[133] Thus, identification of bacteraemia based on the diagnosis codes registered in the Danish National Patient Registry may be inadequate for epidemiological research.

Entries in **the North Denmark Bacteraemia Research Database** may be more suitable for research purposes but does not provide nationwide data. The database is maintained by the Department of Clinical Microbiology at Aalborg University Hospital and holds records of all culture-confirmed episodes of bacteraemia in the North Denmark Region.[17] Since its establishment, the department have utilised three

different laboratory systems for blood cultures. However, throughout the study period covered by study I-III only the current system was used; the Bact/Alert blood culture system (bioMérieux, Marcy-l'Étoile, France).[134] For adult patients, one set of blood cultures consist of three culture bottles (two aerobic and one anaerobic).[17] Medically trained clinical microbiologists supervised the blood culturing and determined the clinical relevance of the findings based on the species and clinical information. Coagulase-negative staphylococci, *Corynebacterium spp.*, and *Cutibacterium acnes* were regarded as contaminants unless isolated from two or more separate blood culture sets.[13] Entries from 1981 to 1991 were registered retrospectively from archived blood culture reports. From 1991 and onwards, the episodes have been recorded prospectively.[17] The database include information on date of venepuncture for the first positive blood culture, date of admission, time of incubation until positive result, hospital and department at time of venepuncture, number of positive blood culture bottles, place of acquisition of infection (community-acquired, health care-associated, or hospital-acquired), focus of infection, information on other related specimens, number of isolates, microbiological species, antimicrobial susceptibility, and appropriateness of the empirical antibiotic therapy.[17] Linkage to medical registries is viable by means of the CPR-number. The North Denmark Bacteraemia Research Database contributes to the Danish Collaborative Bacteraemia Network Database that also include episodes from the Danish Capital Region.[135]

3.2. STUDY DESIGN AND POPULATION

The Danish Healthcare System is primarily tax-funded and consist of general practitioners and specialists in private practice as well as hospitals.[136] There are only few private hospitals, which primarily handle non-acute referrals and account for less than 1% of hospital beds in Denmark. The public healthcare system is organised in three levels: the national level, the regional level, and the local level.[136] The organising entity at the national level is the Ministry of Health, which is responsible for the framework through legislation, national guidelines, patient's rights, audits and monitorisation. On the regional level, Denmark is divided into five Regions (prior to 2007: 14 counties). The Regions are governed by regional councils that follow a 4-year election cycle. The Regions govern primary healthcare provided by general practitioners and secondary health care services provided by specialist practices. The public hospitals are owned and operated by the Regions. On the local level, municipalities handle certain health services for disadvantaged resident groups and elderly including long-term-care facilities along with social and community care.

The North Denmark Region operate three hospitals with 24-hour emergency department care along with five hospitals without 24-hour emergency department care.[136] Aalborg University Hospital serves as referral hospital for the region and as district hospital for the greater Aalborg area. With the recent constitution of the Department of Dermatology in 2018 all specialities are represented in the region. Additionally, the transregional centre for treatment of intestinal failure is located at

Aalborg University Hospital. However, patients requiring solid organ or allogenic bone marrow transplantation are referred to centralised national centres.

To investigate hospital interventions as possible risk factors in **study I,** we designed a case-control study with inclusion running from the 15th of October 2019 to the 14th of October 2020. Cases were defined as adult patients (≥ 18 years of age) who attracted hospital-acquired bacteraemia during hospital stay. Bacteraemia was classified as hospital-acquired if the first positive blood culture was drawn later than 48 hours after admission. The study was limited to Aalborg University Hospital to ensure uniform collection of information from patient records with the possibility for follow-up questions to patients and staff in case of uncertainties. Cases were identified using the laboratory information system, WWBakt, by daily review of the positive blood cultures that were deemed clinically relevant by the attending clinical microbiologist in cooperation with the attending physician. Recurrent episodes of bacteraemia with the same aetiology within 30 days of a prior episodes were excluded.

Controls were selected using an incidence density or risk-set sampling technique, where controls were selected from the current hospital population on the day a corresponding case was evident. The controls were matched by sex and age group (18-44, 45-64, and ≥65 years of age). The controls could be matched to several cases but only once for each case. Patients that had a previous episode of hospital-acquired bacteraemia were not eligible as controls.

Cases and controls underwent thorough review of their electronic medical records to determine interventions leading up to inclusion in the study and possible confounders. The variables collected and the time of interest for each category are provided in Table 10. Information on critical values and biochemical surveys proved difficult to collect consistently as the different types and reasons for admissions resulted in a wide variety of tests and examinations. Therefore, these variables were not examined further in the analyses. Study data was collected and stored using REDCap electronic data capture tools hosted at the North Denmark Region.

Table 10: Variables collected during study I to examine interventions as risk factors for hospital-acquired bacteraemia

Category (Timing)	Variables	Category (Timing)	Variables
Administrative (Current admission)	Case (or control) Sex Birthday (age) Date of admission Date of inclusion Department at admission Department at inclusion Transfers prior to inclusion Intensive care prior to inclusion	**Critical values (48 hours or more prior to inclusion)**	Temperature Mean arterial pressure Systolic arterial pressure Diastolic arterial pressure Use of vasopressor Heart rate or pulse Respiratory rate Glasgow coma scale Peripheral saturation
Social and lifestyle (Previous and current)	Weight Height Alcohol abuse (current, previous, never) Tobacco use (current, previous, never) Living arrangement	**Biochemical surveys (48 hours or more prior to inclusion)**	Sodium Potassium Haematocrit White blood cell count Platelets Albumin Bilirubin Creatinine Urea INR Arterial pH PaO_2 FiO_2 (supplement) $PaCO_2$ Bicarbonate Lactate
Comorbidities (On admission day)	Diabetes without complications Diabetes with complications Liver disease (mild to moderate) Liver disease (severe) Local solid tumour malignancy Metastatic cancer Haematologic cancer AIDS Chronic kidney disease (and eGFR) Congestive heart failure (and last known LVEF) Ischemic heart disease Chronic obstructive lung disease (and last known FEV1) Peripheral vascular disease Previous stroke Dementia Other neurological disorders Connective tissue disease Peptic ulcer	**Interventions (From admission to inclusion)**	Central venous catheters Arterial catheters Mechanical ventilation Catheter-a-demure Device insert in the central nervous system Haemodialysis Peritoneal dialysis Drainage/catheter in the abdominal cavity Drainage/catheter in the thoracic cavity Surgery (including type) Immunosuppressive treatment including chemotherapy (30 days prior to admission to inclusion)
Foreign bodies prior to admission (Present on admission day)	Pacemaker or ICD Valve or vascular prosthetics Orthopaedic prosthetics Permanent urinary catheters Permanent vascular catheters Other prosthetics Other foreign bodies	**Diagnostics**	Primary admission diagnosis Suspected source of bacteraemia (physician) Colonised or infected with MDR (including type)

Abbreviations: eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; FEV1, forced expired volume in the first second; ICD implantable cardioverter-defibrillator.

In **Study II** and **Study III,** we used the Danish National Patient Registry to define a population-based cohort of all adults (≥ 18 years of age) with an admission lasting longer than 48 hours at a hospital in the North Denmark Region from 2006 through 2018. Readmission within 48 hours were considered a continuation of the prior admission, as bacteraemia within this period would be considered a hospital-acquired case. Complete 30-day follow-up was available using the Civil Registration System and the Danish National Patient Registry. Bacteraemia episodes were identified from the North Denmark Bacteraemia Research Database using the time of venepuncture and admission date. Episodes that occurred within 48 hours of admission were classified as non-hospital-acquired episodes and excluded. Contrary to previous studies, I included all episodes including repeat episodes more than 30 days apart to improve generalisability. Information on the admission, previous admissions and comorbidity were available through linkage to the Danish National Patient Registry.

3.3. EXPOSURES AND OUTCOMES

In **Study I**, a set of a priori selected hospital interventions were considered as risk factors. These included immunosuppressive treatment including chemotherapy 30 days and 90 days prior to inclusion and any of the following occurring between admission and inclusion: Central venous catheter including peripherally inserted central catheter, arterial catheter, mechanical ventilation, catheter à demeure, device inserted in the central nervous system, thoracic- and abdominal drainage or catheters, haemodialysis, and neuro- abdominal-, orthopaedic- and vascular surgery.

In **Study II**, we investigated the incidence of hospital-acquired bacteraemia episodes pr. 10,000 hospital patient-days. The primary outcome was 30-day mortality from hospital-admission. Vital status including dates were obtained from the Civil Registration system. The 30-day mortality was examined for all episodes of hospital-acquired bacteraemia and by source of bacteraemia.

Additionally, to improve comparison with previous studies investigating only in-hospital mortality of incident episodes of hospital-acquired bacteraemia, we also estimated in-hospital mortality, probability for discharge alive, and post-hospital mortality.

In **Study III**, the primary outcomes were the excess length of stay and the risk of readmission following an episode of hospital-acquired bacteraemia. The excess length of stay was considered as the number of additional days, on average, a patient with hospital-acquired bacteraemia would stay in hospital compared to patients without, i.e., the average residual length of stay in patients with hospital-acquired bacteraemia compared those patients without and still admitted on the same day of admission.[106] Additionally, we examined the relative probability of all-cause end of stay (both dead and alive) and discharge alive, to understand what effect the dynamics of discharged alive and mortality had on the excess length of stay. To investigate the risk of

readmission in patients who survived the hospital stay, we considered the endpoint of readmission within day 2 and 30 after discharge while considering the competing endpoint, death before readmission.

3.4. STATISTICAL ANALYSES

3.4.1. STUDY I

To estimate the association between the possible risk factors and hospital-acquired bacteraemia, we applied conditional logistic regression. The associations were reported as odds ratios; however, given the use of risk-set sampling of controls the odds ratios may be interpreted as estimates of the underlying incidence rate ratios[137]. To address possible confounding, we applied multivariate conditional logistic regression and reported the associations as adjusted odds ratios. The possible confounders were selected a priori based on literature review and included days of hospitalisation prior to inclusion (continuous), type of admission (medicine and acute surgery or elective surgery), and the updated Charlson Comorbidity Index score categorised into low (score of 0), moderate (score of 1-2) and high (score of ≥3) levels of comorbidity.[138,139]

Simulation studies have indicated that conditional logistic regression may lead to biased estimates of association in case-controls with risk-set sampling.[140] Therefore, we conducted a similar analysis of using unconditional multivariate logistic regression with adjustment for matching variables (sex and age-group).

3.4.2. STUDY II

Trend over time in incidence of hospital-acquired bacteraemia pr. 10,000 hospital patient-days were evaluated using Poisson regression. We computed crude mortality proportions (number for deaths/total number of patients) in exposed and unexposed patients and 30-days mortality rates (deaths pr. 1,000 person-days)

To investigate 30-day mortality in relation to hospital-acquired bacteraemia, we used a multi-state approach. Following this approach, we considered the patients' course of hospitalisation and possible infection as transition through a set of states. We used an illness-death model with recovery as presented in Figure 1. A patient enters the model at 'hospitalised' upon hospitalisation unless the patient had previous hospital-acquired bacteraemia within 30 days prior to admission. In that case the patient would enter at state 'hospital-acquired bacteraemia' and transition to 'hospitalised' at day 30 since positive venepuncture. Patients transition to 'hospital-acquired bacteraemia' upon development of an episode of hospital-acquired bacteraemia. Patients were followed from admission until death or end of follow-up (30 days since admission date). Individuals could be included multiple times, even with overlapping follow-up periods (in case of readmission within 30 days of prior admission).

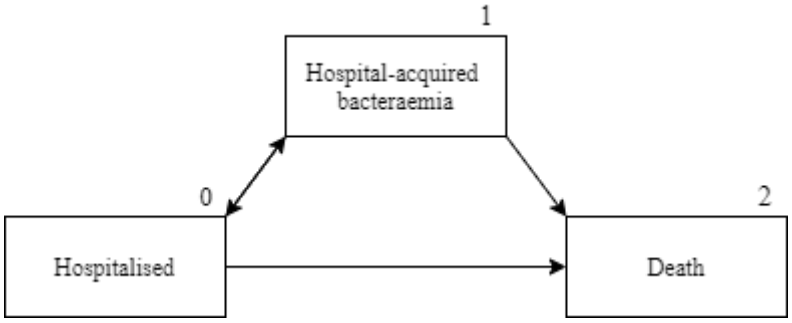

Figure 1: Illness-death multi-state model with recovery. Each arrow represents a transition hazard between the corresponding states. Upon admission patients enter state 0, hospitalised; with possible transition to state 1, hospital-acquired bacteraemia; or state 2, death. Patients can only move between states according to the direction arrows. Adopted from Mortensen VH, Søgaard M, Mygind LH, Wolkewitz M, Kristensen B, Schønheyder HC. Incidence and mortality of hospital-acquired bacteraemia: A population-based cohort study applying a multi-state model approach. Clin Microbiol Infect. Published online 17 December 2021.

The daily probability of transitions (transition intensity) within the model was evaluated using cumulative hazard curves based on the Nelson-Aalen estimator. We computed the transition intensities from unexposed, 'hospitalised', and exposed 'hospital-acquired bacteraemia', towards death.

To estimate the association between hospital-acquired bacteraemia and 30-day mortality compared to hospitalised patients at risk of hospital-acquired bacteraemia, we estimated transition-specific hazard ratios using a Cox regression model with hospital-acquired bacteraemia as a time-dependent variable. For adjusted estimates confounders were selected based on the disjunctive cause criterion[141] and included sex, age (penalised spline), type pf admission ('surgical' or 'non-surgical'), urgency of admission ('acute' or 'elective'), and the following predisposing conditions (dichotomous); diabetes mellitus with and without complications, rheumatic disease, leukaemia, lymphoma, localised cancer, metastatic cancer, chronic pulmonary disease, renal disease, cerebrovascular disease, dementia, mild and severe liver disease, HIV and AIDS, congestive heart failure, peripheral vascular disease, ischemic heart disease, and inflammatory bowel disease.[142] The analyses were conducted for all episodes and for episodes with a specific source of bacteraemia while censoring other episodes of hospital-acquired bacteraemia.

Subgroup analyses was conducted according to major demographic variables: Sex, age groups (18-40, 41-60, 61-80, and 81-105 years of age), level of comorbidity based on the original Charlson Comorbidity Index (low: 0, moderate: 1-2, high: ≥3),[143] type and urgency of admission.

To examine the dynamics of hospital-acquired bacteraemia, in-hospital mortality, discharge alive, and post-discharge mortality, we further defined a five-state model (Figure 2). This model only included the first admission for each patient within the study period. All patients entered the model as hospitalised and if infected they transitioned to 'hospital-acquired bacteraemia'. From 'hospitalised' and hospital-acquired bacteraemia' patients could transition to 'discharged' or 'death' and following discharge (with or without prior hospital-acquired bacteraemia) to 'death'.

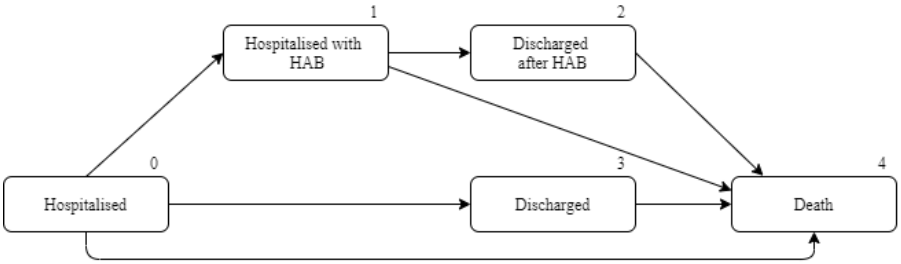

Figure 2: 5-state model for estimating dynamics of hospital-acquired bacteraemia (HAB), in-hospital mortality, discharge, and post-discharge mortality. Adopted from Mortensen VH, Søgaard M, Mygind LH, Wolkewitz M, Kristensen B, Schønheyder HC. Incidence and mortality of hospital-acquired bacteraemia: A population-based cohort study applying a multi-state model approach. Clin Microbiol Infect. Published online 17 December 2021.

We computed the following transition intensities using cumulative hazard curves: 1) hospitalised to hospital-acquired bacteraemia, 2) hospitalised and hospital-acquired bacteraemia to death, 3) hospitalised and hospital-acquired bacteraemia to discharge alive, and 4) discharge with and without prior hospital-acquired bacteraemia to death. For the three pairs of transitions (2, 3, and 4), transition specific hazard ratios were estimated using Cox regression with time-dependent variables for each state. Adjusted estimates were achieved by including the previously mentioned possible confounders in a multivariate Cox regression.

3.4.3. STUDY III

The excess length of stay is, in theory, a result of the probability of all-cause end of stay, which may occur in two ways (discharge alive or death). As hospital-acquired bacteraemia and cofounders may affect these differently, we estimated the association between hospital-acquired bacteraemia and all-cause end of stay and between hospital-acquired bacteraemia and discharge alive. In Cox regression, we threated hospital-acquired bacteraemia as a time-dependent variable. For adjusted estimates, the following covariates were considered possible confounders in a multivariate Cox regression model: sex, age group (20-year interval), type pf admission ('surgical' or 'non-surgical'), urgency of admission ('acute' or 'elective'), and the same predisposing conditions as in study II.[142]

To investigate the excess length of stay, we adopted a four-state illness-discharge model (Figure 3). Patients entered the model upon hospitalisation at 'hospitalised' and could transition through a transition state of bacteraemia. Patients were followed until end of stay (either alive or dead) or end of follow-up at day 45 at which they were censored. Estimates of the excess length of stay following a hospital-acquired bacteraemia were computed using a non-parametric approach including several steps. First, a matrix of transition probabilities was calculated based on the Aalen-Johansen estimator for all admission days.[144] This matrix of transition probabilities account for the daily probability that patients change from one state to another (i.e., hospitalised to hospital-acquired bacteraemia, hospitalised to end of stay, or hospital-acquired bacteraemia to end-of stay). Second, using these matrices of daily probabilities, it is possible to compute the daily difference of residual length of stay between currently infected and currently uninfected patients.[145] Third, a weighted average of these differences in residual length of stay was computed using weights based on the probability of acquiring hospital-acquired bacteraemia each day. This average estimate is coined 'excess length of stay' but may also be presented as change in length of stay in the literature.

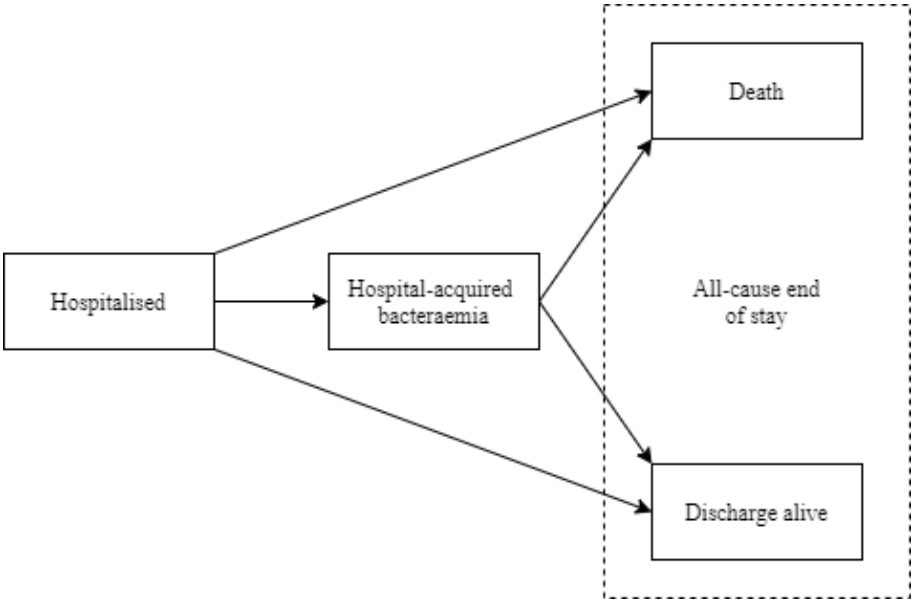

Figure 3: Illness-discharge model without recovery to investigate the excess length of hospital stay attributable to hospital-acquired bacteraemia. 'Death' and 'Discharge alive' was aggregated to a single state: All-cause end of stay. Adopted from Mortensen VH, Mygind LH, Schønheyder HC, Staus P, Wolkewitz M, Kristensen B, Søgaard M. Extended length of stay and readmission following hospital-acquired bacteraemia: A population-based cohort study. Submitted.

As the non-parametric estimates are unadjusted, we explored the effect of possible confounders on the expected excess length of stay. Based on a resampling technique called jack-knife, the analysis of excess length of stay was computed repeatedly, while leaving all observations out one by one. The difference between estimates of every subset and the estimate of the original cohort was recorded and hold information on how that observation along with additional covariates (confounders) affected the estimates of excess length of stay. The values of this process are often referred to as pseudo values and is the basis of pseudoregression.[146] We applied a generalised linear model treating the pseudo values as the dependent variable and possible confounders as independent variables. The model should be interpreted as follows; the intercept is the expected length of stay for the baseline patient (41–60-year-old male without prior admission and comorbidity admitted non-acutely to a surgical ward) and estimates for the covariates is the expected difference in days compared to the baseline patient.

To access the relative rate of readmission following discharge of an admission including hospital-acquired bacteraemia, we compared patients discharged alive following an episode of hospital-acquired bacteraemia with those who was discharged alive but did not experience hospital-acquired bacteraemia during hospitalisation. Comparison was made using a competing risk Cox regression with hospital-acquired bacteraemia as time-fixed dependent variable and with death before readmission as a competing endpoint.

CHAPTER 4. RESULTS

4.1. STUDY I

Demographics

During the one-year study period, 209,858 person-days were spent hospitalised at Aalborg University Hospital among which we identified 2,115 positive blood cultures in 28,048 blood culture sets. Using the 48-hour cut-off, we classified 115 episodes as incidents of hospital-acquired bacteraemia representing an incidence of 5.48 hospital-acquired bacteraemia episodes pr. 10,000 person-days.

The COVID-19 pandemic started during the study period. On the 11th of March approximately 4 months into the study, the Danish government introduced a comprehensive lockdown and suspended non-urgent elective surgery and outpatient visits. Of the 115 cases, 44 episodes occurred prior to the lockdown and only one case and five controls were admitted due to COVID-19.

To estimate the association between possible risk factors and hospital-acquired bacteraemia, we selected 230 matched controls; however, records for one patient were missing resulting in 229 controls. The cases and controls were 34% females and similar of age (median age of 72 and 71 years, respectively). Most notably, cases were hospitalised for longer time before inclusion in the study than controls (median of 20 vs 12 days) and were more often admitted in a medicine ward or for emergency surgery (94% vs 87%). Levels of comorbidity were, on average, lower in cases than in controls (58% vs 49% had a score of 0); however, cases were more likely to have haematologic (15% vs 6%) or metastatic cancer (13% vs 10%).

Risk factors for hospital-acquired bacteraemia

Comparison of cases and controls revealed that placement of central venous catheters (odds ratio of 3.96, 95% CI 2.31 – 6.79) and haemodialysis (odds ratio of 4.00, 95% CI 1.20 -13.28) were associated with hospital-acquired bacteraemia (Figure 4). These estimates diminished but remained statistically significant in adjusted analyses with adjusted odds ratios of 3.46 (95% CI 1.92 – 6.23) and 5.05 (95% CI 1.41 – 18.06), respectively.

In unadjusted analyses, immunosuppressive treatment including chemotherapy within 30 days prior to admission were associated with hospital-acquired bacteraemia. However, the association attenuated with adjustment (adjusted odds ratio of 1.72, 95% CI 1.00 – 2.96).

Beside orthopaedic surgery that were non-significantly associated with decreased risk of hospital-bacteraemia (adjusted odds ratio of 0.31, 95% CI 0.09 – 1.04), all proposed risk factors were associated with hospital-acquired bacteraemia with adjusted odds ratios above the null (Figure 4).

Risk factors	Case (n=115) Count (%)	Control (n=229) Count (%)	Model	OR	(95% CI)
Central venous catheter	60 (52.2)	56 (24.5)	Unadjusted	3.96	(2.31 – 6.79)
			Adjusted	3.46	(1.92 – 6.23)
Arterial catheter	35 (30.4)	66 (28.8)	Unadjusted	1.09	(0.65 – 1.83)
			Adjusted	1.04	(0.56 – 1.94)
Mechanical ventilation	50 (43.5)	91 (39.7)	Unadjusted	1.20	(0.74 – 1.94)
			Adjusted	1.49	(0.84 – 2.63)
Catheter à demure	59 (51.3)	96 (41.9)	Unadjusted	1.47	(0.93 – 2.31)
			Adjusted	1.40	(0.84 – 2.33)
Device inserted to CNS	15 (13.0)	16 (7.0)	Unadjusted	1.92	(0.93 – 3.95)
			Adjusted	1.63	(0.72 – 3.69)
Thoracic drain or catheter	12 (10.4)	20 (8.7)	Unadjusted	1.22	(0.58 – 2.55)
			Adjusted	1.18	(0.51 – 2.73)
Abdominal drain or catheter	17 (14.8)	19 (8.3)	Unadjusted	1.86	(0.94 – 3.67)
			Adjusted	2.11	(0.98 – 4.53)
Haemodialysis	8 (7.0)	4 (1.7)	Unadjusted	4.00	(1.20 – 13.28)
			Adjusted	5.05	(1.41 – 18.06)
Immunosupressive treatment incl. chemotherapy (30 days)	38 (33.0)	49 (21.4)	Unadjusted	1.82	(1.10 – 3.02)
			Adjusted	1.72	(1.00 – 2.96)
Neuro surgery	5 (4.3)	6 (2.6)	Unadjusted	1.67	(0.51 – 5.46)
			Adjusted	1.66	(0.46 – 6.04)
Thoracic surgery	10 (8.7)	13 (5.7)	Unadjusted	1.54	(0.67 – 3.51)
			Adjusted	1.57	(0.59 – 4.20)
Abdominal surgery	20 (17.4)	34 (14.8)	Unadjusted	1.21	(0.67 – 2.19)
			Adjusted	1.26	(0.64 – 2.47)
Orthopaedic surgery	5 (4.3)	20 (8.7)	Unadjusted	0.47	(0.17 – 1.30)
			Adjusted	0.31	(0.09 – 1.04)
Vascular surgery	6 (5.2)	9 (3.9)	Unadjusted	1.33	(0.47 – 3.75)
			Adjusted	1.54	(0.51 – 4.66)

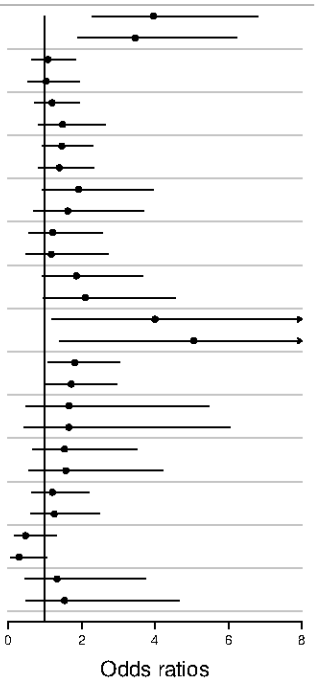

Figure 4: Risk factors for hospital-acquired bacteraemia among adult patients hospitalised for more than 48 h. The adjusted models were adjusted for days of hospitalisation prior to index (continuous variable), type of admission ('medicine and acute surgery' or 'elective surgery'), and the updated Charlson Comorbidity Index score (categorized). Adopted from Mortensen VH, Søgaard M, Kristensen B, Mygind LH, Schønheyder HC. Risk factors for hospital-acquired bacteraemia – an explorative case–control study of hospital interventions. Infect Dis (Lond). 2022;54(3):178-185.
Abbreviations: CNS, central nervous system; OR, odds ratio; CI, confidence interval.

4.2. STUDY II

Incidence

From 2006 through 2018, we identified 3,060 incident episodes among a total of 3,588 episodes of hospital-acquired bacteraemia in 484,264 admissions. Throughout the study period, 205,962 unique patients had a hospital stay for ≥48 hours, and we found a proportional annual increase of 1.02 (95% CI 1.01 – 1.03) in the incidence of hospital-acquired bacteraemia (Figure 5).

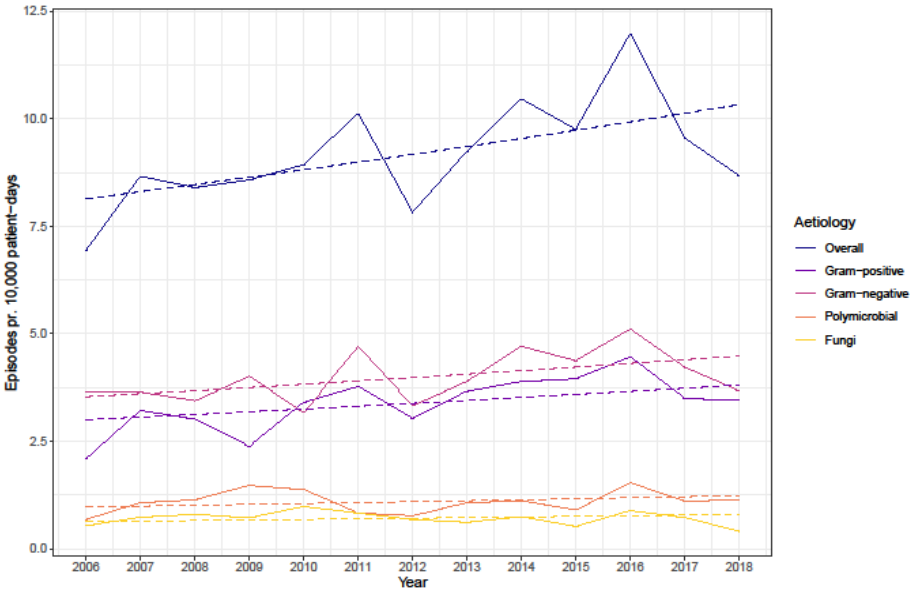

Figure 5: Incidence rates for hospital-acquired bacteraemia in North Denmark Region between 2006 and 2018 overall and according major pathogens. Reported in episodes pr. 10.000 days of hospital stay. The dotted lines depict trends based on Poisson regression. Adopted from Mortensen VH, Søgaard M, Mygind LH, Wolkewitz M, Kristensen B, Schønheyder HC. Incidence and mortality of hospital-acquired bacteraemia: A population-based cohort study applying a multi-state model approach. *Clin Microbiol Infect*. Published online 17 December 2021.

Demographics

Patients who acquired bacteraemia during hospital stay were more often male, more likely to be admitted to a non-surgical ward and had more previous hospital stays in the year before index admission. Patients with hospital-acquired bacteraemia had higher levels of comorbidity in particular; diabetes mellitus with complications (9.6%

vs. 5.5%), haematologic cancer (leukaemia 5.8% vs. 1.0%, lymphoma 6.0% vs. 1.9%), and metastatic cancer (9.1% vs. 4.3%).

Aetiology

The distribution of pathogens varied according to source of infection (Figure 6). Bacteraemia stemming from 'thorax incl. pneumoniae', 'heart & vascular', and 'skin, soft tissue, & bone' were predominantly caused by *S. aureus*, beta-haemolytic streptococci, and *S. pneumoniae.* IV-catheter related bacteraemia was more often caused by *S. aureus* and coagulase negative staphylococci. Enterobacteriaceae (*E. coli* and others) were the most frequent cause of bacteraemia from abdomen, 'liver & biliary system', and the urinary pathway. Episodes of unknown origin were primarily caused by enterococci, fungi, or of polymicrobial aetiology.

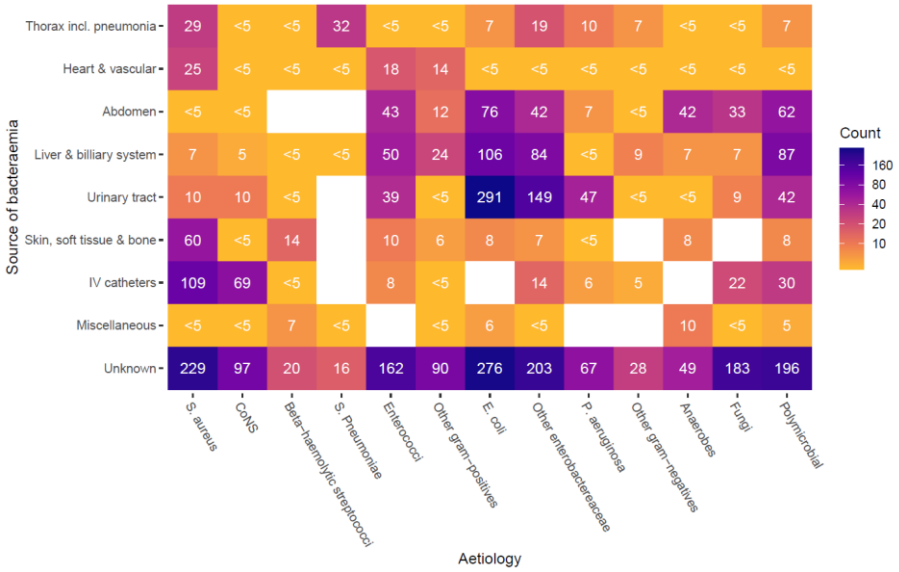

Figure 6: Aetiology according to source of hospital-acquired bacteraemia in the North Denmark Region, 2006 – 2018. Adopted from Mortensen VH, Søgaard M, Mygind LH, Wolkewitz M, Kristensen B, Schønheyder HC. Incidence and mortality of hospital-acquired bacteraemia: A population-based cohort study applying a multi-state model approach. Clin Microbiol Infect. Published online 17 December 2021.

30-day mortality

As evidenced by the cumulative hazard curves, patients with hospital-acquired bacteraemia experienced higher mortality throughout follow-up (Figure 7). Correspondingly, the unadjusted mortality rates were higher for patients with hospital-acquired bacteraemia than in patients without hospital-acquired bacteraemia (11.64 versus 1.91 deaths pr. 1.000 person-days, respectively) (Table 11).

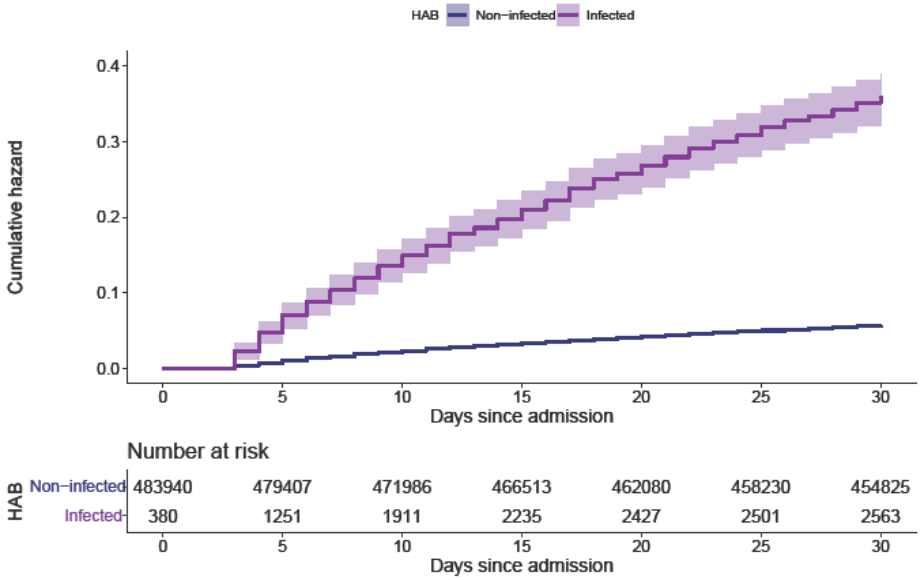

Figure 7: Cumulative transition hazards for death in patients with hospital-acquired bacteraemia (HAB) and hospitalised patients in risk of hospital-acquired bacteraemia (Non-HAB). Adopted from Mortensen VH, Søgaard M, Mygind LH, Wolkewitz M, Kristensen B, Schønheyder HC. Incidence and mortality of hospital-acquired bacteraemia: A population-based cohort study applying a multi-state model approach. Clin Microbiol Infect. Published online 17 December 2021.

The relative difference in mortality was 4-6-fold higher in patients with hospital-acquired bacteraemia (crude hazard ratio of 6.28, 95% CI 5.80 – 6.80, and adjusted hazard ratio of 4.32, 95% CI 3.95 – 4.72) when compared to patients without bacteraemia. This association was strongest for hospital-acquired bacteraemia of unknown source (adjusted hazard ratio of 6.42, 95% CI 5.67 – 7.26), followed by 'thoracic incl. pneumonia' (adjusted hazard ratio of 5.89, 95% CI 3.45 – 10.12), and abdomen (adjusted hazard ratio of 4.33, 95% CI 3.27 – 5.74). Episodes stemming from the urinary pathway had the lowest impact on mortality (adjusted hazard ratio of 1.83, 95% CI 1.41 – 2.37).

The relative impact on mortality associated with hospital-acquired bacteraemia did not differ by sex (Table 12). In relative terms, the strength of the association diminished with age (adjusted hazard ratios of 5.66, 95% CI 2.00 – 16.01 in patients aged 18-40 years versus 3.69, 95% CI 3.14 - 4.32 in patients aged 81-105 years), and with increasing levels of comorbidity (adjusted hazard ratios of 5.75, 95% CI 4.45 – 7.42 in patients with low comorbidity versus 3.55, 95% CI 3.16 – 3.98 in patients with high comorbidity). However, the absolute risk of death increased with increasing age and comorbidity (Table 12). The strongest association between hospital-acquired bacteraemia was found in patients admitted for elective procedures (adjusted hazard ratio of 9.09, 95% CI 7.14 – 11.57).

Table 11: Crude, univariate, and adjusted analyses of transition-specific hazards for death comparing patients with hospital-acquired bacteraemia (HAB) and hospitalised patients at risk of hospital-acquired bacteraemia (Non-HAB). Adopted from Mortensen VH, Søgaard M, Mygind LH, Wolkewitz M, Kristensen B, Schønheyder HC. Incidence and mortality of hospital-acquired bacteraemia: A population-based cohort study applying a multi-state model approach. Clin Microbiol Infect. Published online 17 December 2021.

	Count	Death	Observation time in person days	Deaths pr. admission (%)	Death pr. 1,000 person-days	Univariate Hazard ratio (95% CI)	Adjusted Hazard ratio (95% CI)
Non-HAB admission	480,712	2,6784	14,027,127	5.57	1.91	Ref.	Ref.
Overall HAB	3,588	694	59,625	20.67	11.64	6.28 (5.80 – 6.80)	4.32 (3.95 – 4.72)
Thoracic including pneumonia	126	28	1,870	22.22	14.97	8.15 (5.54 – 11.99)	5.89 (3.43 – 10.12)
Heart and vascular	77	8	1,535	10.39	5.21	2.75 (1.40 – 5.40)	2.02 (1.02 – 4.00)
Abdomen	328	63	5,542	19.21	11.37	6.18 (4.80 – 7.97)	4.33 (3.27 – 5.74)
Liver and biliary system	397	53	7,467	13.35	7.10	3.81 (2.91 – 4.99)	2.74 (2.06 – 3.64)
Urinary pathway	605	67	11,436	11.07	5.86	3.11 (2.43 – 3.98)	1.83 (1.41 – 2.37)
Skin, soft-tissue, and bone	126	20	2,491	15.87	8.03	4.17 (2.69 – 6.46)	3.43 (2.12 – 5.55)
IV-catheter	269	17	4,226	6.32	4.02	2.22 (1.37 – 3.61)	2.47 (1.49 – 4.10)
Miscellaneous[1]	44	0	952	0.00	0	-	-
Unknown	1,616	438	24,106	27.10	18.17	9.89 (8.91 - 10.97)	6.42 (5.67 – 7.26)

[1]Miscellaneous includes oral (4), central nervous system (10), female genitalia (26), and transfusion or IV-misuse related (4).

[2]Adjusted for sex, age (penalised spline), type of admission (‘surgical’ or ‘non-surgical’), urgency of admission (‘acute’ or ‘elective’ and predisposing conditions (dichotomous). Observations with missing values for sex (261 patients) were excluded from the adjusted analysis.

Abbreviation: CI, confidence interval.

Table 12: Stratified analyses of transition-specific hazard for death comparing patients with hospital-acquired bacteraemia and hospitalised patients at risk of hospital-acquired bacteraemia. Adopted from Mortensen VH, Søgaard M, Mygind LH, Wolkewitz M, Kristensen B, Schønheyder HC. Incidence and mortality of hospital-acquired bacteraemia: A population-based cohort study applying a multi-state model approach. *Clin Microbiol Infect*. Published online 17 December 2021.

	Reference			Hospital-acquired bacteraemia			Univariate	Adjusted
	Death	**Observation time in person-days**	**Death pr. 1.000 person-days**	**Death**	**Observation time in person-days**	**Death pr. 1,000 person-days**	**Hazard ratio (95% CI)**	**Hazard ratio (95% CI)**
Sex								
Female	12,650	7,795,090	1.62	253	21,598	11.71	7.489 (6.56 – 8.56)	4.85 (4.17 – 5.64)
Male	14,157	6,224,383	2.27	441	38,027	11.60	5.24 (4.74 – 5.78)	4.07 (3.64 – 4.54)
Age								
18-40	241	2,620,257	0.09	8	3,401	2.35	26.61 (12.94 – 54.71)	5.66 (2.00 – 16.01)
41-60	2,830	3,078,068	0.91	110	12,580	8.74	9.75 (7.97 – 11.92)	5.38 (4.27 – 6.77)
61-80	12,643	5,885,337	2.15	384	32,757	11.72	5.58 (5.01 – 6.20)	4.32 (3.84 – 4.86)
81-105	11,103	2,443,465	4.54	192	10,887	17.64	3.99 (3.42 – 4.65)	3.69 (3.14 – 4.32)
CCI scores								
0	3,477	6,062,177	0.57	78	14,359	5.43	9.87 (7.81 – 12.47)	5.75 (4.45 – 7.42)
1-2	10,850	5,197,442	2.09	272	23,026	11.81	5.94 (5.23 – 6.74)	5.95 (5.21 – 6.80)
≥ 3	12,490	2,767,508	4.51	344	22,240	15.47	3.47 (3.10 – 3.88)	3.55 (3.16 – 3.98)
Type of admission								
Surgical	5,004	5,845,462	0.86	171	22,813	7.50	9.07 (7.76 – 10.59)	4.17 (3.48 – 5.00)
Non-surgical	21,813	8,181,665	2.67	523	36,812	14.21	5.48 (5.00 – 6.02)	4.32 (3.90 – 4.79)
Urgency of admission								
Acute	24,929	10,343,420	2.41	612	46,804	13.08	5.59 (5.14 – 6.09)	4.03 (3.67 – 4.42)
Elective	1,888	3,683,707	0.51	82	12,821	6.40	12.37 (9.85 – 15.54)	9.09 (7.14 – 11.57)

[1]Not including the stratum specific variable adjustments were made on following covariates; sex, age (penalised spline), type of admission ('surgical' or 'non-surgical'), urgency of admission ('acute' or 'elective') and predisposing conditions (dichotomous). Observations with missing values for sex (261 patients) were excluded from the adjusted analysis.

Abbreviation: CI, confidence interval; CCI, Charlson Comorbidity Index

In-hospital mortality, probability of discharge, and post-discharge mortality

The risk of hospital-acquired bacteraemia increased with increasing length of hospital-stay (Figure 8). The in-hospital mortality was greater following hospital-acquired bacteraemia with an adjusted hazard ratio of 3.11 (95% CI 2.62 – 3.70) while the daily probability for being discharged alive were reduced (adjusted hazard ratio of 0.36, 95% CI 0.33 – 0.40) (Table 13). The increased mortality following hospital-acquired bacteraemia persisted through discharge (alive) with adjusted hazard ratio of 2.94 (95% CI 1.62 -5.32).

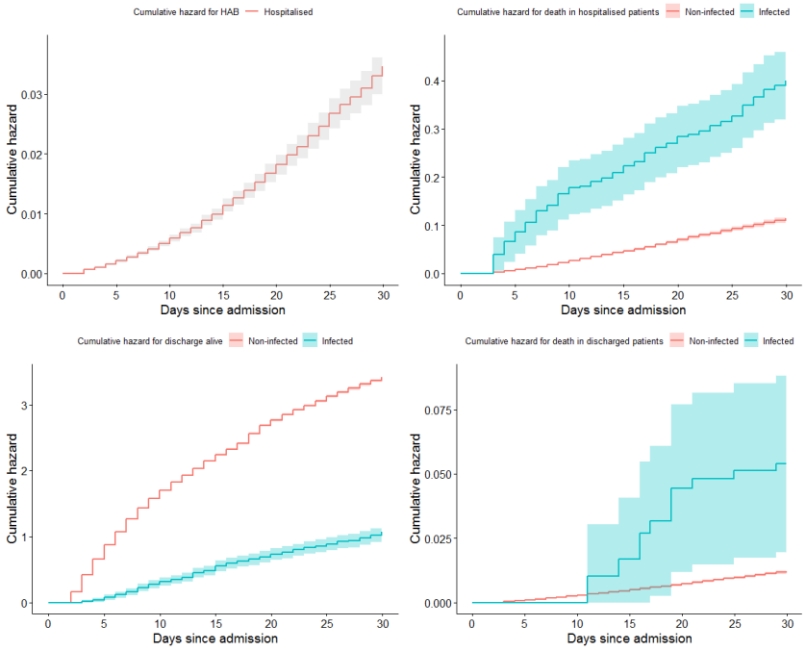

Figure 8: Cumulative hazards based on the Nelson-Aalen estimator for hospital-acquired bacteraemia (HAB), in-hospital mortality, discharge alive, and post-discharge mortality.
Adopted from Mortensen VH, Søgaard M, Mygind LH, Wolkewitz M, Kristensen B, Schønheyder HC. Incidence and mortality of hospital-acquired bacteraemia: A population-based cohort study applying a multi-state model approach. *Clin Microbiol Infect*. Published online 17 December 2021.

Table 13: Univariate and adjusted in-hospital mortality, discharge alive, and post-discharge mortality comparing patients with hospital-acquired bacteraemia and hospitalised patients at risk of hospital-acquired bacteraemia. Adopted from Mortensen VH, Søgaard M, Mygind LH, Wolkewitz M, Kristensen B, Schønheyder HC. Incidence and mortality of hospital-acquired bacteraemia: A population-based cohort study applying a multi-state model approach. *Clin Microbiol Infect*. Published online 17 December 2021.

	Hospital-acquired bacteraemia			**Reference**			**Univariate**	**Adjusted**
	Events	**Observation time in person-days**	**Events pr. 1,000 person-days**	**Events**	**Observation time in person-days**	**Events pr. 1,000 person-days**	**Hazard ratio (95% CI)**	**Hazard ratio (95% CI)**
In-hospital mortality	3,484	1,435,806	2.43	143	11,028	13.97	3.14 (2.64 – 3.73)	3.11 (2.62 – 3.70)
Discharged alive	195,837	1,435,806	136.40	419	11,028	37.99	0.36 (0.33 – 0.40)	0.36 (0.33 – 0.40)
Post-discharge mortality	2,071	4,633,107	0.45	11	5,295	2,08	4.42 (2.44 – 7.99)	2.94 (1.62 – 5.32)

[1]Adjustmented for sex, age (penalised spline), type of admission (‘surgical’ or ‘non-surgical’), urgency of admission (‘acute’ or ‘elective’) and predisposing conditions (dichotomous). Observations with missing values for sex (261 patients) were excluded from the adjusted analysis.

Abbreviation: CI, confidence interval

4.1. STUDY III

Probability of end of stay

Hospital-acquired bacteraemia was associated with lower adjusted hazard for all-cause end of stay with an adjusted hazard ratio of 0.60 (95% CI 0.57- 0.62) (Table 14). The association varied according to source of infection with adjusted hazard ratios ranging from 0.72 (95% CI 0.69 – 0.82) for urinary pathway to 0.30 (95% CI 0.23 – 0.40) for 'heart & vascular' source. The association was stronger for discharge alive compared (adjusted hazard ratios of 0.46, 95% CI 0.46 – 0.48) to all-cause end of stay as a result; the underlying higher in-hospital mortality following hospital-acquired bacteraemia.

Table 14: Relative probability of all-cause end of hospital stay, discharge alive, and extended length of stay attributed to hospital acquired bacteraemia (HAB). Adopted from Mortensen VH, Mygind LH, Schønheyder HC, Staus P, Wolkewitz M, Kristensen B, Søgaard M. Extended length of stay and readmission following hospital-acquired bacteraemia: A population-based cohort study. Submitted.

		All-cause end of stay Hazard ratio (95% CI)		**Discharge alive Hazard (95% CI)**		**Excess length of stay Days (95% CI)**
	Count	**Unadjusted**	**Adjusted[2]**	**Unadjusted**	**Adjusted[2]**	
Overall HAB	3457	0.59 (0.57 – 0.62)	0.60 (0.57 – 0.62)	0.46 (0.44 – 0.47)	0.46 (0.44 – 0.48)	6.6 (6.2 – 7.1)
Thoracic including pneumonia	124	0.50 (0.40 – 0.61)	0.48 (0.39 – 0.59)	0.30 (0.23 – 0.40)	0.30 (0.23 – 0.39)	9.9 (9.5 – 10.3)
Heart and vascular	78	0.27 (0.20 – 0.36)	0.30 (0.23 – 0.40)	0.18 (0.13 – 0.27)	0.21 (0.15 – 0.30)	18.3 (17.9 – 18.7)
Abdomen	314	0.46 (0.40 – 0.52)	0.42 (0.37 – 0.48)	0.34 (0.30 – 0.40)	0.31 (0.27 – 0.37)	10.4 (9.9 – 10.9)
Liver and biliary system	365	0.61 (0.54 – 0.68)	0.58 (0.52 – 0.65)	0.55 (0.48 – 0.62)	0.52 (0.46 – 0.59)	6.1 (5.7 – 6.6)
Urinary pathway	574	0.71 (0.65 – 0.78)	0.76 (0.69 – 0.82)	0.68 (0.62 – 0.74)	0.72 (0.66 – 0.79)	3.8 (3.3 – 4.2)
Skin, soft-tissue, and bone	121	0.51 (0.42 – 0.62)	0.51 (0.42 – 0.62)	0.46 (0.37 – 0.57)	0.46 (0.37 – 0.57)	7.0 (6.6 – 7.4)
IV-catheter	259	0.57 (0.50 – 0.66)	0.55 (0.48 – 0.64)	0.54 (0.46 – 0.63)	0.52 (0.45 – 0.61)	8.0 (7.6 – 8.4)
Miscellaneous[1]	43	0.54 (0.39 – 0.76)	0.43 (0.31 – 0.60)	0.56 (0.40 – 0.79)	0.43 (0.30 – 0.60)	6.2 (5.8 – 6.6)
Unknown	1579	0.63 (0.60 – 0.66)	0.65 (0.62 – 0.69)	0.41 (0.38 – 0.44)	0.42 (0.40 – 0.46)	6.2 (5.8 – 6.6)

[1]Miscellaneous contains bacteraemia patients with following foci; oral (4), central nervous system (10), female genitalia (25), and transfusion or IV-misuse related (4).

[2]Adjustments were made for the following covariates: Sex, age groups (20-year intervals), number of previous admissions the past year (continuous), type of admission ('surgical' or 'non-surgical'), urgency of admission ('acute' or 'elective') and predisposing conditions. Observations with missing values for sex (261 patients) were excluded from the adjusted analysis.

Excess length of stay

A loss in probability for end of stay may naturally lead to prolongation of hospitalisation. Excess length of stay was highest in patients who acquired bacteraemia shortly after admission and diminished with increasing length of stay prior to bacteraemia (Figure 9A). As depicted by the weights presented in Figure 9B, most of the episodes occurred around day 4 of hospitalisation.

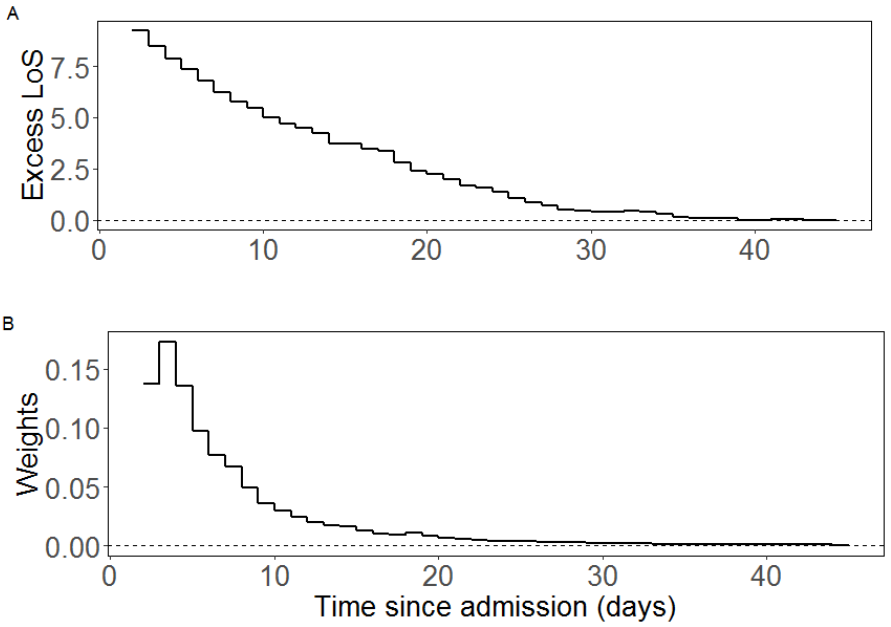

Figure 9: Results of a multi-state model to estimate the excess length of stay (LOS) following an episode of hospital-acquired bacteraemia compared to hospitalised patients who did not develop hospital-acquired bacteraemia. 9A) illustrates the relationship between excess length of stay and the time of hospital-acquired bacteraemia acquisition (computed daily by substation of LOS in patients that had not experienced hospital-acquired bacteraemia from those who had). 9B) illustrates the weights used to calculate the average excess length of stay (e.g., the relative frequency of hospital-acquired bacteraemia each day). Adopted from Mortensen VH, Mygind LH, Schønheyder HC, Staus P, Wolkewitz M, Kristensen B, Søgaard M. Extended length of stay and readmission following hospital-acquired bacteraemia: A population-based cohort study. Submitted.

Following hospital-acquired bacteraemia, patients experienced on average 6.6 days (95% CI 6.2 – 7.1) excess length of stay. The excess length of stay varied substantially by source of bacteraemia from 3.8 days (95% CI 3.3 – 4.2) for urinary pathways to 18.3 days (95% CI 17.9 – 18.7) for 'heart & vascular'.

Using pseudovalue regression, the baseline patient (41–60-year-old male without prior admission and comorbidity admitted non-acutely to a surgical ward) can expect 10.3 (95% CI 8.6 – 12.0) days prolongation of the hospital stay following a hospital-acquired infection (Table 15). Female patients may expect an additional 2.3 (95% CI 1.0 – 3.5) days excess stay. Elderly patients, aged 81 to 100 years, may expect less prolongation (-6.1 days, 95% CI -8.1 – -4.1) compared with the reference (age 41 to 60). Excess length of stay in non-surgical patients were shorter compared to surgical patients (-2.1 days, 95% CI -3.5 – -0.6), while the effect of the possible predisposing varied.

Rates of readmission

Despite higher post-discharge mortality (i.e., death before readmission) among patients with bacteraemia during their previous admission (adjusted hazard ratio of 2.79, 95% CI 2.38 – 3.21), hospital-acquired bacteraemia was associated with readmission rate in the first 30 days after discharge (adjusted hazard ratio of 1.42, 95% CI 1.42 – 1.53) (Table 16). However, this association was not evident for all sources of bacteraemia (‘thoracic incl. pneumonia’ with adjusted hazard ratio of 0.93, CI 0.52 – 1.68, and ‘heart & vascular’ with adjusted hazard ratio of 0.35 – 1.74). The strongest statistically significant association was found for bacteraemia stemming from the abdomen with an adjusted hazard ratio of 1.71 (1.33 – 2.21) while also having a high association with post-discharge mortality (adjusted hazard ratio of 3.68, 95% CI 2.29 – 5.93).

Table 15: Results of pseudo-value regression for excess length of stay following hospital-acquired bacteraemia and influencing covariates. Adopted from Mortensen VH, Mygind LH, Schønheyder HC, Staus P, Wolkewitz M, Kristensen B, Søgaard M. Extended length of stay and readmission following hospital-acquired bacteraemia: A population-based cohort study. Submitted.

Term	Estimate (days)	95% CI
Baseline excess length of stay (Intercept)	10.3	8.6 – 12.0
Female	2.3	1.0 – 3.5
Age 18 to 20	-0.6	-3.8 – 2.8
Age 21 to 40	-2.9	-4.3 – -1.4
Age 41 to 60	Reference	
Age 61 to 80	-0.8	-2.5 – 0.8
Age 81 to 100	-6.1	-8.1 – -4.1
Age 101 to 120	-0.2	-2.1 – 1.8
Previous admissions (1 admission increments)	-0.6	-1.3 – 0.0
Acute admission	0.7	-0.8 – 2.1
Non-surgery	-2.1	-3.6 – -0.6
Diabetes with complications	3.9	0.6 – 7.2
Diabetes without complications	-4.0	-6.7 – -1.2
Rheumatic disease	0.8	-2.6 – 4.2
Leukaemia	20.6	9.9 – 31.3
Lymphoma	1.7	-4.8 – 8.2
Metastatic solid tumour	-8.9	-12.4 – -5.4
Localised solid tumour	-4.0	-5.9 – -2.0
Chronic obstructive pulmonary disease	-1.1	-2.9 – 0.6
Chronic renal disease	0.9	-3.2 – 5.0
Previous stroke	-2.3	-4.4 – -0.3
Dementia	0.7	-3.0 – 4.3
Liver disease (mild to moderate)	-6.7	-13.0 – -0.4
Liver disease (severe)	3.0	-6.3 – 12.3
HIV and AIDS	-10.6	-33.2 – 12.1
Congestive heart failure	-3.7	-6.3 – -1.1
Peripheral vascular disease	2.7	-0.2 – 5.6
Cardiovascular disease	-0.6	-3.4 – 2.3
Inflammatory bowel disease	-2.4	-5.8 – 1.0

The model included all variables as dichotomous covariates aside ‘previous admissions’ (continuous). Estimates reflect additional excess length of stay associated with the covariates given the excess length of stay for the baseline patient group (male, age 41 to 60 years, without previous admissions and comorbidities, admitted non-acutely to a surgical ward).

Table 16: Rates of readmission and the competing outcome of death before readmission following hospitalisations with versus without an episode of hospital-acquired bacteraemia (HAB). Adopted from Mortensen VH, Mygind LH, Schønheyder HC, Staus P, Wolkewitz M, Kristensen B, Søgaard M. Extended length of stay and readmission following hospital-acquired bacteraemia: A population-based cohort study. Submitted.

	Number of episodes	Count (%)	Readmissions pr. 1,000 person-days	Hazard ratio (95% CI)	Adjusted Hazard ratio[2] (95% CI)	Count (%)	Deaths pr. 1,000 person-days	Hazard ratio (95% CI)	Adjusted hazard ratio[2] (95% CI)
Non-HAB	459027	86471 (19)	7.07	Reference		10392 (2)	0.9	Reference	
Overall HAB	2021	664 (33)	14.1	1.99 (1.84 – 2.15)	1.42 (1.31 – 1.53)	175 (9)	3.7	4.22 (3.63 – 4.90)	2.76 (2.38 – 3.21)
Thoracic including pneumonia	53	11 (21)	8.0	1.14 (0.63 – 2.06)	0.93 (0.52 – 1.68)	<5 (<9)	2.9	3.40 (1.28 – 9.07)	3.09 (1.16 – 8.23)
Heart and vascular	31	6 (19)	7.3	1.04 (0.47 – 2.31)	0.78 (0.35 – 1.74)	0 (0)	0	Na	Na
Abdomen	165	59 (36)	16.1	2.27 (1.76 – 2.94)	1.71 (1.33 – 2.21)	17 (10)	4.6	5.22 (3.24 – 8.40)	3.68 (2.29 – 5.93)
Liver and biliary system	265	88 (33)	14.6	2.06 (1.67 – 2.94)	1.45 (1.18 – 1.79)	34 (13)	5.7	6.37 (4.55 – 8.92)	3.70 (2.64 – 5.19)
Urinary pathway	452	120 (27)	10.8	1.52 (1.27 – 1.82)	1.19 (1.00 – 1.42)	31 (7)	2.8	3.21 (2.25 – 4.56)	1.83 (1.28 – 2.60)
Skin, soft-tissue, and bone	82	28 (34)	14.5	2.05 (1.41 – 2.97)	1.72 (1.19 – 2.50)	5 (6)	2.6	2.94 (1.22 – 7.06)	2.27 (0.94 – 5.46)
IV-catheter	163	63 (39)	16.3	2.31 (1.80 – 2.95)	1.43 (1.12 – 1.83)	5 (3)	1.3	1.47 (0.61 – 3.53)	1.43 (0.59 – 3.43)
Miscellaneous[1]	33	7 (21)	7.9	1.12 (0.53 – 2.34)	1.80 (0.86 – 3.77)	0 (0)	0	Na	Na
Unknown	777	282 (36.3)	16.2	2.29 (2.03 – 2.57)	1.50 (1.33 – 1.68)	79 (10)	4.5	5.10 (4.09 – 6.37)	3.23 (2.58 – 4.03)

[1]Miscellaneous contains bacteraemia patients with following foci; oral (4), central nervous system (10), female genitalia (25), and transfusion or IV-misuse related (4).

[2]Adjustments were made for the following covariates: Sex, age groups (20-year intervals), number of previous admissions the past year (continuous), type of admission (‘surgical’ or ‘non-surgical’), urgency of admission (‘acute’ or ‘elective’) and predisposing conditions.

CHAPTER 5. DISCUSSION

The objective of this thesis was to cover knowledge gaps in the current literature on hospital-acquired bacteraemia. I accounted for the incidence of hospital-acquired bacteraemia in the North Denmark Region measured as the rate of infection according to hospital patient-days. I explored the role of hospital interventions as risk factors for developing hospital-acquired bacteraemia and applied various multi-state models to assess prognosis in terms of excess length of stay, death and readmission following hospital-acquired bacteraemia.

5.1. COMPARISON WITH OTHER STUDIES

Study I showed that central venous catheters and haemodialysis were the most likely intervention-related risk factors for hospital-acquired bacteraemia. Immunosuppression from medical treatment may play a role and, in general, there were associations between hospital-acquired bacteraemia and all the investigated interventions beside orthopaedic surgery, arterial catheters, and drains in the thoracic cavity, however these associations were weak and not statistically significant.

The association between hospital-acquired bacteraemia and central venous catheters have been described extensively in the literature.[72,80,81,88–90,92] Our study confirms this association with more recent data and underlines the importance on continued proper use of central venous catheters and discontinuation.

The study confirmed the association between haemodialysis and hospital-acquired bacteraemia, which may overlap with the use of central venous catheters.[40,80,85] However, we could not reproduce the association with urinary catheters that have been reported several times previously.[72,81,82] Two of the previous studies was conducted without any adjustment and may be subject to confounding,[72,82] whereas Yoshia et al found an association when comparing patients with culture positive hospital-acquired bacteraemia and culture negative patients. This may lead to different results as culture-negative patients may not resemble the uninfected patient.

Most previous studies have applied no or a statistical/stepwise approach to confounder selection, which currently are not the recommend approach. We made an a priori selection of confounders and sampled our controls using risk-set sampling, which allows for an interpretation odds ratio as an estimate of the underlying rate ratio, which might ease comparison with future studies.

Study II revealed a two percent annual increase in the incidence rate from 2006 through 2018. This confirm and extend the trend reported by Gubbels et al, while implementing nationwide surveillance in Denmark.[129] Accordingly, the incidence rate was slightly higher than those found previously by Søgaard et al within the same

region.[147] The incidence is comparable with the incidence found in a nationwide study from Finland.[43]

Study II is the first study to apply a multi-state approach on a population-based dataset to estimate the mortality associated with hospital-acquired bacteraemia. The study shows that mortality associated with hospital-acquired bacteraemia is high. Previous population-based studies have reported a high in-hospital mortality in patients with hospital-acquired bacteraemia ranging from 37-44% and a 28-day mortality from 16-39%. However, it is difficult to disentangle the impact of hospital-acquired bacteraemia on mortality from the effect of being hospitalised and at-risk of hospital-acquired bacteraemia. Two comparisons have been made using logistic regressions which revealed a non-significant association for in-hospital mortality[40] and an odds ratio of 1.41 (95% CI 1.34-1.47) for 30-day mortality,[103] respectively. However, these estimates may be affected by time-dependent bias.

Previous non-population-based studies have applied similar methods but are often limited to in-hospital mortality due to lack of follow-up after discharge.[148–150] The in-hospital mortality is affected by the difference in discharge rates between infected and uninfected, which leads to a lower estimated association between death and hospital-acquired bacteraemia. Comparatively, we estimated the 30-day mortality and conducted supplementary analyses of in-hospital mortality, discharge rates, and post-discharge mortality. This highlighted the difference between the two measures and revealed a low post-discharge mortality compared with in-hospital mortality, though post-discharge mortality remained higher in patients with hospital-acquired bacteraemia.

Study III provided estimates of the expected excess length of stay following hospital-acquired bacteraemia across all aetiologies and for specific sources of infection using a non-parametric approach. Previous studies have generally estimated the excess length of stay following hospital-acquired bacteraemia as the difference in mean or median length of stay, hindering a direct comparison of estimates. However, the current study provided estimates free of time-dependent bias while allowing for thorough analysis of covariates effect on excess length of stay.

Furthermore, in addition to excess length of stay and despite post-discharge mortality, hospital-acquired bacteraemia was also associated with an increase in readmission rates, which has not previously been shown in studies of the excess length of stay. This may contribute additionally to the economic burden of hospital-acquired bacteraemia.

5.2. METHODOLOGICAL CONSIDERATIONS

The present studies are subject to random and systematic error. All studies were observational studies aiming to imitate the results of a randomised clinical trial, which would have been unethical to conduct. Random error refers to the uncertainty of statistical estimates and natural occurring variability. While systematic errors stem from systematic errors in the study design and measurements. These are often categorised as selection bias, information bias, or confounding.[151]

5.2.1. SELECTION BIAS

Selection bias arises from differences in the probability of enrolment systematically affecting participation in the study leading to a difference between study population and the target population.[151] As the estimates are conditioned on participation in the studies, the estimates may be biased, hence, not generalisable to the target population. Depending on the literature, selection bias can also refer to a selection of control- or reference population, which may differ from the cases or exposed. This may lead to biased estimates that may be corrected through analysis, but only if the factors are measured.[151] When using this definition, the concept of selection bias and confounding tend to overlap.

As the present studies did not require informed consent and none of the exposures and outcomes were based on self-report, no selection bias due to self-selection or volunteering were introduced.

Study I featured a retrospective case-control study design with matched risk-set sampling. By nature of the study design, matched control sampling introduces selection bias, which may be corrected in the analysis. We sampled controls from the population at-risk, defined as adult patients admitted for ≥48 hours to Aalborg University Hospital. We matched on sex, age group and adjusted our analysis accordingly. Accepting the broader definition of selection bias, controls differed substantially in length of stay prior to enrolment. This may have led to biased estimates as length of stay is considered a risk factor both for interventions and hospital-acquired bacteraemia. This difference was expected, recorded, and included in the adjusted analysis following the a priori drafted statistical analysis plan. As patients might be under close surveillance following interventions or be in a severe condition it may lower the threshold for blood culturing, which may have led to a selection of cases who are more likely to have undergone interventions.

Study II featured two cohorts; an open cohort to estimate the incidence of hospital-acquired bacteraemia in hospitalised patients, and a closed cohort with 30 days follow-up from the date of admission for each patient. The study was population-based, and the population were based on the catchment area of the hospitals in the North Denmark Region. The healthcare system was tax-funded with a low barrier to entry. Follow-up

were based on registry data of high validity. No patients migrated and were lost to follow-up due to migration in the 30-day follow-up period.

Study III featured the same closed cohort used in study II to estimate the excess length of stay and the readmission rates of those who were discharged alive. It has the same limitations and strengths as study II regarding selection bias.

5.2.2. INFORMATION BIAS

Information biases arise from misclassification of exposure, outcome, or covariates used in the analyses: Confounders, modifiers, and mediators. Non-differential misclassification denotes misclassification that are independent of exposure status. The bias introduced from non-differential misclassification of dichotomous variables is predictable in direction; toward or beyond null. Conversely, differential misclassification differs depending on exposure or outcome status leading to a more unpredictable bias in both direction and magnitude.[151]

All three studies used positive cultures following certain criteria to identify patients as cases or exposed individuals. For a patient to have a positive blood culture, the venepuncture must be prescribed by a physician, most often due to symptoms of a severe or persistent infection. However, this may introduce a scenario in which patients with less severe episodes of hospital-acquired bacteraemia are undiagnosed and misclassified as being non-baceteraemic. Another possible scenario is that contraction of hospital-acquired bacteraemia may lead to such a severe condition that end-life care is considered. Thereby, blood cultures may be avoided due to lack of clinical significance. Both scenarios may be examples of differential misclassification and might lead to opposite directed bias of unknown magnitude. However, during hospital stay patients are monitored closely and biochemical markers of infections are frequently used and the threshold for venepuncture is generally low.

Study I relied on exposures being properly reported in the electronic medical records. We relied on both records from physicians and other healthcare personnel to ensure the best capture of possible interventions. However, patients with more complex hospitalisation or worse predicted prognosis may have more comprehensive records. Exposures was registered as dichotomous variables indicating whether the patient had received the given intervention at some time point between admission and enrolment. However, to which extent and for how long the intervention was applied were not recorded.

Study II examined mortality registered in the Danish Civil Registration System and **study III** examined excess length of stay and readmission registered in the Danish National Patient Register. Both registers have high validity with little risk of misclassification. Identification of predisposing conditions and comorbidity used for confounding adjustments relied on diagnosis codes registered in the Danish National

Patient Register. We applied a 5-year look back period to balance the risk of misclassification of past cancer episodes as having cancer while not missing conditions that are less frequently reported after initial treatment. While the validity of these diagnosis codes has proven high, it is not possible to rule out possible differential information bias stemming from this.

5.2.3. CONFOUNDING

Confounding arises in observational studies in which the exposed and unexposed differs on a factor that is related to the outcome, and consequently leading to estimation of an association that is based on this factor.[151] Almost all observational studies are subject to some confounding. However, if the confounding factor (confounder) is properly measured, it may be controlled through adjustment in the statistical analyses.[151]

In **Study I,** as previously mentioned in 'selection bias', the length of stay prior to enrolment in the study differed between cases and controls. This may have a direct effect on the probability of both exposure status (interventions) and outcome (hospital-acquired bacteraemia). We adjusted for length of stay along with other a priori defined possible confounders. However, as length of stay may have a complex relationship with both interventions and risk of infection our linear adjustment may not suffice. It may have been more appropriate to include time-at-risk in the analysis through time-to-event analysis. Using this approach in future analyses of risk factors for hospital-acquired bacteraemia would allow for time-varying exposures to better capture the length of the intervention. While possible founders were selected a priori, the limited sample size precluded extensive adjustment and our estimates could be affected by residual confounding.

Study II and III featured large population-based register cohorts and allowed for thorough adjustment of the estimates. However, unknown, unmeasured, or residual confounding are likely to remain. A limitation of both studies are the complexity and heterogeneity of hospital stays. Interventions are associated with both hospital-acquired bacteraemia and death and may therefore constitute a classical confounder. On the other hand, interventions may in nature be time-varying and be affected by the exposure. This relationship is not readily modelled using the approach applied in the current studies. Additionally, these interventions are not properly captured through the registers that were available for these studies.

Due to possible unmeasured and/or residual confounding that may remain in the studies and the chosen models, caution should be taken not to interpret the associations as casual effects.

5.2.4. TEMPORAL DYNAMICS

The current literature recommends careful consideration of the temporal dynamics of admission, infection, discharge, and death when studying hospital-acquired infections or complications. Studies of non-mortality outcomes should consider possible competing events that may lead to biased estimates of association. Studies of risk factors for disease is one kind of such studies. In **study I**, patients may experience two competing events to hospital-acquired bacteraemia: Discharge or death. The effect of hospital interventions on the probability of either discharge or death may lead to biased estimates of association with hospital-acquired bacteraemia. We did not properly consider this bias in **study I**, but it would require renewed data collection to correct this. For future studies, it we would be relevant to consider recording the time of admission, start and end of interventions, infection, discharge, and death.

In **study II and III,** we adopted a multi-state approach that inherently leads the investigator to consider the temporal dynamics more carefully. **Study II** adopted an illness-death model to properly account for the time-dependency of hospital-acquired infections to occur, while properly contributing the non-infected time to the reference population. Additionally, we adopted a 5-state model to better highlight the dynamics around infection, discharge, and mortality.

In **study III,** we took advantage of the multi-state approach to handle multiple competing outcomes of interest, i.e., discharge alive, all-cause end of stay, readmission, death before readmission, while still handling the time-dependency of the infection.

5.2.5. PRECISION

For all studies, we have chosen to report estimates with a significance level of 5% providing estimates with 95% confidence intervals. However, we have refrained from reporting non-statistically significant results as ‘no difference’ and rather as ‘associations of some level of uncertainty’. We found this distinction important, as significance is a measure of precision of estimate, and not a measure of whether the association is true or false.

The sample size of **study I** may not have provided sufficient power for all the tests carried out. Larger sample size was available for **study II and III** and allowed for thorough stratified analyses.

5.2.5.1 External validity

The current studies were conducted in a tax-funded healthcare system. Healthcare services are offered free of charge with a low barrier to entry through the general practitioners. The population-based design and complete follow-up may further

strengthen generalisability. However, generalisability to more restricted healthcare systems may be reduced, as patients, interventions and infection rates may differ. Incidence and aetiology may vary, and antimicrobial resistance should be considered.

CHAPTER 6. CLINICAL IMPLICATIONS AND PERSPECTIVES

The thesis highlights the challenges associated with hospital-acquired bacteraemia and extend the current literature by exploring hospital interventions as risk factors, and providing updated population-based estimates of incidence, associated mortality, excess length of stay, and rates of readmission using sophisticated statistical modelling to account the temporal dynamics surrounding this topic.

We found that hospital interventions, especially central venous catheters, and haemodialysis, may play a role as risk factors for hospital-acquired bacteraemia. While our study provided rough estimates of the association on the relative risk, the findings emphasize proper use of intravenous access including timely replacement and removal. The literature on use of central venous catheters is comprehensive with suggestion for the optimal choice of catheter, placement, technique, and timing. However, assuming compliance with best practises, our study suggests that there might still be room for improvement. More in-depth studies including adherence to guidelines, more granular exposure specification, and handling of temporal dynamics are needed to confirm central venous catheters along with other interventions as risk factors for hospital-acquired bacteraemia.

Hospital-acquired bacteraemia was associated with a 4-fold increase in 30-day mortality and pose a considerable concern during hospitalisation. While it is evident from previous studies that being hospitalised with hospital-acquired bacteraemia is associated with mortality, the current work suggest that the increased mortality is directly associated with the infection. The associated mortality for hospital-acquired bacteraemia ranged up to a 6-fold increase for episodes of unknown source. The explanation behind the stronger association is likely multifactorial. In some cases, the infection may be worsened by an occult focus inaccessible to antimicrobial treatment, while other episodes may occur in patients for which all treatment options have been exhausted, and further diagnostics are discontinued. These circumstances warrant further investigation of the diagnostics and treatment of patients with hospital-acquired bacteraemia of unknown origin. Comparatively, we found the highest mortality for hospital-acquired bacteraemia caused by fungi or enterococci. Both pathogen groups account for some of the episodes of unknown origin and may represent patients with severe conditions. Furthermore, they share a common trait, their insusceptibility to a broad range of anti-bacterial therapeutics. Most common species of enterococcal bacteraemia is Enterococcus faecalis and Enterococcus faecium, and while both species are resistant to most cephalosporins, E. faecium is generally non-susceptible to most beta-lactam antibiotics. This may limit coverage of commonly used empirical regimens. Studies of the adequacy of empirical

antimicrobial therapy and factors associated with the risk of fungal and enterococcal hospital-acquired bacteraemia may be of interest in future studies.

Despite the high mortality, patients may expect excess length of stay following an episode of hospital-acquired bacteraemia. This will lead to increased expenditure for the hospital, which may be a serious concern for the healthcare system, patient, and society depending on how the hospital stays are funded. Meanwhile, increased rates of readmission lead further economic burden, as it will lead to additional hospital days. This is a considerable concern and provide an economic incentive to initiate preventive initiatives and invest in infection control programs.

Overall, the cause of hospital-acquired bacteraemia is complex, and risk of infection should be considered in relation to interventions. The consequence of hospital-acquired acquired bacteraemia may be severe and pose an economic burden. This thesis emphasises the need for more research to prevent hospital-acquired bacteraemia and infections in general.

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