Socioeconomic Status and Bacteremia: Risk, Prognosis, and Treatment

PhD dissertation

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II. Koch K, Nørgaard M, Schønheyder HC, Thomsen RW, Søgaard M, for the Danish Collaborative Bacteremia Network (DACOBAN). Effect of socioeconomic status on mortality after bacteremia in working-age patients. A Danish population-based cohort study. *PLoS One, 2013; 8(7):e70082*.

III. Koch K, Schønheyder HC, Dalager-Pedersen M, Søgaard M, Thomsen RW, Nørgaard M. Relation between socioeconomic status and inappropriate empirical antimicrobial therapy in bacteremia patients. *[To be submitted]*

Contents

List of abbreviations

CAB	Community-acquired bacteremia
CI	Confidence interval
CRS	Civil Registration System
DACOBAN	Danish Collaborative Bacteremia Network
HR	Hazard rate ratio
IQR	Interquartile range
OR	Odds ratio
PR	Prevalence ratio
RR	Relative risk
SEP	Socioeconomic position
SES	Socioeconomic status

1. Introduction

"Medicine is a social science and politics is nothing else but medicine on a large scale. Medicine as a social science, as the science of human beings, has the obligation to point out problems and to attempt their theoretical solution; the politician, the practical anthropologist, must find the means for their actual solution. The physicians are the natural attorneys of the poor, and social problems fall to a large extent within their jurisdiction."

Rudolf Virchow, a German physician, pathologist, anthropologist and politician, who is considered to be one of the founding fathers of 'social medicine'. He believed that health and disease were products of a person's whole environment, from the cells in the body to the social setting of the person. In early spring 1848 he investigated a typhus outbreak in Upper Silesia and found a relationship between poor living conditions and contagion. In the report from the following year he emphasized the economic, social and cultural factors involved in its etiology and clearly identified the contradictory social forces that prevented any simple solution (1).

Ever since, Rudolf Virchow reported on the relationship between poor living conditions and typhus in 1848, it has been known that the burden of infectious diseases is not evenly distributed across society: most often persons of lower socioeconomic groups have increased risk of acquiring infectious diseases. This association between lower socioeconomic status (SES) and increased risk of infectious diseases may even exist in modern high-income countries with universal welfare systems (2). In addition to increased risk of infections, persons of lower SES may have a worse prognosis after acquiring an infection. The reasons for these socioeconomic differences in the risk of and prognosis after infectious diseases are poorly elucidated. Many different factors may work both independently and interactively to influence the risk and outcomes of infectious diseases in persons of lower SES. In addition, the factors that mediate disparities in infectious diseases have likely changed during the last century, and may be different when comparing low-income with high-income countries, and when comparing countries with publicly funded welfare systems with countries without such welfare systems. Furthermore, it is likely that many of these mediating factors are modifiable and amenable to change. Therefore, a better understanding of the underlying factors that have impact on socioeconomic disparities in risk and prognosis of severe bacterial infections is of importance in order to reduce such disparities.

Bacteremia is associated with considerable morbidity and mortality. It has recently been estimated that bacteremia accounts for more than 250.000 deaths each year in North America and Europe combined (3). This estimate has placed bacteremia among the top eight causes of death in Western populations (4). In addition, there has been an increase in the incidence rate of bacteremia during the last several decades and despite improved treatment strategies the average in-hospital or 30-day mortality from bacteremia remains as high as 15-25% in adults (5-7). Thus, identification of persons or groups at increased risk of bacteremia, and with a poor prognosis after acquiring bacteremia, together with an understanding of the contributing factors involved, remains important not only from a clinical perspective but also from a public health perspective.

In this thesis we therefore used population-based registries to investigate socioeconomic disparities in risk of community-acquired bacteremia, in the prognosis after bacteremia, and in the treatment of bacteremia in a country with a universal welfare system. We further examined several potential mediating factors that may explain these socioeconomic differences.

As an introduction, we will provide a definition of bacteremia and address the overall health burden of the diseases. The second section of the introduction describes the concept and measurement of socioeconomic status in health research. The third section reviews the existing literature on the association between SES and bacteremia. This section is followed by an overview of risk- and prognostic-factor for bacteremia and their association with SES. The last section describes antimicrobial therapy of bacteremia and provides an overview of risk factors for inappropriate antimicrobial therapy.

1.1. Introduction to bacteremia

Definition and classifications of bacteremia

Bacteremia is defined as the presence of viable bacteria in the bloodstream (8). By convention, fungemia (the presence of fungi in the bloodstream) is included in the collective term bacteremia. Microorganisms often enter the bloodstream as a severe complication of primarily localized infections (e.g. pneumonia or urinary tract infection), which represent a failure of the host defence to contain the infection. In this way, the presence of microorganisms in the bloodstream becomes an indicator of disseminated infection and, as such, generally indicates a poorer prognosis than that associated with localized infections. However, microorganisms may also be transiently introduced into the bloodstream, e.g. through breaks in mucosal membranes, which may or may not lead to clinical symptoms. In the clinical context, bacteremia can therefore be defined as detection of bacteria or fungi in the bloodstream, usually by growth in blood cultures, which are considered of etiological significance based on clinical and microbiological assessment (8;9). This definition implies that blood culture contamination has been ruled out. Microorganisms that are usually considered to be contaminants include coagulase-negative staphylococci, *Corynebacterium* spp., *Bacillus* spp. and *Propionibacterium acnes* unless isolated from two or more separate blood culture sets within a short time frame (10).

Bacteremia can be classified according to the causative microbial agent, the focus of infection, and the place of acquisition. Based on the similarity of the isolated microbial agents, bacteremias are usually categorized into those caused by gram-positive, gram-negative, fungal, or anaerobic microorganisms. Furthermore, polymicrobial bacteremia (more than one microbial agent) is distinguished from monomicrobial bacteremia (one microbial agent), as polymicrobial bacteremia is associated with a poor prognosis and because the etiologic agent(s) can be difficult to determine. The causative microbial agents are closely associated with the primary focus of infection. For example, monomicrobial bacteremia with *Escherichia coli* often originate from the urinary tract, while bacteremia with *Streptococcus pneumoniae* commonly has a primary focus in the respiratory tract. In bacteremia patients the most frequent foci of infection include the urinary tract, the respiratory tract, the abdomen, and the skin, bones, and joints. The focus of infection is normally assessed on the combination of microbiological and clinical findings (9).

In reference to the place of acquisition, bacteremia can be classified as either community-acquired (CAB) or nosocomial (arise in a hospital setting), as originally described by Centers for Disease Control and Prevention, US (11). A hospital stay greater than 48 hours is commonly used as a cut-off criterion to distinguish community-acquired bacteremia from nosocomial bacteremia. Thus, bacteremia episodes that are not incubating at the time of admission and occur more than 48 hours after admission to hospital are considered to be nosocomial. In contrast, bacteremia episodes that are present or incubating within 48 hours after hospital admission are considered to be acquired in the community (8;12;13). Others have not used a fixed time limit (e.g., 48 hours) to define community-acquired and nosocomial bacteremias (14). In this case the distinction between community-acquired and nosocomial bacteremias is based on all available clinical information, as has been suggested by Leibovici et al. (15). A third classification with reference to the place of acquisition of bacteremia has been described by Friedman et al. (16). This 'health care-related' group include bacteremia patients with recent contact with the health care system, usually defined as patients with a hospital stay within 30 days prior to admission or who have regular hospital visits (e.g., for hemodialysis or chemotherapy) (14;17).

As shown in Figure 1.1, the distribution of isolated microbial agents in bacteremia patients has changed little in Denmark during the last decades. However, the overall proportion of gram-negative bacteremias increased slightly from 1992 to 2006, while the proportion of gram-positive bacteremias decreased (5). The figure also shows that among community-acquired bacteremias the most commonly isolated microbial agents are *E. coli*, followed by *S. pneumoniae* and *Staphylococcus aureus*. This rank order of the three most commonly isolated microbial agents in community-acquired bacteremias are strikingly consistent in studies from other Western countries (6;18;19). In Denmark *E. coli* is also the most commonly isolated microbial agent in nosocomial and health-care related bacteremia, similar to community-acquired bacteremia; which is followed by other enterobacteria and *S. aureus* (5).

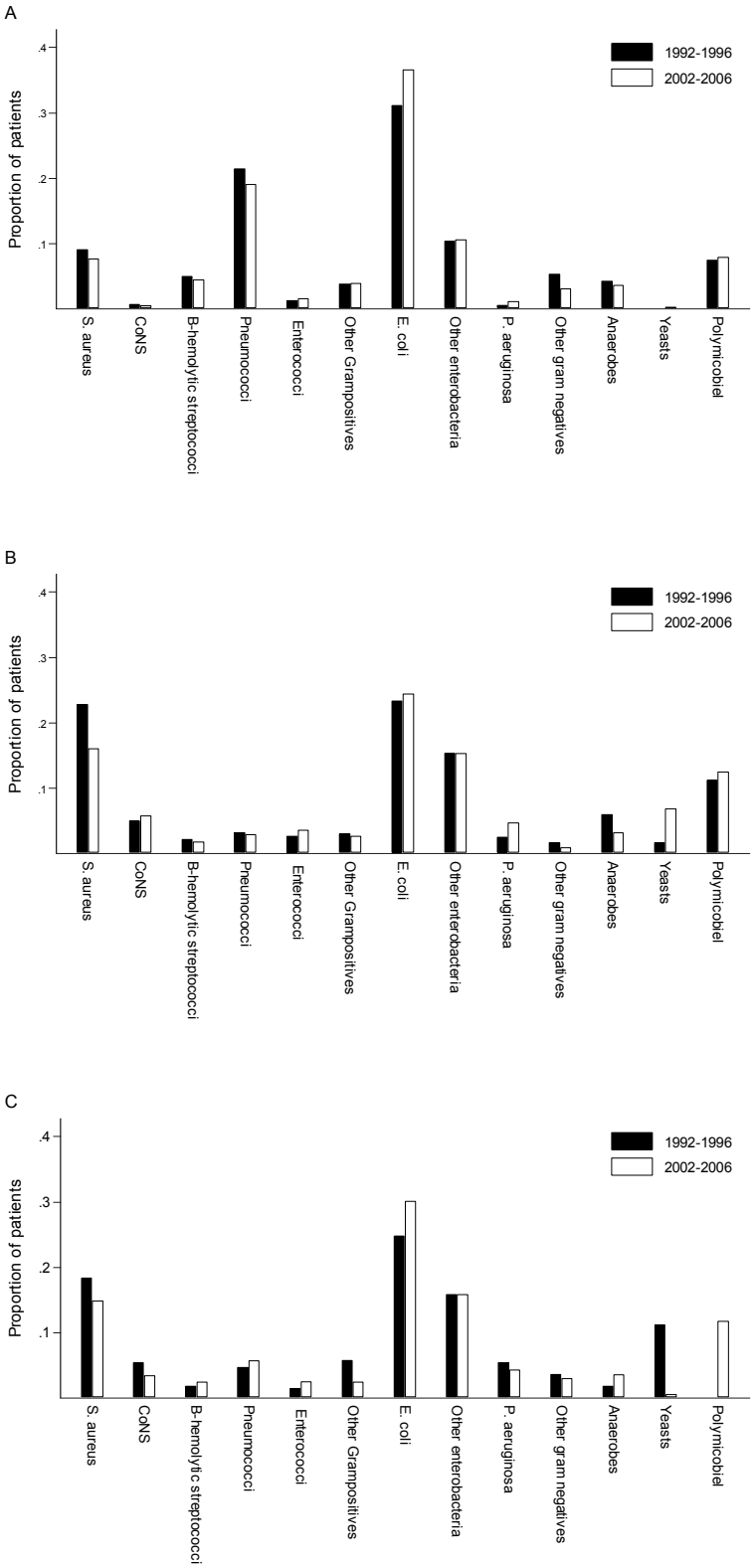


Figure 1.1. Distribution of microbial agents for (A) community-acquired bacteremia, (B) nosocomial bacteremia, and (C) health care-associated bacteremia by study period (1992-1996 [3327 bacteremia episodes] or 2002-2006 [4946 bacteremia episodes]). With permission from Søgaard et al.(5)

Bacteremia is closely related to the clinical syndrome termed sepsis. Sepsis is a multifaceted and dynamic systemic response to an infectious process. By definition, sepsis is characterized by a range of clinical and paraclinical criteria including the presence of fever or hypothermia, tachycardia, tachypnea, and leukocytosis or leukopenia, among others (20;21). Sepsis may progress over time to severe sepsis, i.e. sepsis with organ dysfunction or hypoperfusion, and eventually to septic shock (22;23). According to the latest international sepsis definition a patient with a suspected infection will fulfil the criteria for sepsis (20). Thus, infections do not need to be microbiologically confirmed or otherwise documented. Previous studies have documented bacteremia in no more than 50% of patients with sepsis (21;24). However, a higher probability of positive blood cultures is seen in patients with severe sepsis (~25%) and septic shock (~70%) than in patients with sepsis (~15%)(24-26). In contrast, the majority of patients with bacteremia will fulfil the criteria of sepsis and between 7% and 24% of bacteremia patients are reported to have septic shock (26-30).

The overall health burden of bacteremia

Bacteremia is associated with a substantial burden for patients, clinicians, the healthcare system, and society. Recent estimates of the overall incidence rate in Western populations remains above 100 per 100,000 person-years and the 30-day mortality averages 15-25% (4-7;31). Bacteremia is also associated with severe complications of which some are long-lasting or permanent (e.g. cardiovascular disease and renal failure) (32;33). Physical and psychological stress in hospitalized patients with bacteremia may carry on after discharge, leading to prolonged sick leave or permanent disability (34;35). These poor health outcomes after bacteremia are associated with a high economic burden for both the individual patient and society. Previous studies have reported that the indirect economic costs of sepsis and bacteremia (productivity loss due to mortality, temporary and permanent morbidity) may outweigh the direct costs (medical expenses during hospitalisation) by as much as two-fold (36;37).

It has been proposed that the best way of defining the epidemiology of bacteremia is in a population-based study design (31;38). Population-based studies intend to capture all cases of bacteremia occurring in residents in a well-defined geographic area within a given time period (39). In these studies, selection bias is minimized and the population at risk is known, which allows incidence rates to be determined and thereby the overall burden of the disease. Standardizing the

incidence rates against a reference population allows comparison between different regions and time periods. However, most previous studies on the epidemiology of bacteremia stem from selected patients in a given clinic, emergency department or hospitals with the risk of significant selection bias. Furthermore, many studies have not distinguished between first episodes and later episodes making it difficult to calculate the incidence rate.

The first population-based study of bacteremia incidence rates was conducted in the defined population of Charleston County, South Carolina, USA (approximately 250,000 inhabitants) in the period from 1974 to 1976 (40). In this study the authors reported an overall incidence rate of 80 per 100,000 person-years. Of the 291 cases of bacteremia identified in the study, 62.2% (181/291; 42 per 100,000 person-years) were classified as community-acquired, 28.5% (83/291; 31 per 100,000 person-years) were classified as nosocomial, and 9.3% (27/291) cases were not classified.
More recent population-based studies have reported higher bacteremia incidence rates of 159 per 100,000 person-years in Finland (approximately 5.2 million inhabitants) during 2004-07, 189 per 100,000 person-years in Olmsted County, Minnesota, USA (124,277 inhabitants) during 2003–05, and 189 per 100,000 person-years in England (51 million inhabitants) during 2008 (6;7;41).

In addition to the high incidence rates of bacteremia reported in recent population-based studies, Søgaard et al. reported an increase in the incidence over time in Northern Denmark. The authors found a 46% increase in the overall age- and sex-standardized incidence rate of bacteremia, from 114 incident bacteremia cases per 100,000 person-years in 1992 to 166 per 100,000 person-years in 2006 (5). Of the 14,303 episodes of bacteremia identified from 1992 to 2006, 47.4% were first-time episodes of community-acquired bacteremia, 36.9% were first-time episodes of nosocomial bacteremia and 15.8% were first-time episodes of health care-associated bacteremia. There was a significant change over time in incidence rates according to place of acquisition with the largest increase in the incidence rate of health care-associated bacteremia (Figure 1.2). The authors also examined changes in 30-day mortality rates over the study period and found an increase in the absolute number of patients who died within 30 days after a bacteremia diagnosis, but a decrease in the adjusted relative mortality.

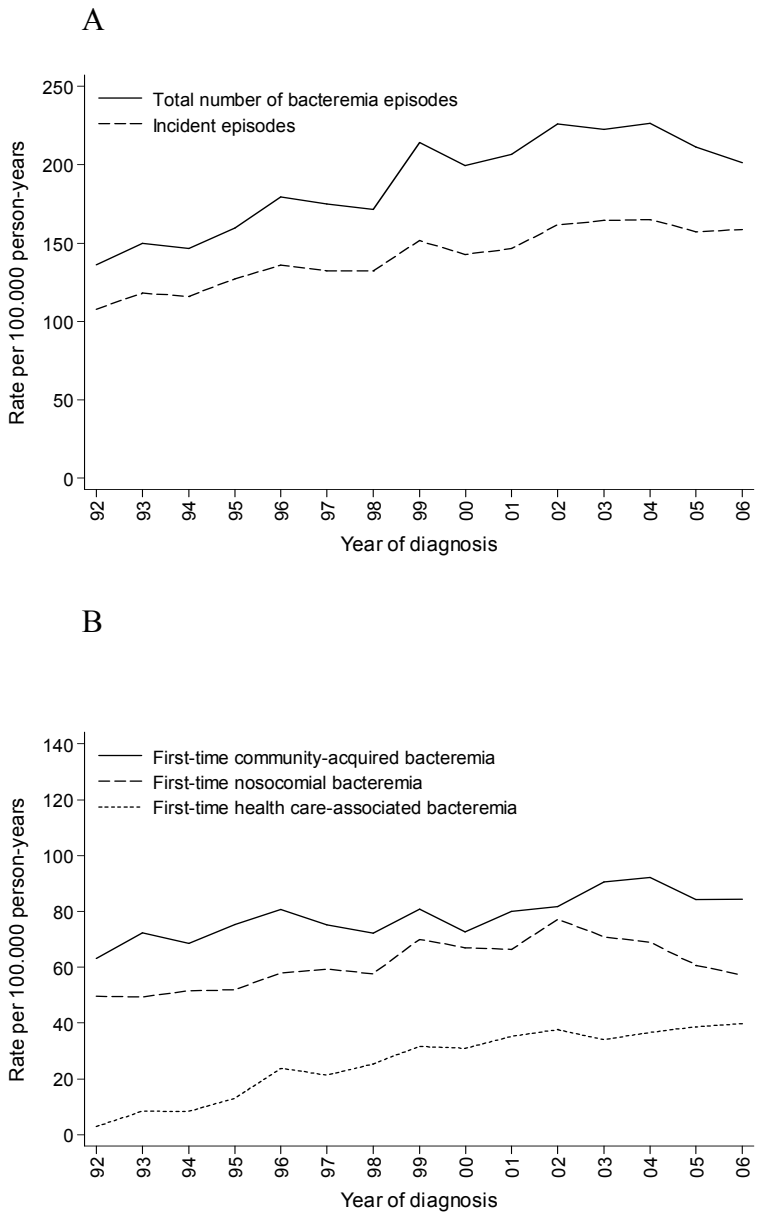


Figure 1.2. Age- and sex-standardized overall rates of bacteremia (A) and incidence by place of acquisition (B). With permission from Søgaard et al.(5)

The incidence of bacteremia increases with advancing age. More than 60% of the patients with first-time bacteremia are aged 65 years or older (5-7). This higher incidence in the elderly may be partly explained by a greater burden of chronic diseases in these age-groups (42). In addition, the increase in incidence of bacteremia is also most pronounced in patients above 65 years (43). Thus, the overall increase in bacteremia incidence may, in part, be due to population aging and increased longevity of patients with chronic diseases. However, the incidence has also increased over time in patients younger than 65 years, and other factors must therefore contribute to the increasing incidence. These factors may include an increase in the prevalence of patients receiving

chemotherapy and immunosuppressive treatment, and the increase in invasive medical procedures performed, which are known risk factors for bacteremia (44). Other contributing factors that must be taken into account include the improvement in blood culture systems and media, changes in the indications for ordering blood cultures, and recognition of an optimal blood volume for detection of microorganisms (45-47).

1.2. Socioeconomic status – concept and measurement in health research

Social stratification according to socioeconomic conditions has been described in numerous ways. The many different terms used (social class, social stratification, social status, etc.) reflect both the complexity of conceptualizing and measuring socioeconomic stratification in a given society as well as different theoretical orientations. Throughout this thesis, we use the common term 'socioeconomic status' (SES) to conceptualize "the economic and sociological factors that influence what positions individuals or groups hold within society"(48).

The different approaches to measure SES in previous health research generally reflect the orientations of the two major social theorists, Max Weber and Karl Marx (48;49). The Marxist approach, describes SES as entirely determined by 'social class', where individuals are defined by their relation to the 'means of production'. Groups are characterized by their place in the production process and by the opposing interests of exploited workers and exploiting owners who control the means of production. Marx described this relation as purely structural and locked in inevitable conflict. The Marxist approach highlights that these structural relations are exogenous to an individual (one may find oneself accidentally by birth or other exigencies in different social classes) and affect the 'life chances' of an individual.
In contrast, the Weberian approach suggests that hierarchically stratifications in a society are based on many dimensions (not only by social class). Individuals of different groups that are created in a hierarchically stratified society share a common status and life possibilities. 'Life chances' are actively created by the individual. The Weberian approach has tended to use objective measures of SES such as income or education (50). Thus, Weber's theories on social stratification are behind the use of multiple markers such as education, occupation, and income as measures of these dimensions.

Various markers have been used in health research to classify individuals according to SES. Krieger et al. have described the markers with reference to both the level and the time at which they are measured (51). From a level perspective, the different markers of SES can be categorized into individual-level, household-level and neighbourhood-level markers (52). While individual-level markers measure some types of individual resource or asset, household-level markers try to capture resources available at the household level. Area-level markers are used when the object of analysis is a geographical area. The area-level markers of SES are usually obtained by aggregating data such as proportion with higher education, proportion of unemployed, or the average income at the area level (identified by census tracts or zip/post codes). Area-based indices of deprivation which are composite measures at the area-level that combine different individual-level markers (unemployment rate, overcrowding, car ownership etc.), are also widely used (53). When individual-level measures of SES are not available, area-level SES markers may be used as proxies for individual-level SES. In this case the area-level SES marker is merely a proxy for a missing individual-level measure and used without the purpose of measuring a contextual effect on health outcomes (54). From a time perspective, the different markers can be classified according to the stage of the life course to which they refer. Figure 3 shows the different individual-level measures of SES across the life course. Parental education and occupation, household conditions in childhood, and educational attainment in young adulthood are markers of SES in early life, whereas, assets and wealth are measures of socioeconomic conditions during retirement.

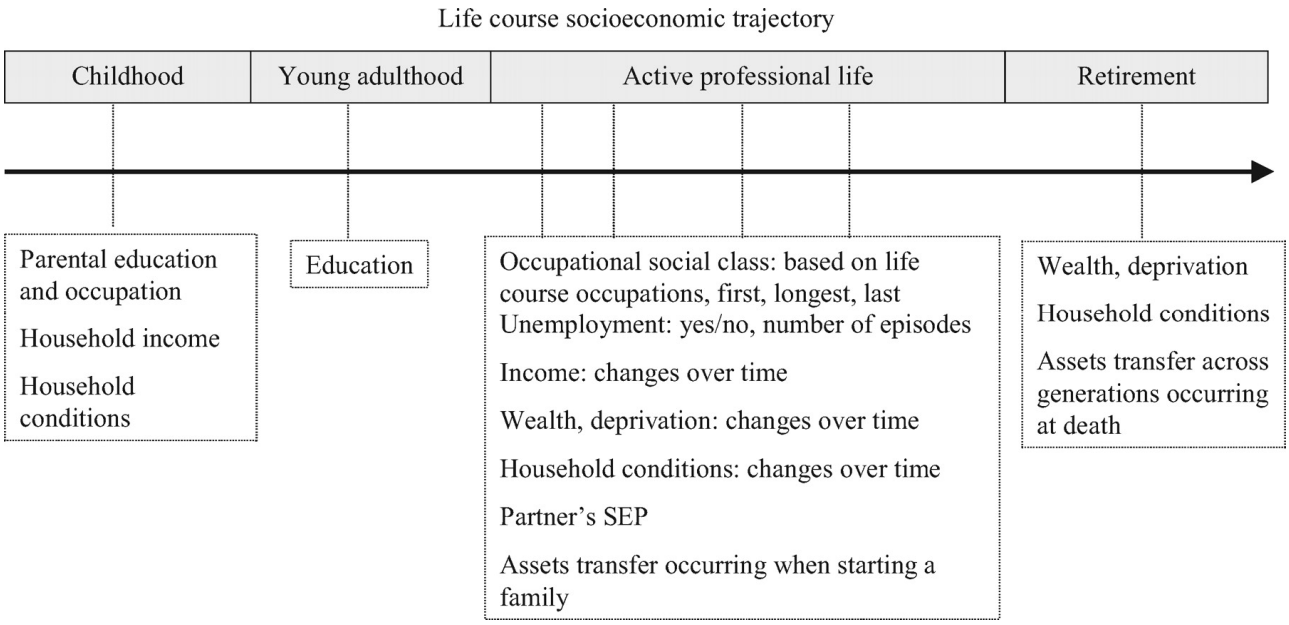


Figure 1.3. Examples of markers of socioeconomic status over the life course (Galobardes et al.)(54).

Galobardes et al. have proposed using different individual-level markers of SES within in a life course framework to better capture variations in the association between SES and specific health outcomes (54). In this thesis, we use individual-level information on education and income as measures of SES. In a life course framework, although related, these two markers of SES capture different aspects of socioeconomic stratification. The different aspects of socioeconomic stratification they measure, as well as their strengths and limitations, are reviewed below.

Education

Education is a widely used marker of SES in health-related epidemiological research and is thought to measure the knowledge-related assets of a person (48;49). As a marker of SES it has several strengths compared with other markers. Formal education is normally completed in young adulthood and will usually be fixed thereafter. It is therefore unlikely that poor health in adulthood will influence educational achievements. This makes education less sensitive to 'reverse causation', i.e. that poor health determines SES, which makes it a favorable marker of SES in causal models. Furthermore, as education has little fluctuation and is strongly influenced by parental characteristics, it will to some extent measure early life SES (54;55).
Although education has strengths, it also has some limitations. Bias may be introduced by birth cohort effect. Through time there has been an overall improvement in educational attainment, and older cohorts may therefore be over-represented among those categorized with low educational attainment. The meaning of education as a marker of SES may also differ for specific subgroups (56). For example, for many health outcomes the association to educational level is weaker for women than for men. This pattern may, however, have changed since there have been considerable improvements in educational achievements among women over recent decades. These cohort effects may be examined in analyses stratified by sex and age groups. Finally, although poor health in adulthood cannot influence education achieved before adulthood, poor health in childhood may influence educational attainment and predispose to adult disease, generating 'health selection' (52).

Income

Income is thought to influence health through a direct effect on material resources and it is the SES marker that most directly measure material living standards. It is a useful measure of SES in

individuals of working-age, if the aim is merely to examine if a socioeconomic gradient exists for a particular outcome. However, income as a measure of SES has certain limitations that should be considered. For example, income may not be an ideal measure of SES for young and older individuals as income are normally low in these age groups (52;57). Therefore, the interpretation of income as a measure of SES is undoubtedly most clear for individuals during their primary earning years. In contrast to education, income can change on a short term basis and may fluctuate considerably during an individual's primary earning years. Furthermore, lower income may reflect the influence of health status, generating 'reverse causality' (58;59).

1.3. Socioeconomic status and bacteremia

Previously published articles on the association between SES and bacteremia were located through PubMed MEDLINE searches. As sepsis is closely related to bacteremia, we also included "sepsis" in our search. Articles on bacteremia and sepsis were identified with the medical subject heading terms "bacteremia" and "sepsis", combined with the free text word-combinations "bacteremia", "bacteraemia", "bloodstream infections", "bloodstream infection", "blood stream infections", "blood stream infection", "septicemia", "septicaemia", or "sepsis", to account for different spelling variations of the terms, as previously suggested by Søgaard et al. (60). By this search strategy we identified 143,968 articles on bacteremia or sepsis. We conducted another PubMed search for articles related to SES with the following medical subject heading terms: "socioeconomic factors", "social class", "poverty", "marital status", "social support", "social conditions", "income", "educational status", "occupations", "employment", "residence characteristics", or "housing", combined with similar free text word-combinations as well as "socioeconomic status" and "socioeconomic position". Some of these search terms have previously been used by Cohen et al. to identify articles on 'social epidemiology' (61). This search strategy returned 504,646 articles. Race and ethnicity may also be measures of social stratification in a society and related to SES. However, we did not include the terms "race" and "ethnicity" in our search strategy since the assessment of racial and ethnic disparities was beyond the scope of this thesis.

Combining the queries retrieved 828 articles. A review of abstracts revealed that only very few studies were related to both SES and bacteremia or sepsis. However, the combined set of articles did include some studies that examined socioeconomic difference in the risk of bacteremia or sepsis, as well as studies that examined socioeconomic differences in the prognosis after bacteremia

or sepsis. Some articles examined both risk and prognosis. We reviewed studies that were written in English, those that included adults, and those that were conducted in Western countries. Furthermore, we searched the references of relevant articles.

Table 1.1 summarizes studies that examined the association between measures of SES and the risk of bacteremia or sepsis. As appears the existing literature is sparse and based on different measures of SES. Three studies used area-based measures to proxy persons' SES (62-64). Their results may be biased by their use of an aggregate area-based measure of SES, which may have caused inaccuracy due to misclassification of individual SES. One study used marital status as measure of exposure and two studies used self-reported information on educational level and income (65-67). One of the studies that used self-reported information on educational level and income was hampered by a high percentage of nonresponders to questions on education (54% missing) and income (67% missing) (66). Furthermore, of the four studies that examined SES and risk of bacteremia, three were confined to selected bacteremia types, including *S. aureus* bacteremia, and bacteremic pneumonia with *S. pneumoniae*, *Haemophilus influenzae*, group A streptococci, or group B streptococci (62;63;66).

Although the previous studies may have limitations they reveal a relatively consistent pattern of an inverse association between SES and risk of sepsis or specific types of bacteremia. However, it still remains uncertain if the increased risk of bacteremia among persons of lower SES exist for all types of infective agents or if the increased risk only pertains to specific agents. In addition, most of the previous studies were conducted in the United States (63;65;66) and only one study was conducted within a country with a universal welfare system (New Zealand) (62). Thus, there is a lack of population-based studies, conducted within countries with universal welfare, using valid individual-level measures of SES to examine the association between SES and the risk of severe bacterial infection. Furthermore, none of the previous studies have evaluated which factors contribute to the socioeconomic variations in the risk for bacteremia or sepsis. An understanding of the underlying factors that influence socioeconomic disparities in severe bacterial infections is needed to better direct prevention efforts.

Table 1.1 Prior studies on SES and risk of bacteremia or sepsis

Authors	Country	Study period	Study design	Study population (Setting)	Age group	Type of infection	Measures of SES	Outcome	Adjustement	Risk estimate (unadjusted)		Risk estimate (adjusted)
Flory et al. (66) 2009	US	2002-2004	Case-control study	609 patients hospitalized in five county regions in Southeastern Pennsylvania. Controls: 5% sample of adults from the population	≥18 years old	Bacteremic pneumococcal pneumonia	Self-reported information on education and annual income obtained by telephone interviews	Hospitalization for community-acquired bacteremic pneumococcal pneumonia	Age, sex, race, and annual income or education	Education College graduate Some college High-school graduate No high-school diploma Annual income ≥$50,000 $25,000-$49,999 $12,000-$24,999 $6000-$11,999 0-$5999	 1.0 (reference) 1.1 (0.7-1.5) 1.5 (1.1-2.1) 2.7 (2.0-3.7) 1.0 (reference) 2.3 (1.8-3.2) 4.0 (2.9-5.9) 6.7 (4.9-11.0) 10.5 (6.5-15.0)	 1.0 (reference) 0.7 (0.5-1.1) 0.6 (0.4-0.8) 0.7 (0.5-1.1) 1.0 (reference) 2.1 (1.4-3.2) 3.1 (1.7-5.7) 6.0 (3.7-9.6) 11.5 (7.4-18.1)
Seymour et al. (65) 2010	US	2006	Population-based cohort study	37,524 sepsis patients hospitalized in New Jersey	≥20 years old	Sepsis	Marital status	Hospitalization for sepsis	Age, sex, and race/ethnicity	Married Widowed Single Legally separated	Unadjusted estimates not given	1.00 (reference) 1.4 (1.2-1.6) 3.5 (3.1-3.9) 1.5 (1.2-1.8)
Huggan et al. (62) 2010	New Zealand	1998-2006	Population-based cohort study	779 patients hospitalized in the Canterbury District (app. 478,000 inhabitants)	0-98 years old (median age 64 y)	*Staphylococcus aureus* bacteremia	Address-based measure of deprivation (New Zealand Deprivation Index Deciles)	Hospitalization for *Staphylococcus aureus* bacteremia	Age and sex	9-10 (most deprived) 7-8 5-6 3-4 1-2 (least deprived)	1.00 (reference) 1.20 (0.92-1.57) 1.30 (1.00-1.70) 0.98 (0.75-1.28) 0.75 (0.57-1.0)	1.00 (reference) 1.08 (0.82-1.41) 1.13 (0.86-1.47) 0.88 (0.67-1.15) 0.74 (0.56-0.98)
Burton et al. (63) 2010	US	2003-2004	Cohort study	4870 patients hospitalized in 9 US states (Connecticut, Minnesota, California, Colorado, Georgia, Maryland, New York, Oregon, and Tennessee – 8.7% of the US adult population)	≥18 years old	Bacteremic pneumonia with *Streptococcus pneumoniae*, *Haemophilus influenzae*, group A streptococci, or group B streptococci	Area-based socioeconomic measures: percentage of census tract poverty (percentage of persons living below the federal poverty cut-off, median income at the census tract level, Townsend index (composite measure of deprivation)	Hospitalization for community-acquired bacteremic pneumonia	Age, race/ethnicity, surveillance site	Percentage of census tract poverty <5% 5%-9.9% 10%-19.9% ≥20% Median income Lowest quintile Second quintile Third quintile Fourth quintile Highest quintile Townsend index Lowest quintile Second quintile Third quintile Fourth quintile Highest quintile	 Unadjusted estimates not given	 1.00 (reference) 1.17 (1.07-1.27) 1.45 (1.32-1.58) 2.39 (2.16-2.64) 2.45 (2.19-2.74) 1.67 (1.49-1.86) 1.50 (1.34-1.67) 1.27 (1.14-1.41) 1.00 (reference) 1.00 (reference) 1.15 (1.03-1.29) 1.25 (1.12-1.40) 1.50 (1.34-1.67) 2.17 (1.94-2.43)

Table 1.1 Continued (Prior studies on SES and risk of bacteremia or sepsis)

Authors	Country	Study period	Study design	Study population (Setting)	Age group	Type of infection	Measures of SES	Outcome	Adjustement	Risk estimate (unadjusted)		Risk estimate (adjusted)
Mendu et al. (64) 2012	US	1997-2007	Hospital-based case-control study	Intensive care units at two academic teaching hospitals in Boston, Massachusetts. Cases: 2,435 bacteremia patients. Controls: 12,162 blood culture-negative patients	18-100 years old	Bacteremia	Neighborhood poverty rate (percent of residents with income below the federal poverty level cut-off)	Presence of bacteremia 48 hrs before critical care initiation or 48 hrs subsequent to critical care initiation	Age, sex, race, patient type (medical or surgical), Deyo-Charlson Index, (comorbidity score), parenteral nutrition, hematocrit, white blood count, creatinine, and blood urea nitrogen	<5% 5%-10% 10%-20% 20%-40% >40%	1.00 (reference) 0.97 (0.87-1.08) 1.00 (0.89-1.13) 1.21 (1.05-1.40) 1.39 (0.99-1.95)	1.00 (reference) 0.98 (0.88-1.09) 1.02 (0.90-1.16) 1.26 (1.09-1.47) 1.49 (1.05-2.11)
Wang et al. (67) 2012	US	2003-2011	Cohort study	975 sepsis patients identified in the REGARDS cohort study (30,239 individuals), hospitalized across the US (mainly in the Southeastern US, including North Carolina, South Carolina, Georgia, Tennessee, Mississippi, Alabama, Louisiana, and Arkansas)	≥45 years old	Sepsis	Self-reported information on education and income obtained by telephone interviews	Hospitalization with incident sepsis event	None	<u>Education</u> College or higher Some college High school graduate Less than high school <u>Income</u> <$20,000 $20,000-$34,000 $35,000-$74,000 ≥$75,000 Refused	 1.00 (reference) 1.41 (1.19-1.67) 1.52 (1.28-1.80) 1.88 (1.54-2.29) 1.78 (1.49-2.13) 1.41 (1.19-1.67) 1.00 (reference) 0.77 (0.61-0.96) 1.07 (0.85-1.35)	Adjusted estimates not given

Table 1.2 summarizes the studies that have examined the association between measures of SES and mortality after bacteremia or sepsis. To our knowledge, the existing literature is limited to only three studies. Two studies used an area-based measure of individuals' SES (62;64) and one study used marital status as measure of exposure (65). Groups of patients with different type of infections including *S. aureus* bacteremia patients (62), bacteremia patients (all bacteremia types) (64), and patients with sepsis have been studied (65). The outcome measures have included 30-day all-cause mortality and in-hospital mortality. The three previous studies have reached conflicting conclusions. In a cohort study of 37,524 hospitalizations for sepsis, Seymour et al. concluded that, compared with married patients, widowed, single, and legally separated patients had greater odds of in-hospital death (65). In contrast, Huggan et al. concluded that there was no relationship between an address-based measure of deprivation and mortality in a study of 779 *S. aureus* bacteremia patients, but did not present any estimates (62). The third study by Mendu et al. of 2,435 bacteremia patients admitted to intensive care units concluded that neighborhood poverty was not associated with mortality after bacteremia. However, the authors did report an unadjusted relationship between neighborhood poverty rate and 30-day mortality after bacteremia (64).

The previous studies have all aimed to assess whether SES is an independent prognostic factor for survival after bacteremia or sepsis, i.e. independent of other known prognostic factors. Equally important is to elucidate the intermediary factors which link SES to poor prognosis after severe bacterial infection, if disparities in prognosis after bacteremia exist. Thus, it is important to disentangle the intermediary/or mediating factors that contribute to disparities in prognosis, and to differentiate these factors into those operating prior to the bacteremia episode from those operating during or following the episode. A better understanding of the factors that mediate disparities in the prognosis after bacteremia may help facilitate interventions to reduce prognostic differences.

Table 1.2 Prior studies on SES and prognosis after bacteremia or sepsis

Authors	Country	Study period	Study design	Study population (Setting)	Age group	Type of infection	Measures of SES	Outcome	Adjustement	Risk estimate (unadjusted)		Risk estimate (adjusted)
Seymour et al. (65) 2010	US	2006	Cohort study	37,524 patients hospitalized in New Jersey	≥20 years old	Sepsis	Marital status	In-hospital mortality	Age, sex, race/ethnicity, urbanicity, area-based measure of median income, Medicaid payer status, comorbidity, readmission, source of sepsis, presence of organ dysfunction, and type of pathogen	<u>Men</u> Married Divorced Widowed Single Legally separated <u>Women</u> Married Divorced Widowed Single Legally separated	 1.00 (reference) 1.02 (0.88-1.18) 1.29 (1.17-1.42) 0.78 (0.73-0.85) 0.89 (0.68-1.17) 0.86 (0.80-0.95) 0.84 (0.79-0.93) 1.38 (1.28-1.50) 0.98 (0.88-1.09) 0.81 (0.63-1.05)	 1.00 (reference) 1.19 (1.03-1.40) 1.00 (0.91-1.10) 1.13 (1.03-1.24) 1.13 (0.86-1.50) 0.95 (0.87-1.03) 0.90 (0.74-1.09) 1.00 (0.93-1.08) 1.16 (1.03-1.30) 0.96 (0.73-1.26)
Huggan et al. (62) 2010	New Zealand	1998-2006	Cohort study	779 patients hospitalized in the Canterbury District	0-98 years old (median age 64 y)	*Staphylococcus aureus* bacteremia	Address-based measure of deprivation (New Zealand Deprivation Index Deciles)	30-day all-cause mortality	Age and sex	No association between address-based measure of deprivation and mortality, estimates not given.		
Mendu et al. (64) 2012	US	1997-2007	Hospital-based cohort study	2,435 ICU patients at two academic teaching hospitals in Boston, Massachusetts	18-100 years old (mean age 62 y)	Bacteremia	Neighborhood poverty rate (percent of residents with income below the federal poverty level cut-off)	30-day cumulative all-cause mortality	Age, sex, race, patient type (medical or surgical), Deyo-Charlson Index, (comorbidity score), presence of sepsis, parenteral nutrition, hematocrit, white blood count, creatinine, and blood urea nitrogen	<5% 5%-10% 10%-20% 20%-40% >40%	1.00 (reference) 0.99 (0.91-1.09) 0.90 (0.81-1.00) 0.87 (0.76-0.99) 0.72 (0.50-1.02)	1.00 (reference) 0.98 (0.89-1.08) 0.89 (0.80-1.00) 0.93 (0.81-1.08) 0.80 (0.55-1.15)

1.4. Risk factors for community-acquired bacteremia

A risk factor for bacteremia may be defined as a characteristic of a patient or an exposure that is associated with an increased risk of acquiring bacteremia (68). Many different factors have been associated with increased risk for severe bacterial infection, including bacteremia. These risk factors may work at different levels (the individual- or community-level), and they may work both independently and interactively to influence the risk of infections in individuals. Individual-level risk factors for bacteremia and sepsis include age, gender, race/ethnicity and genetic factors. Previous studies have shown that older persons, men and African-Americans and other non-whites have higher incidence of sepsis (69-71). It has also been documented that mutations of genes involved in the innate immune system may increase risk for bacteremia and sepsis (72-74). Furthermore, it has been suggested that genetic variations between men and women, and between races influence host immunological response and in part explain the risk differences for severe infection according to race/ethnicity and gender. For example, polymorphisms in lipopolysaccharide-binding protein and tumor necrosis factor-β have been associated with increased risk of sepsis in men (75-77).

It is clear that that these risk factors (age, gender, race/ethnicity, and genetic factors) are fixed and that little can be done to change them. Other risk factors for severe bacterial infection, operating at both the individual- and community-level, are amenable to change. These factors range from individual behavioral factors, such as smoking, substance abuse, and hygienic practices to living and working conditions, and environmental exposures. For example, Nuorti et al. found that otherwise healthy smokers were four times as likely to be hospitalized with invasive pneumococcal disease than non-smokers, after adjustment for age, study site, male sex, black race, chronic illness, low level of education, and living with young children who were in day care (odds ratio (OR) = 4.1; 95% confidence interval (CI): 2.4-7.3) (78). In the same study, the authors also found that exposure to environmental tobacco smoke was associated with increased risk of invasive pneumococcal disease (passive smoking among nonsmokers vs. non-smokers/no passive exposure to smoke: OR = 2.5; 95% CI: 1.2-5.1). Other behavioral factors have also been associated with increased risk for severe bacterial infection, including alcohol abuse and intravenous drug abuse. In a US study of Navajo adults, Watt et al. found that alcoholism was associated with a nearly three times increased

risk of invasive pneumococcal disease when compared with no alcohol use (OR = 2.9; 95% CI: 1.5-5.4) (79).

Furthermore, it is well-established that several chronic diseases are associated with increased risk for severe bacterial infections, including bacteremia (67;80). Previous studies have shown that chronic conditions such as chronic heart disease (81;82), chronic pulmonary disease (67;81), liver disease (83), diabetes (67;84;85), cancer (44;67;81), HIV/AIDS (86), are independently associated with increased risk of severe bacterial infections. The biological mechanisms that contribute to an increased risk of bacterial infections in persons with different chronic conditions are likely multifactorial and complex. For example, different chronic conditions may weaken local barriers to infection and/or impair the functions of neutrophils and macrophages.

Risk factors operating at the community-level have been also been identified and include such factors as crowding and poor housing conditions (2;87-90). Even in a developed country like New Zealand, Baker et al. found an inverse association between overcrowding (measured by the number of adolescent and adult household members per room) and the risk of serogroup B meningococcal disease, after controlling for age, ethnicity, season, and socioeconomic factors (88). A similar inverse association between overcrowding and risk of meningococcal disease has been reported in a Danish population (90).

Socioeconomic status and the association with risk factors for community-acquired bacteremia

It is likely that many different risk factors contribute to an increased risk of severe bacterial infections among persons of lower SES compared with those of higher SES, and that many of these risk factors are modifiable. Cohen has categorized these risk factors into those that attribute to increased *exposure* to infectious agents and those that increase a persons' *susceptibility* to infection (91;92). Risk factors categorized as increasing the exposure to infectious agents in persons of lower SES may include crowding, poorer housing conditions and hygienic practices (2;88;89;91;93). While a decreased resistance to bacterial infections may be caused by a higher burden of chronic diseases, alcohol and drug abuse, lesser uptake of vaccination programmes, more smoking and poorer nutrition in persons of lower SES (78;94;95).

Knowledge about the potential contributors for any increased risk of CAB in individuals with lower SES is crucial for effective intervention against risk factors, and thereby for prevention and treatment of infections in persons of lower SES. In this thesis we investigate the contribution of chronic diseases and substance abuse to socioeconomic differences in CAB risk, which is motivated by the following facts. The chronic diseases investigated are well-established risk factors for severe bacterial infection and there is substantial evidence for a higher prevalence of these chronic diseases (e.g. cardiovascular disease, cerebrovascular disease, chronic pulmonary disease, liver disease, diabetes mellitus, several cancer types) in persons of lower SES compared with those of higher SES (96). Furthermore, it is acknowledged that in industrialized countries, such as Denmark, the burden of chronic diseases have overtaken infectious diseases as the main threat to population health, as described by Omran in his 'epidemiologic transition theory' (97). This replacement of infectious diseases by chronic diseases has taken place during the twentieth century and is due to several factors, including expanded public health, sanitation, and better housing conditions. At the same time, there has been a 'social transition' with the increasing burden of chronic diseases concentrating more on the disadvantaged sections of society. Much of the socioeconomic inequalities in many chronic diseases appear to be mediated through differences in health behaviours (96). With this knowledge in mind one might speculate that today, much of the SES inequalities in the risk of severe bacterial infections in industrialized countries may be explained by differences in the prevalence of chronic diseases and unhealthy behaviours. We therefore found it important to examine how much of the inequalities in CAB risk were attributed to differences in existing chronic diseases and substance abuse, as many of these CAB risk factors are preventable or modifiable.

1.5. Prognostic factors for bacteremia

Prognostic factors for bacteremia may be defined as characteristics of a patient or exposures that influence the outcome after bacteremia (98). The outcome is a clinical event and can be defined either as death, disease, discomfort, disability, or dissatisfaction (99). In this thesis the outcome of interest is 30-day mortality after bacteremia.

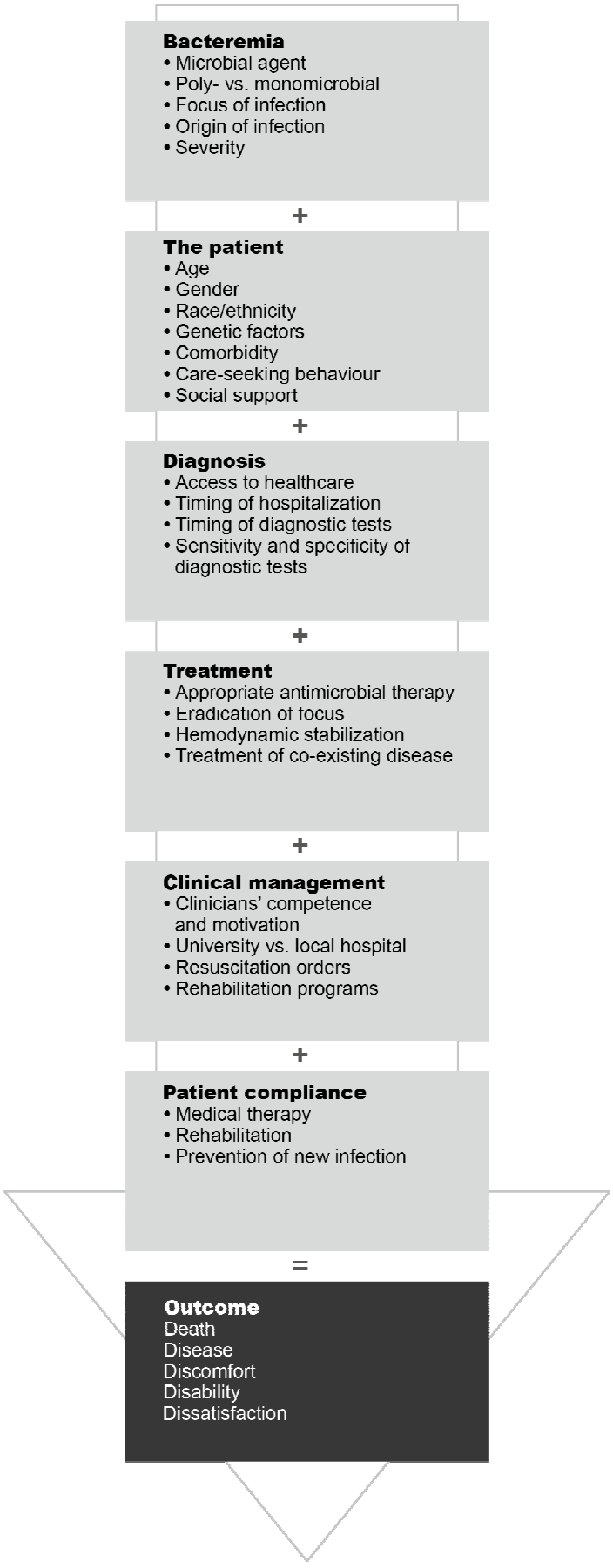


Figure 1.4. Prognostic factors of bacteremia (Modified from Sackett's figure in "Clinical Epidemiology"(104)).

There are several reasons to study prognostic factors for bacteremia (100-103). For the clinicians it is important to predict prognosis and to know prognostic factors in order to ultimately improve the outcomes for certain patient groups. Knowledge of the prognosis is also important for the patients who wish to know what to expect from their disease and how their prognosis can be improved. In addition, researchers would like to obtain knowledge of prognostic factors for bacteremia in order to better design, analyze, and interpret bacteremia studies. Finally, healthcare policy makers would like to understand how/or if they can improve the prognosis after bacteremia by changing the organization of healthcare. In a public health context, prognostic studies may therefore provide an evidence base for decision-makers in the development of future policies.

As illustrated in Figure 1.4, many different factors influence the outcomes after bacteremia (104). These factors work at different levels and at several points in the continuum of the disease, and together they influence the overall outcome after bacteremia.

At the patient-level some prognostic factors overlap with risk factors for bacteremia, i.e. age, comorbidity, and genetic factors. Increasing age and number of comorbid conditions have repeatedly been associated with a poorer prognosis after bacteremia (105-110). Søgaard et al. found that aging and comorbidity were strong prognostic factors for 30-day mortality in patients with CAB, but that increasing levels of comorbidity with increasing age could not entirely explain the impact of age on mortality after bacteremia (42). Genetic factors may also contribute to adverse outcomes after sepsis and bacteremia. For example, polymorphisms of lipopolysaccharide-binding protein and tumor necrosis factor-β have been associated with higher in-hospital mortality in sepsis patients (76;77;111).
As shown in the figure (Figure 1.4), measures of a persons' social support are also associated with prognosis after hospitalization for severe infection. Measures of social support can be structural/quantitative assessing to which extent a person is involved in relationships and groups, or functional/qualitative assessing persons' perception that there are others available to them (112;113). In a US study of 37,524 sepsis patients, Seymour et al. examined the impact of a structural/quantitative measure of social support, namely marital status, on in-hospital mortality. The authors found that single and divorced men and single women had greater odds of in-hospital mortality than married men (65). In addition, studies have reported that unmarried patients tend to

have a higher severity of illness at admission to hospital compared with married patients, which will impact the prognosis (114).

Several factors in reference to infection characteristics have repeatedly been associated with a poor prognosis after bacteremia. These include certain microbial agents (bacteremia with *S. aureus*, *Pseudomonas aeruginosa*, *Candida* species, or polymicrobial bacteremia), certain foci of infection (a pulmonary, abdominal or undetermined focus of infection), and nosocomial acquisition of the infection (16;105;115-122).

Finally, it has also been documented that factors related to treatment and care of bacteremia patients influence their prognosis. For example, early administration of appropriate empirical antimicrobial therapy has repeatedly been associated with increased survival in bacteremia patients (105;123-126). Previous studies have also reported that survival after severe infection is influenced by characteristics of the admitting hospital, which may be an indirect measure of the quality of care and treatment provided by the institution. Studies have reported that treatment in small nonteaching hospitals and hospitals with a low annual volume of patients with severe sepsis is associated with higher in-hospital mortality in this patient group (127-129). However, others reported no association between the annual volume of severe sepsis admissions and in-hospital mortality (130).

Socioeconomic status and the association with prognostic factors for bacteremia

It is important to elucidate the potential mediating factors for any SES-outcome differences following bacteremia. Any disparity in the prognosis after bacteremia is likely multifactorial and the potential mediating factors may be related to the patient, the infection, the diagnosis of bacteremia, the treatment, and/or the admitting hospital.
In view of the existing literature on prognostic factors for bacteremia, patient-related factors such as genetic factors and/or existing comorbidity at the time of bacteremia diagnosis, could contribute to socioeconomic differences in prognosis after bacteremia. Previous studies have shown clear evidence for an inverse relation between SES and the prevalence of comorbid conditions. As described in the previous section the burden of pre-existing comorbid conditions have repeatedly been shown to have a strong adverse impact on survival after bacteremia, and variations in pre-

existing comorbid conditions may therefore contribute to socioeconomic differences in mortality after bacteremia.

Different measures of social support have consistently been associated with SES. Persons of higher socioeconomic groups are more often married or in a relationship, have more friends, or report higher perceived support (113;131;132). This has led researchers to consider the socioeconomic differences in social support as one of the mechanisms through which socioeconomic circumstances influence health (113). As low social support, measured by marital status, has been associated with a poor prognosis after sepsis, differences in the availability of social support between socioeconomic groups may be an important mediator of a SES-outcome gradient after severe infection.

Characteristics of the infection (causative microbial agent, focus of infection, place of acquisition), and the specialty (internal medicine, surgery or intensive care) which is related to the focus of infection, are associated with mortality in bacteremia patients. Any differences in these infection characteristics across socioeconomic groups may therefore also explain inequalities in survival after bacteremia.

Studies from Western countries, especially the US have documented socioeconomic inequalities in access to health care and disparities in the quality of care provided (133;134). In countries with tax-funded health-care system, such as the Danish health-care system, disparities in access to health care are less likely. However, socioeconomic differences in the delivery and quality of care may even exist in countries with a tax-funded health-care system, due to differences in the type of institutions treating patients with severe infections. Institutions caring for a greater number of patients in lower socioeconomic groups may be more likely to be small, urban, nonteaching hospitals, which care for a low annual volume of patients with severe infections. If differences in the quality of care exist across hospitals, this alone could result in disparities in the quality of care received across socioeconomic groups. Socioeconomic disparities in health care may also be affected by 'within-hospital' differences in the quality of care delivered. Decision-making in the physician-patient encounter can be influenced by the patient's condition and understanding, which may differ according to the patient's SES. Furthermore, it has been reported that physicians' perceptions of patients are influenced by patients' SES. Compared with patients of higher

socioeconomic groups, physicians tend to perceive patients of lower socioeconomic groups more negatively on several dimensions (i.e. patients of lower SES are more likely to be seen as at risk for noncompliance with treatment, less intelligent, and physicians have less affiliative feelings toward patients of lower SES) (135). These differences in perceptions may influence the quality of care delivered.

Taken together, there are several factors related to both SES and mortality after bacteremia. In this thesis we examine whether differences in social support, pre-existing comorbidity, substance abuse, infection characteristics, and/or characteristics of the admitting hospital can explain any socioeconomic differences in mortality after bacteremia.

1.6. Antimicrobial therapy of bacteremia

The key elements in the treatment of bacteremia patients include 1) early recognition of the patient's condition, 2) early and appropriate antimicrobial therapy, 3) identification and eradication of the focus of infection, and 4) administration of fluid, inotropes, and vasopressors (33). In addition to these key elements, different adjunctive treatments (other than antimicrobials and supportive care) have been tested in clinical trials in patients with severe sepsis and septic shock with mixed results (e.g. non-specific anti-inflammatory and immunosuppressive drugs, neutralisation of pro-inflammatory cytokines, and neutralisation of microbial toxins such as lipopolysaccharide) (136;137).
In this thesis we focus on the treatment with antimicrobials. We use the term 'antimicrobials', as this term cover both antibacterial agents (antibiotics) and antimycotic agents (used for treatment of fungemia). The treatment of bacteremia patients should include adequate administration of antimicrobials with in vitro bactericidal or bacteriostatic activity against the infecting agent(s). Use of antimicrobials without activity against the infecting agent(s) and/or inadequately administered (inadequate dosage or formulation) are considered to be inappropriate (138). In bacteremia patients, the initial treatment with antimicrobials is given on an empirical basis until the infecting agent(s) have been identified and susceptibility test results have become known. As much as 20-40% of bacteremia patients receive inappropriate empirical antimicrobial therapy prior to the first notification of a positive blood culture (139-141). It is therefore important for physicians to obtain timely information on positive blood cultures that can be used to guide antimicrobial therapy.

Information on positive blood cultures results are provided by microbiological laboratories, commonly in two stages. At the time of first notification of a positive blood culture the information provided is typically based on the result of a gram stain (142). In addition, a qualified guess in reference to the infecting agent and susceptibility pattern can often be made based on concurrent microbiological samples from other body fluids and sites than the blood cultures. At the first notification, 10-20% of bacteremia patients are not treated with any antimicrobial therapy, which is considered to represent inappropriate antimicrobial therapy. Furthermore, in as many as 30-45% of patients the empirical antimicrobial treatments are adjusted (105;141;143). This first notification is followed by a second notification within 12-24 hours with a tentative or definitive identification of the infecting agent(s) and results of susceptibility testing.

Previous studies have documented that the administration of inappropriate empirical antimicrobial therapy prior to the first notification of a positive blood culture is associated with development of severe sepsis and septic shock, prolonged length of hospital stay and increased mortality (105;126;144-146). Therefore, it is important to identify patient groups at increased risk and risk factors for delays in effective antimicrobial therapy for bacteremia. Several risk factors for the administration of inappropriate antimicrobial therapy to bacteremia patients have been identified and include recent antimicrobial therapy, infection due to antibiotic-resistant pathogens (e.g. extended-spectrum beta-lactamase-producing *E. coli*, methicillin-resistant *S. aureus*, vancomycin-resistent enterococci), presence of an intravascular catheter, lack of infectious diseases consultation, and infection due to specific types of pathogens (e.g. *Candida* species, coagulase-negative staphylococci, and polymicrobial infections) (126;140;147;148).

To our knowledge, no previous published study has addressed the relation between SES and inappropriate empirical antimicrobial therapy in bacteremia patients. We searched the existing literature in PubMed MEDLINE by use of the search strategies for locating articles related to SES and bacteremia, as defined in an earlier section. These search strategies were combined with the following medical subject heading terms and free text word-combinations “anti-infective agents”, “anti-bacterial agents”, “antibacterial agents“, “antibiotics”, or “antimicrobial therapy”. However, our search strategy did not identify any studies addressing our research question.

2. Aims of the thesis

The aims of this thesis were

1. To examine the association between SES and the risk of hospitalization for community-acquired bacteremia and the contribution of chronic diseases and substance abuse to socioeconomic differences in bacteremia risk (Study I)

2. To examine the effect of SES on 30-day mortality in bacteremia patients and the underlying factors that may mediate differences in mortality (Study II)

3. To examine the relation between SES and inappropriate empirical antimicrobial therapy in bacteremia patients (Study III)

3. Material and methods

3.1. Data sources

The studies in this thesis were based on data from several Danish medical and administrative registers. These registers and the data that they contain are described below.

The Civil Registration System

The Danish Civil Registration System (CRS) was established in April, 1968 (149;150). All individuals in Denmark are registered in the CRS at birth or at time of immigration by a unique ten-digit personal identification-number (CRS number). The first six digits encode the date of birth, while the last four digits encode the century of birth and the sex. The CRS contains individual-level information on current residence, migration, date of death, citizenship, marital status, and place of birth, among other variables. Changes in residence, migration, marital status and citizenship are updated on a daily basis without old data being deleted. The unique CRS number is used in all Danish medical and administrative registers to identify a given person, which allows accurate linkage between all national registers.

The North Denmark Bacteremia Research Database

Since 1981, all patients diagnosed with bacteremia in North Jutland have been registered in a research database (14;141). This database is maintained by the Department of Clinical Microbiology at the Aalborg University Hospital, which provides clinical microbiology services for the entire North Denmark Region (and previously for the County of North Jutland). Information on bacteremia patients diagnosed from 1981 through 1991 was collected retrospectively from archived blood culture reports. Since 1992 and onward the information has been recorded prospectively and concurrently with the bacteremia episode. Information in the database includes the patient's CRS number, date of sampling the first positive blood culture, date of admission, hospital and department of admission, date of notification of positive blood culture, number of positive culture bottles, number of bacterial isolates, place of acquisition of infection (community-acquired, health

care-associated, or nosocomial), focus of infection, microbiological species, antimicrobial susceptibility of the infecting microorganisms (antibiogram), and empirical antimicrobial therapy.

The Danish Collaborative Bacteremia Network (DACOBAN) Database

The Danish Collaborative Bacteremia Network (DACOBAN) research database covers bacteremia patients resident in the North Denmark Region and the Capital Region. The DACOBAN database was established in cooperation with the Center of Clinical Epidemiology, Odense University Hospital to enable coordinated surveillance of all cases of bacteremia in the two regions and to study risk factors and prognostic factors for bacteremia (151;152). Three departments of clinical microbiology (at Aalborg University Hospital - North Denmark Region, and Herlev Hospital and Hvidovre Hospital - Capital Region) serve the two regions and use the same electronic laboratory information systems (Autonik, Ramsta, Sweden) to record data on all microbiological specimens, including blood cultures. The core information in the DACOBAN database consists of microbiological data on positive blood cultures drawn from these laboratory information systems. The database is continuously updated and at present holds information on 39,292 patients with 49,951 bacteremia episodes from 1 January 2000 to 31 December 2011. The main variables in the database are similar to those in the North Denmark Bacteremia Research Database and includes the patient's CRS number, date of sampling the first positive blood culture, date of admission, clinical department and hospital, place of acquisition, microbiological species, and antibiogram. Unlike the North Denmark Bacteremia Research Database, the DACOBAN database lacks valid information on focus of infection and empirical antimicrobial therapy. In the DACOBAN database, variables classifying the bacteremia episode as monomicrobial vs. polymicrobial and community-acquired vs. nosocomial have been derived by the use of computer algorithms (153). To evaluate the validity of these classifications in the DACOBAN database, we have compared these classifications with physicians' assessments of the same classifications, using the North Denmark Bacteremia Research Database as reference. The agreement between the DACOBAN database and the North Denmark Bacteremia Research Database was high for both monomicrobial vs. polymicrobial (95.5% agreement, Kappa=0.84), and community-acquired vs. nosocomial bacteremia (90.7% agreement, Kappa=0.80).

The Danish Population's Education Register

The Danish Population's Education Register (PER), which is maintained by the government agency Statistics Denmark, is a widely used education register in Danish health research (154;155). The register is considered to have a high validity and a high coverage in an international context. In 2008, the PER contained individual-level educational information on 96.4% of the Danish population aged 15-69 years. For immigrants the coverage was 85-90% in the same age-group. Furthermore, Statistics Denmark has reported less than 3% misclassification in PER. The educational information in PER is recorded as individuals' highest completed education. Only information on educations approved by the Danish Ministry of Education and of more than 80 hours of duration is recorded in the PER. For the Danish population born in 1970 and onwards the educational information in PER is mainly generated from the educational institutions' administrative records through a collaboration between Statistics Denmark and the Danish Ministry of Education. For the population born before 1970 an increasing percentage of the information in PER has been obtained from surveys carried out by Statistics Denmark (1970 Population and Housing Census). Still, for ethnic Danes born in 1960, 97% of the information in PER is based on the educational institutions' records. A unique eight-digit education code defines the educational level of the individual in the PER. This eight-digit code can easily be transformed into the International Standard Classification of Education (ISCED) codes (156).

The Income Statistics Register

The Income Statistics Register at Statistics Denmark was established in 1970 (157;158). This register holds information on more than 160 variables that include salaries, entrepreneurial income, taxes, public transfer payments, capital income, and payouts at the individual level. Information is drawn from a variety of smaller specific registers, but the main income variables are based on annual tax assessments obtained from the Central Taxpayers' Register and the Salary Information Register. Data are considered to be of high quality. Only persons who have submitted a tax return to the Danish Tax Administration are registered in the Income Statistics Register. Still, the percentage of missing income data for Danes of working-age is less than 2%. Information from the Tax Administration's registers is assumed to reflect individual's real income. However,

misclassification of persons' taxable income likely occurs because of undeclared earnings and faulty reports to the tax authorities.

The Danish National Registry of Patients

Since 1977 all admissions to Danish somatic hospitals have been registered in the Danish National Registry of Patients (159). Contacts to emergency rooms and outpatient clinics have been registered since 1995. Admissions and contacts to psychiatric hospitals are not recorded. Data are received from the Patient Administrative Systems that contain information on hospital activities collected by all regions in Denmark. The main variables include dates of admission and discharge, information on hospital and departments, and one primary and up to 20 secondary discharge diagnoses per admission. The diagnosis codes are given by the discharging physician at the time of hospital discharge or ending of an outpatient contact. From 1977 to 1993, diagnosis codes have been classified according to the 8th edition of the Danish version of the International Classification of Diseases (ICD-8). Since 1994, codes have been classified according to the 10th edition (ICD-10). The 9th edition (ICD-9) has not been used in Denmark. The register comprises data on 99.4% of all discharges in Denmark.

The Danish Registers on Labor Market Affiliation

These registers at Statistics Denmark provide information on the Danish population's affiliation to the labour market (160). One of these registers, the Register-based Labor Force Statistics, contains information on the total Danish population's attachment to the labour market at the end of November each year. The categorization follows the international guidelines set by the International Labour Organisation and divides the population into those that are employed, unemployed and outside the labour force.

3.2. Measures and definitions of variables

Socioeconomic status

In all three studies in this thesis the 'exposure' variable was SES. As measures of the individuals' SES we used education and income. The categorization of the two measures is described in details below.

Education

We obtained information on individuals' highest completed education from the Danish Population's Education Register. Data from the year preceding the index date of the bacteremia episode or corresponding index date for controls was used to assess individuals' educational level. Persons were grouped into those who had obtained a primary/lower secondary education (low education), an upper secondary education (medium), or a tertiary education (high). This categorization was in accordance with the International Standard Classification of Education (1997) (156). Primary and lower secondary education is equivalent to compulsory education in Denmark. Compulsory education corresponds to 7 years of schooling for persons born before 1958 and 9 years of schooling for those born after 1958. Upper secondary education is non-mandatory and includes general education qualifying for access to higher education and vocational or technical education qualifying primarily for access to the labour market (up to 12 years of schooling). Tertiary education is equivalent to higher education obtained at universities, university colleges, or academies of professional higher education (more than 12 years of schooling).

Income

Information on individuals' annual income was obtained from the Income Statistics Register. Income was defined as taxable income (wages and salaries, and all types of benefits and pensions). Since our study period covered 9 years from 2000 through 2008, we adjusted income for inflation according to the year 2000 value of the Danish crown (DKK). We used information from Statistics Denmark's price index for this purpose. Subsequently, we categorized personal income into tertiles:

low-income (1st tertile), middle-income (2nd tertile), and high-income (3rd tertile). For bacteremia patients in the age-group 30-65 years registered in the DACOBAN research database, the first tertile corresponded to a median personal income of 93,998 DKK (interquartile range, IQR: 80,193-100,569 DKK, [1 Danish crown is set to be equivalent to 13 € cents), the second tertile corresponded to a median income of 135,364 DKK (IQR: 123,387-150,562 DKK), whereas the third tertile corresponded to a median income of 237,986 DKK (IQR: 203,863-300,728 DKK). These median income values within tertiles varied slightly between the three studies because we used different source populations.

Bacteremia

In Study I and Study II, we used the Danish Collaborative Bacteremia Network (DACOBAN) database to identify adult patients with a first episode of bacteremia during the period from Januar 1, 2000 to December 31, 2008. In Study III, information on bacteremia patients were obtained from the North Denmark Bacteremia Research Database, as this database holds valid information on the appropriateness of the empirical antimicrobial therapy given to the patient at first positive blood culture notification. In all studies, we only included the patient's first episode of bacteremia. Furthermore, we classified the bacteremia episodes according to the isolated microbial agent and the place of acquisition (community-acquired, nosocomial, or health care-related). In Study I, we only included community-acquired episodes of bacteremia and in Study III we obtained additional information on the focus of infection. We defined the focus as the organ or tissue infected at the time when bacteremia episode became clinically apparent and were determined on the basis of microbiological, clinical, and paraclinical findings.

As we used education and income as markers of SES, we restricted our studies to bacteremia patients aged 30 to 65 years, assuming that most persons in this age group had completed their education and were in their earning years. Our cut off at 65 years equalled the age when optional retirement with public pension was possible. Assessment of socioeconomic status after retirement and among older age groups is particularly challenging (161) and we restricted our studies to persons below 65 years because education and income are considered to be less reliable markers of SES in older retired persons (52;57). Education may be an imprecise measure of SES in the elderly because many of today's elderly in Denmark were early school leavers. If we had included older

age groups in our study a bias could have been introduced by such birth cohort effects, because older cohorts would have been over-represented among those categorized with low educational attainment. Furthermore, educational attainment of persons above 65 years of age is available to only a limited extent in the Danish Population's Education Register at Statistics Denmark, resulting in increasing numbers of missing data with increasing ages above 65 years. Likewise, income may be a less reliable marker of SES in older age groups because income decreases with age and in particular after retirement (52). Thus, the interpretation of income as a measure of SES becomes clearer for persons in their primary earning years.

Chronic diseases, comorbidity, and conditions related to alcohol abuse and substance abuse

In Study I, we obtained data from the Danish National Registry of Patients on any previous hospital diagnosis prior to the date of admission with CAB (cases) or corresponding index date (population controls). Chronic diseases were defined by ICD-8 and ICD-10 codes used in previous studies to categorize the 19 major disease groups in the Charlson Comorbidity Index (162-165).
Data from the National Registry of Patients was also used in Study II and Study III to classify pre-existing comorbidity according to the Charlson Comorbidity Index. Each disease group in the Charlson index is assigned a specific weight depending on the severity of the pre-existing condition (162). Based on the Charlson index scores, we defined three levels of comorbidity: 0 (low), corresponding to patients with no recorded comorbidity; 1-2 (medium), and >2 (high) (Study II).
Substance abuse (alcohol and drug abuse) may influence the risk for and prognosis after bacteremia. Therefore, we also obtained data on conditions related to substance abuse from the National Registry of Patients in both Study I and Study II.

Social support

In Study II, we used cohabitation status and marital status as markers for social support. We categorized cohabitation status as persons living alone or in a relationship. Persons living in a relationship included married couples, persons of the same sex living in a registered partnership, unmarried couples with children living at the same address, and unmarried couples living at the same address but without children and with a maximum age difference of 15 years. Marital status was categorized as persons being married, divorced/widowed, or never married.

Hospital characteristics

In Study II and Study III, we categorized the admitting hospitals according to size, volume and medical school affiliation. We characterized hospital size according to number of hospital beds, setup and staffed for use (<300 beds or ≥300 beds). Hospital volume were categorized according to the annual number of bacteremia patients treated at the institution (low-volume: ≤99 patients treated per year; medium-volume: 100-299 per year and high-volume ≥300 per year). Hospitals directly affiliated with a medical school were defined as teaching hospitals.

Death

In Study II, the outcome was mortality within 30 days after the date of the first positive blood culture was drawn. From the Civil Registration System, we obtained precise dates of death of the bacteremia patients. Mortality was defined as all-cause mortality, thus, we had no information on the precise cause of death. Valid information about cause-specific death may be difficult to obtain from historical data and not easily determined in patients with severe infection. Nevertheless, by including only deaths occurring within 30 days after the bacteremia diagnosis we assumed that most deaths would be at least to some extent related to the infection.

Appropriateness of empiric antimicrobial therapy

In Study III, the antimicrobial therapy administered prior to first notification of a positive blood culture was defined as empiric. Empiric antimicrobial therapy was considered inappropriate if it was found inactive against the isolated organism(s) on the basis of in vitro susceptibility data and not consistent with current clinical practice recommendations (if given in inadequate doses and/or by inadequate route of administration). Bacteremia patients not receiving any antimicrobial therapy at the time of first positive blood culture notification was categorized as receiving inappropriate therapy. Anitimicrobial susceptibility tests were performed by use of tablet diffusion (Neo-Sensitabs®; Rosco, Taastrup, Denmark). Each plate was reviewed by a senior physician using the

breakpoint system of the Swedish Reference Group for Antibiotics (SRGA) for susceptibility assessment (166).

3.3. Study design and statistical analyses

Table 3.1 gives an overview of the designs of the three studies. The different designs and statistical analyses are described in more detail below.

Table 3.1. Design of the studies in the thesis

Study	Setting, period	Study design	Measures of SES ('exposure')	Outcome
I	North Denmark Region and Capital Region, 2000-2008	Case-control study within the two regions	Educational level and personal income	Community-acquired bacteremia
II	North Denmark Region and Capital Region, 2000-2008	Cohort study of all hospitalized patients aged 30-65 years with a first time episode of bacteremia	Educational level and personal income	30-day mortality
III	North Denmark Region, 2000-2008	Prevalence study of all hospitalized patients aged 30-65 years with a first time episode of bacteremia	Personal income	Inappropriate empirical antimicrobial therapy

Study I

To investigate the association between SES and the risk of hospitalization with CAB, we conducted a population-based, case-control study. Cases of community-acquired bacteremia were identified in the DACOBAN research database. Using the Civil Registration System, we randomly selected 10 population controls for each bacteremia case. We matched the population controls by age, sex, and region of residence (North Denmark Region and Capital Region). The population controls were selected by incidence density sampling (i.e., controls subjects for a given case were sampled among persons of the source population who were alive and at risk of a first hospitalization with CAB at

the time the case was diagnosed) (167). Since cases and controls were matched, we used conditional logistic regression analysis to estimate odds ratios (ORs) with 95% confidence intervals (CIs) for risk of hospitalization with CAB according to each marker of SES. Given the incidence density sampling of population controls, the ORs were unbiased estimates of the incidence rate ratios for CAB in the source population (168). Initially, we analyzed data by calculating frequencies and proportions of cases and controls within categories of SES and for sex, immigrant status, employment status, cohabitation status, marital status, and chronic diseases. Furthermore, we used log-binomial regression analysis to calculate age- and sex-adjusted prevalence ratios (PRs) and their 95% CIs for the association between SES and chronic diseases and substance abuse.
To evaluate the contribution of chronic diseases and substance abuse to the association between SES and bacteremia risk, we calculated ORs with and without adjustment for chronic diseases and substance abuse. The percentage reduction in the β-coefficient after adjustment was calculated by use of the formula: $100\times(\beta_{unadjusted}- \beta_{adjusted})/(\beta_{unadjusted})$. This method has been used previously by Stringhini et al. (113). We calculated 95% confidence intervals for the percentage attenuation using a bootstrap method with 1000 re-samplings.

In addition to these analyses, we performed several supplementary analyses. To examine whether the association between SES and risk of CAB was consistent in different subgroups, we performed stratified analyses according to age-group, sex, and number of chronic diseases. To examine whether the association varied by infectious agents, we performed stratified analyses according to infectious agent. To examine the association between income and risk of CAB independent of educational attainment, we performed analyses in subgroups of persons with different levels of education.

Study II

The association of SES with mortality after bacteremia was examined in a cohort study. Bacteremia patients were identified in the DACOBAN research database. Patients were followed from the date when the patient's first positive blood culture was drawn, until emigration, death, or end of 30-day follow-up. First we analyzed data by constructing tables on baseline characteristics and cumulative mortality according to both markers of SES. We then used Kaplan-Meier plots to examine mortality within 30 days after bacteremia according to SES.

Cox proportional-hazards regression analysis was used to compare mortality according to SES, with estimation of hazard ratios with corresponding 95% CIs. We used log-minus-log plots to confirm that the proportional hazards assumption was not violated (169).

To examine whether differences in social support (cohabitation and marital status), pre-existing comorbidity (comorbidity included in the Charlson Comorbidity Index and conditions related to substance abuse), infection characteristics (place of acquisition, microbial agent, and admitting specialty) or hospital characteristics (number of hospital beds, hospital volume, and medical school affiliation) accounted for socioeconomic differences in mortality, we performed a sequential cumulative adjustment analysis. The potential mediators were included in our analyses in a sequence that we assumed to reflect the temporal relation of the potential mediators (e.g., we assumed that SES would normally precede comorbidity existing at the time of the bacteremia diagnosis). In the first step, we adjusted only for demographic characteristics. In the second step, we adjusted for both demographic characteristics and social support; continuing up to the final step, in which we simultaneously adjusted for all the potential mediators. In this way, comparing the hazard ratios between the different steps indicated the incremental contribution of a given mediator after adjustment for all previous mediators (e.g., the contribution of characteristics of the admitting hospital after adjustment for all other mediators).

Study III

To examine the relation between SES and appropriateness of empirical antimicrobial therapy, we performed a prevalence study of bacteremia patients in North Denmark Region. Personal annual income was used as marker of SES. We first calculated frequencies and prevalence proportions within income groups for patient characteristics (age, sex, immigrant status, and comorbid conditions). Then we examined differences in infection characteristics, characteristics of the admitting hospital and status at first notification of positive blood culture across income groups.

To examine the relation between SES and the risk of inappropriate empirical antimicrobial therapy, we performed log-binomial regression analyses (170). We calculated age- and sex-adjusted relative risk (RR) estimates with 95% CIs for receiving inappropriate antimicrobial therapy according to income overall and for subgroups of patients according to acquisition of infection, focus of infection, and microbial agent.

Linkage between registries and statistical analyses were performed with use of Stata statistical software, version 11.2 (StataCorp. LP, College Station, Texas). De-identified datasets were kept at a research server maintained by Statistics Denmark. Access to the server was made possible by a secured remote internet connection. All studies in the thesis were approved by the Danish Data Protection Agency (Record no. 2010-41-5650). Informed consent was not required by Danish law.

4. Results

The main results of our three studies are summarized below.

4.1. Study I

In study I we included 4,117 incident cases with a first hospitalization with CAB and 41,170 matched population controls. Both cases and control subjects were in the age-group of 30-65 years (median age: 54 years, interquartile range: 44-60 years) and 52.8% were men.

Among bacteremia cases the proportion of persons with a short education or low income was markedly higher than among matched control subjects (short education: 40.1% versus 27.3%; low income 50.4% versus 31.4%). A considerably higher proportion of cases than controls (51.2% versus 17.5%) had one or more pre-existing chronic diseases. In addition, we found that more cases than control subjects were alcohol abusers (16.4% versus 2.5%) and/or drug abusers (6.6% versus 0.7%).

We found a clear association between markers of SES and prevalence of chronic diseases and substance abuse. Cases and control subjects with short education versus long education were 1.5 times more likely to have one or more pre-existing chronic diseases and 2.6-3.0 times more likely to be substance abusers. Similar patterns were found for low versus high income groups.

Table 4.1 shows our finding of a graded inverse association between SES and risk of CAB. Persons with short education had more than two-fold increased odds for hospitalization with CAB compared with persons of long education (unadjusted OR = 2.30 (95% CI: 2.10-2.52)). The unadjusted OR for CAB in persons with low income versus high income was 2.77 (95% CI: 2.54, 3.02). Higher prevalence of chronic diseases and substance abuse among persons of low SES versus high SES contributed with 43-48% to the observed disparities in CAB risk. Still, we found a 1.6- to 1.7-fold increased risk for CAB among persons of low SES after adjustment for differences in the burden of chronic diseases and substance abuse.

In stratified analyses according to infectious agent we found that the inverse association between SES and risk of CAB was consistent for all agents (Figure 4.1).

Table 4.1. Association between SES and risk of CAB and effect of adjustment for chronic diseases and substance abuse.

Socioeconomic markers	**Unadjusted**	**Adjusted**[c,d]	**% Attenuation**[e]
	OR (95% CI)	**OR (95% CI)**	**(95% CI)**
Educational level[a]			
Short	2.30 (2.10-2.52)	1.60 (1.45-1.77)	43 (36-50)
Medium	1.39 (1.27-1.52)	1.18 (1.07-1.29)	51 (31-70)
Long	1.00 (reference)	1.00 (reference)	
Income category[b]			
Low (1st tertile)	2.77 (2.54-3.02)	1.69 (1.54-1.86)	48 (42-54)
Middle (2nd tertile)	1.41 (1.28-1.55)	1.20 (1.09-1.32)	47 (29-66)
High (3rd tertile)	1.00 (reference)	1.00 (reference)	

Abbreviation: CI, confidence interval; OR, odds ratio

[a]The measure of education attainment was available for 96.7% of the cases and therefore only 3983 cases were included in the analysis

[b]Available for 99.8% of the cases; 4107 cases included in the analysis

[c]Odds ratios adjusted for pre-existing chronic diseases, and conditions related to alcohol and drug abuse

[d]Test for trend (all three markers of SES $P<0.001$)

[e]Percent attenuation=$100\times(\beta_{unadjusted}- \beta_{adjusted})/(\beta_{unadjusted})$

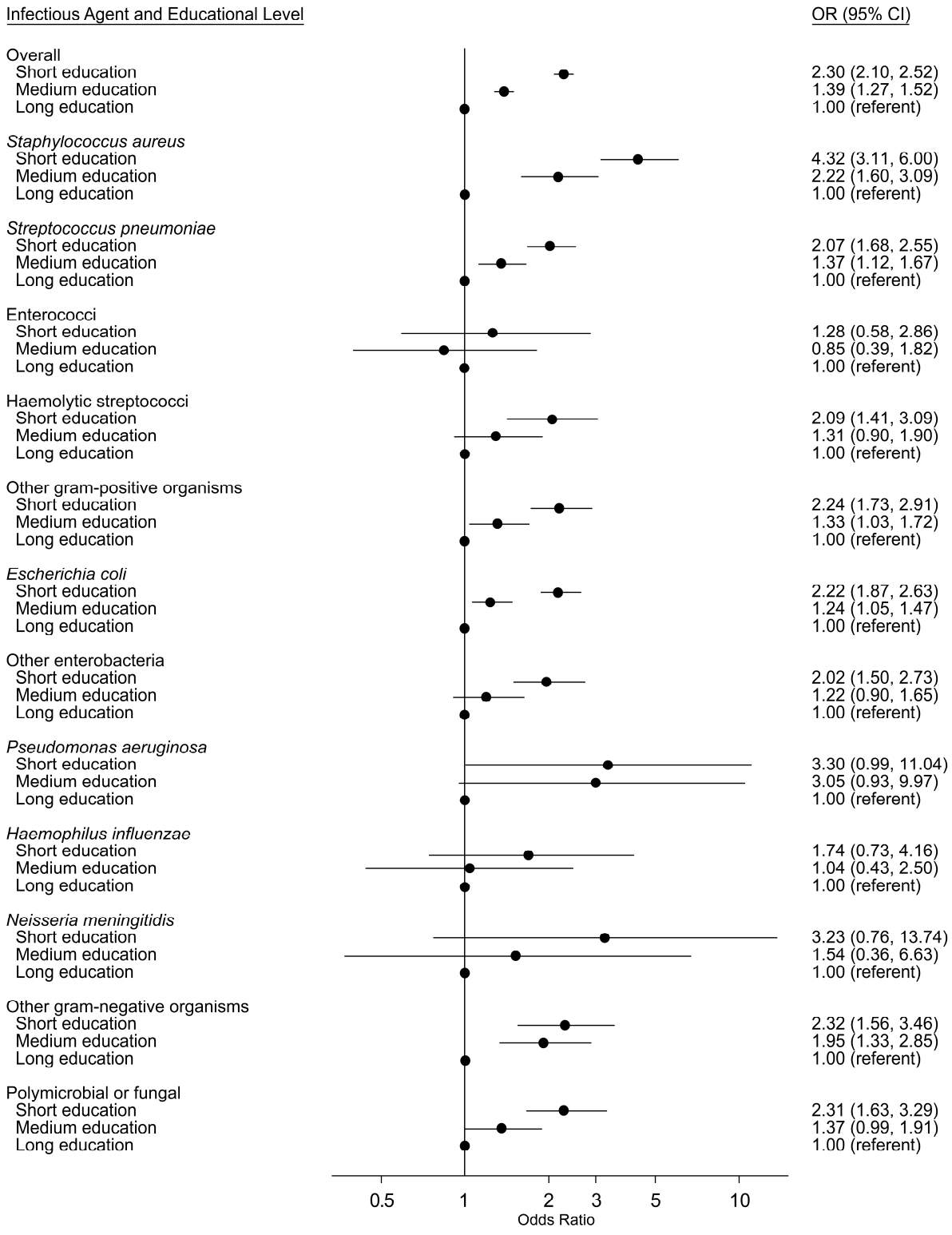


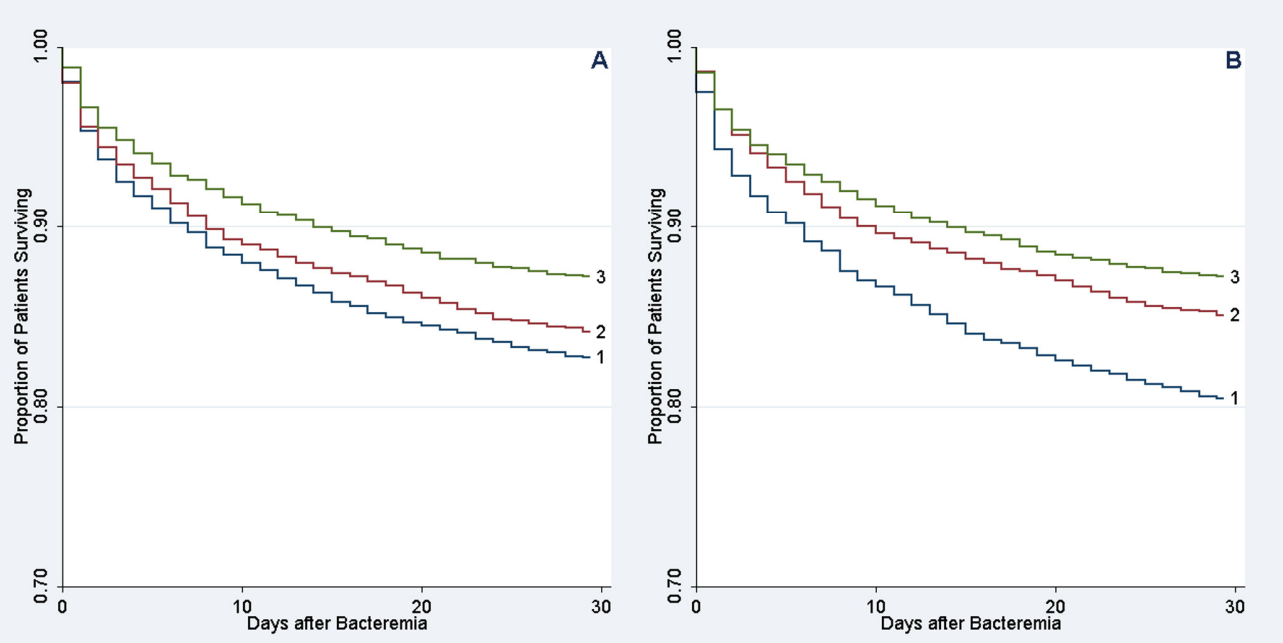
Figure 4.1. Odds ratios (ORs) for hospitalization with CAB according to educational level, stratified by infectious agent. Bars, 95% confidence intervals (CIs).

4.2. Study II

Study II included 8,653 patients aged 30-65 years hospitalized with a first time episode of bacteremia. The median age of the cohort was 55 years (interquartile range: 47-61 years) and 44.5% were women.

We found that bacteremia patients with a short education were slightly older, less affluent, had less social support, and were substantially more likely to be out of the workforce than bacteremia patients with long education. Moreover, patients with low education had a higher prevalence of pre-existing comorbidities and conditions related to alcohol and drug abuse, were more likely to have *S. aureus* bacteremia and nosocomial infection, were more likely to be admitted to an intensive care unit, and to be treated at small, nonteaching, and low-volume hospitals when compared with patients with a long education. Similar but more pronounced differences were seen for the low income versus high income groups.

Figure 4.2. Crude Kaplan-Meier survival curves according to SES. A) Educational level (low 1, medium 2, high 3), B) Income (low 1, middle 2, high 3).



The overall 30-day cumulative mortality was 15.9%. Kaplan-Meier survival curves showed marked differences in mortality across both education and income categories. Furthermore, mortality

differences across socioeconomic groups were apparent within the first few days after bacteremia diagnosis and persisted throughout the 30 days of follow-up (Figure 4.2). The absolute difference in 30-day cumulative mortality was 4.5% (95% CI: 2.4-6.5%) for low education versus high education and 6.7% (95% CI: 4.8-8.6%) for low income versus high income.

In a cox proportional-hazards regression analysis, we found increased hazard for death within 30 days after bacteremia among patients of low SES compared with high SES (crude HR = 1.38 (95% CI: 1.18-1.61) for low versus high education; crude HR = 1.58 (95% CI: 1.39-1.80) for low versus high income) (Table 4.2 and Table 4.3).

Cumulative sequential adjustment for differences in social support, pre-existing comorbidity, substance abuse, and infection characteristics attenuated the effect of both education and income on mortality and thereby partly mediated the SES-mortality differences after bacteremia. Further adjustment for differences in characteristics of the admitting hospital had only marginal impact on the adjusted hazard ratios. After full adjustment for all mediators considered in our study, we still found a residual difference in mortality according to both education (low vs. high education, 1.14 (95% CI: 0.97-1.35) and income (low vs. high income, 1.30 (95% CI: 1.13-1.49)).

Table 4.2. 30-day mortality risk after first time diagnosis of bacteremia according to educational level and effect of adjustment for social support, pre-existing comorbidity, substance abuse, characteristics of infection, and hospital characteristics.

	Educational level		
	Low	**Medium**	**High**
Unadjusted	1.38 (1.18-1.61)	1.25 (1.07-1.47)	1.00 (reference)
Adjusted			
Demographic characteristics[a]	1.33 (1.14-1.56)	1.17 (0.99-1.37)	1.00 (reference)
+ social support[b]	1.27 (1.08-1.49)	1.15 (0.98-1.35)	1.00 (reference)
+ pre-existing comorbidity[c]	1.20 (1.02-1.41)	1.08 (0.92-1.28)	1.00 (reference)
+ characteristics of infection[d]	1.15 (0.98-1.36)	1.04 (0.88-1.22)	1.00 (reference)
+ hospital characteristics[e]	1.14 (0.97-1.35)	1.03 (0.88-1.22)	1.00 (reference)

[a]Age, sex, and nationality
[b]Cohabitation and marital status
[c]Comorbidities included in the Charlson Comorbidity Index and conditions related to substance abuse
[d]Microbial agent, place of acquisition, and admitting specialty
[e]Number of hospital beds, hospital volume, and medical school affiliation

Table 4.3. 30-day mortality risk after first time diagnosis of bacteremia according to income and effect of adjustment for social support, pre-existing comorbidity, substance abuse, characteristics of infection, and hospital characteristics.

	Income Category		
	Low (1st tertile)	**Middle (2nd tertile)**	**High (3rd tertile)**
Unadjusted	1.58 (1.39-1.80)	1.18 (1.02-1.35)	1.00 (reference)
Adjusted			
Demographic characteristics[a]	1.69 (1.48-1.93)	1.22 (1.07-1.41)	1.00 (reference)
+ social support[b]	1.58 (1.38-1.81)	1.16 (1.01-1.33)	1.00 (reference)
+ pre-existing comorbidity[c]	1.37 (1.19-1.57)	1.08 (0.92-1.22)	1.00 (reference)
+ characteristics of infection[d]	1.29 (1.12-1.49)	1.03 (0.89-1.18)	1.00 (reference)
+ hospital characteristics[e]	1.30 (1.13-1.49)	1.03 (0.89-1.19)	1.00 (reference)

[a]Age, sex, and nationality
[b]Cohabitation and marital status
[c]Comorbidities included in the Charlson Comorbidity Index and conditions related to substance abuse
[d]Microbial agent, place of acquisition, and admitting specialty
[e]Number of hospital beds, hospital volume, and medical school affiliation

4.3. Study III

In study III, analyses were based on 2,253 patients with a residence in the North Denmark Region and a first time diagnosis of bacteremia. Patients were in the age-group of 30-65 years and the median age at diagnosis was 55 years (interquartile range 47-61 years). The proportion of men was 53%.

Patients with community-acquired bacteremia accounted for 46.2%, while 33.2% had nosocomial bacteremia, and 20.6% had health-care related bacteremia. The proportion of patients hospitalized in medical wards was 62.7%, followed by surgical wards 27.8%, and intensive care units 9.5%. The majority of patients had a focus in the urinary tract (22.2%), followed by the gastrointestinal tract (16.8%), and the respiratory tract (13.8%).

At the time of first blood culture notification a total of 97 (4.3%) patients was dead and in another 56 (2.5%) patients the treatment was ceased. Of the remaining 2,100 patients a total of 667 (31.8%) received inappropriate empirical antimicrobial therapy.

We used income as marker of patients' SES to examine any association between SES and the appropriateness of empirical antimicrobial therapy at the time of first blood culture notification. The proportion of patients in the low income group receiving inappropriate therapy was 34.6% compared with 29.0% of patients in the high income group (Table 4.4). In a log-binomial regression analysis this corresponded to a sex- and age-adjusted risk difference of 6.8% (95% CI: 1.9-11.8) and a relative risk of 1.24 (95% CI: 1.06-1.46) for receiving inappropriate therapy in the low income group versus high income group.

Table 4.4. Relation between income group and risk for inappropriate empirical antimicrobial therapy at the time of positive blood culture notification.

	Income group (tertiles)			**Relative risk[a] (95% CI)**	
	Low	**Middle**	**High**	**Middle vs. high income**	**Low vs. high income**
All patients	34.6%	31.7%	29.0%	1.14 (0.97-1.34)	1.24 (1.06-1.46)
Community-acquired	25.5%	19.1%	20.8%	0.95 (0.69-1.30)	1.28 (0.96-1.71)
Nosocomial	48.4%	48.6%	42.7%	1.19 (0.98-1.45)	1.13 (0.92-1.39)
Health care-related	33.8%	31.5%	24.5%	1.34 (0.92-1.95)	1.42 (0.98-2.06)

[a]Sex- and age-adjusted risk estimates

Stratified analyses according to acquisition of infection, focus of infection, and microbial agent rendered imprecise risk estimates. Nevertheless, stratified analyses showed the same pattern of an inverse association between income and risk of inappropriate antimicrobial therapy. Furthermore, risk estimates tended to be most pronounced among patients with health care-related bacteremia (RR = 1.42 (95% CI: 0.98-2.06) for low vs. high income), *S. pneumoniae* bacteremia (RR = 3.63 (95% CI: 0.92-14.30)), and with a respiratory tract focus (RR = 3.55 (95% CI: 1.19-10.53)).

Differences in the appropriateness of antimicrobial therapy across income groups could potentially be explained by differences in antimicrobial resistance of the infectious microorganisms. Therefore, we examined difference in antimicrobial resistance of the isolated pathogens across income groups. Only small differences were seen, yet the overall proportion of antimicrobial resistant pathogens was greater among patients in the low income group than those in the high income group. Of note, we found that resistance of Enterobacteriaceae to third-generation cephalosporins (ceftazidime, cefotaxime, and/or ceftriaxon) was slightly more common in patients with low income (17 patients, 5.9% (17/288)) than in patients with high income (13 patients, 4.6% (13/291)).

5. Methodological considerations

5.1. Study I

Selection bias

Selection bias in our case-control study could arise if cases and population controls were not selected independently of their exposure status, namely SES (167). Our setting within a country with a universal health care system with free and equal access to treatment and care at public hospitals is an important strength of our study and in itself it reduced selection bias in our study. Furthermore, the use of population-based registries allowed for a well-defined source population and random sampling of controls independent of their SES.

Nevertheless, we included only hospitalized CAB cases in our study and we do not know the percent of CAB cases captured in our source population. We assume that the number of undetected cases of severe bacteremia in Denmark is low, since cases of such severe infections would be hospitalized because of severe symptoms. This assumption is supported by the fact that the vast majority of patients hospitalized with CAB in our setting fulfil the criteria for sepsis at admission (27;30). Still, persons of lower SES might have an increased likelihood of being diagnosed as a bacteremia case compared with persons of higher SES. We can speculate that general practitioners may be more likely to hospitalize persons with low versus high SES, due to concerns about poor self-care, treatment compliance, and lack of social support. The possible surveillance bias could lead to an overestimation of the difference in bacteremia risk between persons of lower SES and persons of higher SES. In addition, general practitioners likely have a lower threshold for admitting persons with coexisting chronic diseases that were associated with low SES in our study. However, our finding of a consistent inverse association between SES and bacteremia risk in subgroups of persons with different levels of chronic diseases speaks against presence of a major selection bias.

Information bias

Information bias is a systematic error in a study and could arise in our case-control study if the information on our exposure ('SES') was erroneous (171). In our study we used three categories to define persons' SES (e.g. low-, middle-, and high-income) and any error that would lead a person to be placed in an incorrect category would cause a misclassification of our exposure variable. The misclassification is nondifferential if it is unrelated to our outcome, namely the presence of bacteremia. In contrast, if the misclassification is different for our cases and controls (for persons with and without disease), it is differential. Differential misclassification can lead to unpredictable information bias, while nondifferential misclassification of categorised variables will tend to bias the results towards the null or no-effect value.

Information on persons' SES was obtained from administrative registries and in the same way for both cases and controls. This avoided a common type of information bias in case-control studies, namely 'recall bias', as the information on SES was collected prospectively and independently of our study. Nevertheless, misclassification of persons' annual income may be present in our study, because of undeclared earnings and faulty reports to tax authorities. We expect such misclassification to be nondifferential, since misclassification of the exposure variable would occur among both cases and controls, which would lead to conservative risk estimates.

Misclassification of chronic diseases and conditions related to alcohol and substance abuse could also influence our findings. The information on pre-existing chronic diseases and substance abuse was based on discharge diagnoses recorded in the National Registry of Patients. The quality of the information in this registry may be affected by incorrect data entry or lack of entry of available information. In a recent Danish study it was documented that the discharge diagnoses for the chronic diseases that was considered in our study, all have high validity in the National Registry of Patients (163). Still, it is likely that misclassification of the diagnoses in this registry exits. Any nondifferential misclassification would lead us to underestimate the contribution of chronic diseases and substance abuse to the association between SES and bacteremia risk. Moreover, we can speculate that differential misclassification of chronic diseases and substance abuse may occur if coding and diagnosis are more complete for persons of lower SES due to more frequent hospitalizations. However, the opposite may also be the case, that is the diagnostic coding in

persons of lower SES are less complete due to poor self-care and delayed diagnosis. Such differential misclassification could lead to both an overestimation and underestimation of the contribution of chronic diseases to the gradient in bacteremia risk.

Statistical precision

We used 95% confidence intervals to express the statistical precision of our risk estimates. If our study was unbiased, we can express this statistical precision in words by saying that we are 95% confident that the true risk estimate lies within the limits of our confidence interval (172). Even though our study was large and included more than 4,000 cases of CAB, we still had low precision in some of our stratified analyses. Analyses stratified by infectious agent yield particularly wide confidence intervals.

Furthermore, we used the formula $100\times(\beta_{unadjusted}- \beta_{adjusted})/(\beta_{unadjusted})$ to calculate the percentage reduction in the β-coefficient after adjustment for chronic diseases and substance abuse. A formula that has been used previously by Stringhini et al. (113). The use of the log of the odds ratios in the calculation of the attenuation of risk estimates, are reflecting an assumed linear relation between SES and bacteremia risk. An alternative formula $(100\times(OR_{unadjusted}-OR_{adjusted})/(OR_{unadjusted}-1)$, which has also been used in previous studies, is based on the odds ratios. Compared with the second formula, the first formula provides more conservative estimates of the attenuation. If we had used the second formula, then differences in the prevalence of chronic diseases and substance abuse would seem to explain 51-61% of the socioeconomic gradient in bacteremia risk instead of the reported 43-48%. However, this would not have altered our overall conclusion.

5.2. Study II and III

Selection bias

In Study II and III, selection bias would arise if the association between the exposure (SES) and the outcome (mortaltiy or inappropriate antimicrobial therapy) differed between patients included in the study and those not included (171).

In Study II, our study population consisted of persons with a residence in the North Denmark Region and Capital Region who were hospitalized with a first time episode of bacteremia. While in Study III, our study population only included residents in the North Denmark Region with first time bacteremia. Selection into these study populations depended on the detection of bacteremia, which may be influenced by admission patterns and the timing of blood sampling for culture. In addition, bacteremia could remain undetected if rapidly fatal or if appropriate antimicrobial therapy is initiated before blood sampling for culture.

In our cohort study (Study II) selection bias might have occurred if the association between patients' SES and mortality differed between patients included in our study and patients who remained undetected. We can speculate that the proportion of patients with a rapidly fatal outcome of bacteremia, that remained undetected, might be higher among patients of lower SES compared with those of higher SES. This would lead to an underestimation of the mortality in bacteremia patients of lower SES. On the other hand, as previously discussed, general practitioners may be more likely to hospitalize persons with low versus high SES, and less severe cases of bacteremia in persons of lower SES may have been admitted and diagnosed at hospital. This increased surveillance would lead to treatment of bacteremia at an earlier stage of the infection in patients of lower SES, which again would lead to an underestimation of the true mortality.

In our cohort study (Study II), we also had to consider selection bias caused by loss to follow-up. We obtained information on our outcome, namely death within 30 days of follow-up, from the Civil Registration System. This registry has virtually complete follow-up on death for Danish residents including all patients in our cohort, thus, selection bias due to loss to follow-up did not occur.

In our prevalence study (Study III), selection bias might have occurred if patients who received appropriate antimicrobial therapy initiated before blood sampling for culture were less likely to be selected into our study because of clearance of the infecting microorganism(s) from the blood stream. In itself this would lead to a higher proportion of patients receiving inappropriate antimicrobial therapy at the time of first blood culture notification. Any socioeconomic differences in the appropriateness of antimicrobial therapy initiated before blood sampling for culture would cause selection bias in our study. This could either exaggerate or underestimate the relation between SES and the risk of receiving inappropriate antimicrobial therapy at the time of first notification of positive blood culture.

Furthermore, at the time of first notification of a positive blood culture, 6.8% of the bacteremia patients included in our prevalence study were dead or had had their treatment ceased. We lacked information on antimicrobial therapy administered to these patients and were unable to determine the appropriateness of any administered antimicrobial therapy in these patients. Since inappropriate antimicrobial therapy is associated with increased mortality, we might speculate that a relatively high proportion of these patients received inappropriate therapy. The majority of these patients were of lower SES and selection bias may therefore have been introduced in our study. This could lead to an underestimation of the relation between SES and the risk of inappropriate antimicrobial therapy at first positive blood culture notification.

Information bias

Exposure data (SES) were collected prospectively and independently of our hypotheses in both Study II and Study III. Thus, the introduction of bias due to differential misclassification of our exposure variable is unlikely. The information on persons' educational attainment and annual income was obtained from administrative registries at Statistics Denmark, which is considered to have high validity and coverage (154;157). Still, some misclassification of educational and income data is likely. This may have led us to underestimate any differences in prognosis and the appropriateness of antimicrobial therapy between bacteremia patients with low SES versus high SES.

Likewise, data on the outcome variables in Study II and Study III (death and inappropriate antimicrobial therapy) were recorded independently of exposure data, which made information bias due to differential misclassification of our outcome variables unlikely. However, while data on death was complete, we can not entirely rule out nondifferential misclassification of the information on appropriateness of antimicrobial therapy. This may have lead to an underestimation of the relation between SES and risk of inappropriate empirical antimicrobial therapy.

Furthermore, we have to consider misclassification of data for the different mediators evaluated in Study II. Potentially, all of the associations of interest – SES and mortality after bacteremia, SES and mediator, and mediator and mortality – could be influenced by measurement error that may have biased our findings. However, since all data for the mediating factors were obtained from

medical and administrative registries and were recorded independently of our study, we find it most likely that any misclassification of a mediator would be nondifferential. It is however, reasonable to assume that some nondifferential misclassification of the mediators has occurred. For example, any problems with the quality of the data in the National Registry of Patients leading to misclassification, may have affected the evaluation of pre-existing comorbitidy as a mediator. Any nondifferential misclassification of a mediator would dilute the contribution of this mediator in the SES-mortality gradient after bacteremia. Moreover, use of crude categories for a mediator could also lead to 'residual-mediation', which would lead to an underestimation of the contribution of this mediator to the association between SES and mortality after bacteremia. Taken together, our finding of a residual impact of SES on mortality after bacteremia may therefore simply reflect that our measures of the evaluated mediators (social support, pre-existing comorbidity, substance abuse, characteristics of the infection, and hospital characteristics) are rather crude and may be misclassified.

Statistical precision

Despite the fact that we included more than 8,000 bacteremia patients in Study II and more than 2,000 patients in Study III, we still lacked statistical precision in these studies. In Study II, statistical imprecision was especially seen in the sequential cumulative adjustment analysis when we used education as marker of SES. However, analyses with income as marker of SES showed similar overall results and were not limited by statistical imprecision. A major limitation to Study III was the imprecision of risk estimates in most of the stratified analyses. However, our overall conclusions of increased risk for receiving inappropriate antimicrobial in bacteremia patients of low SES versus high SES, were supported by the consistent pattern in subgroup analysis.

6. Discussion in relation to the existing literature

6.1. Study I

Our study confirms previous research with regard to an increased risk of bacteremia among persons of lower SES as compared with those of higher SES. The previous studies have used different measures of SES (62-67) and some are confined to selected bacteremia types. As discussed below, previous studies have shown evidence for an inverse association between SES and risk for *S. aureus* bacteremia, and bacteremic pneumonia with *S. pneumoniae*, *H. influenzae*, group A streptococcus, or group B streptococcus (62;63;66).

In a population-based study from New Zealand, Huggan et al. analyzed 779 patients with incident *S. aureus* bacteremia (62). An address-based measure of deprivation was used as a proxy for persons' SES. After adjusting for age and sex, the incidence of *S. aureus* bacteremia in the least deprived areas was lower than in the most deprived areas (adjusted rate ratio 0.74, 95% CI: 0.56-0.98). The effect of deprivation on the incidence of *S. aureus* bacteremia was only demonstrated between the least and most deprived areas. Thus, the authors found no graded association between SES and risk of *S. aureus* bacteremia, as we demonstrated in our study. This finding, together with a less pronounced effect of SES on risk for *S. aureus* bacteremia, may in part be explained by their use of an area-based measure of SES, which may have diluted any true association between individual SES and bacteremia risk.

More recently, two studies conducted in the US have reported an increased risk of bacteremic pneumonia in persons on lower SES compared with those of higher SES. In a study of 609 patients hospitalized with bacteremic pneumococcal pneumonia, the authors used self-reported information on SES and found that persons with no high-school education were more likely to be admitted with bacteremic pneumococcal pneumonia compared with persons who had attained a college degree (unadjusted OR = 2.7 (95% CI: 2.0-3.7)) (66). Moreover, the authors found that persons with incomes less than 6,000$ per year had a substantially increased risk for pneumococcal pneumonia compared with those with incomes higher than 50,000$ per year (unadjusted OR = 10.5 (95% CI: 6.5-15.0)). Of note, the authors found no association if an area-based measure of census block-group median income was used as a proxy for self-reported income. Even though this study is in line with our findings, it was hampered by a high percentage of non-responders to educational (54%

missing) and income (67% missing) questions, which may affect the interpretation of the findings. Furthermore, a more direct comparison of risk estimates with our findings may be difficult because of important differences between the US and the Danish setting, the categorization of SES measures, and the populations studied. The other study, by Burton et al., used area-based socioeconomic measures to examine disparities in the incidence of microbiologically verified bacteremic community-acquired pneumonia among 4,870 adults in 9 US states (63). They found that the incidence of bacteremic pneumonia was more than two-fold higher (incidence rate ratio = 2.39 (CI: 2.16-2.64)) among persons living in most impoverished areas (20% or more of persons in poverty) than of the least impoverished areas (less than 5% of persons in poverty). This finding is in accordance with our finding of an inverse association between SES and risk of pneumococcal bacteremia. Still, a more direct comparison of risk estimates may be difficult because of differences in study settings and measures of SES.

In addition to these studies, at least three studies have examined the association between different measures of SES and the overall risk of bacteremia (all bacteremia types) or sepsis. Despite the use of different measures of SES, these studies provide additional evidence for a consistent inverse association between SES and the risk of bacteremia or sepsis, which is in accordance with our results. In a US study, Mendu et al. included 14,597 patients who had blood cultures drawn while admitted to intensive care units at two academic teaching hospitals in Boston (64). The authors found an association between neighbourhood poverty rate and the risk of bacteremia near critical care initiation, with an inverse risk gradient across neighbourhood poverty rate quintiles. Wang et al. conducted a longitudinal cohort study nested within the REGARDS cohort (The Reasons for Geographic And Racial Differences in Stroke – a cohort study designed to evaluate geographic and black-white stroke mortality variations), encompassing 30,239 community-dwelling participants across the US (67). Even though it was not a primary aim, the authors found that low education and income were associated with increased incident sepsis risk. Finally, in a US study, Seymour et al. used marital status as exposure variable to examine its association with the risk of hospitalization for sepsis (65). The authors found that hospitalization for sepsis were more common among single (age, sex, and race-adjusted incidence rate ratio = 3.5 (95% CI: 3.1-3.9)), and legally separated individuals (incidence rate ratio = 1.5 (95% CI: 1.2-1.8)), compared with married.

Although no previous study has specifically examined an association between SES and the risk of invasive infections caused by enterobacteria, a previous study has reported an increased prevalence of bacteriuria in females of lower SES compared with those of higher SES (93). Bacteriuria has been associated with the risk of development of pyelonephritis, which may cause bacteremia (173). Furthermore, diabetes is associated with increased risk of enterobacterial bacteremia and more prevalent in persons of lower SES, which may in part explain the inverse association between SES and risk of enterobacterial bacteremia we found in our study (85).

Our study is the first to evaluate the contribution of chronic diseases and conditions related to substance abuse to socioeconomic differences in bacteremia or sepsis risk. However, several prior studies have linked chronic disease with increased risk for severe bacterial infection (44;67;81-84;86). For example, Wang et al. reported a clear association of baseline chronic diseases (including chronic lung disease, peripheral artery disease, chronic kidney disease, myocardial infarction, diabetes, deep vein thrombosis, coronary artery disease, hypertension, atrial fibrillation, and dyslipidemia) with the risk of future sepsis events within the REGARDS longitudinal cohort study (67).

6.2. Study II

We are aware of only three studies that have examined the association between SES and mortality after bacteremia or sepsis. In agreement with our findings, Mendu et al. found an unadjusted gradient between neighborhood poverty rate and 30-mortality in bacteremia patients admitted to intensive care units at two academic teaching hospitals in Boston, US (64). However, comprehensive adjustment for differences in demographic factors, patient type, comorbidity, parenteral nutrition, laboratory data, and severity of illness attenuated this association and the authors concluded that neighborhood poverty was not associated with mortality after bacteremia. The fact that the authors found no statistical significant residual gradient in mortality after adjustment for covariates, may in part be explained by their use of an area-based SES measure as a proxy for individual SES. As previously discussed, the use of an area-based measure of SES might have diluted any association between individual SES and mortality after bacteremia. Furthermore, a more direct comparison of risk estimates with our findings may be hampered because of important

differences in study populations. Of note, the study population in the study by Mendu et al. was highly selected and included a high proportion of patients living in areas with low poverty rates. The association between marital status and in-hospital mortality following sepsis, reported in another US study, is also in accordance with our finding. In a cohort study of 37,524 sepsis patients, Seymour et al. concluded that, compared with married men, single and divorced men and single women are at greater odds of in-hospital death (65). These results are in line with our finding of low social support partly mediating the SES-mortality gradient after bacteremia.
In contrast to these two studies as well as our study, Huggan et al. found no association between an area-based measure of deprivation and mortality in a cohort of 779 patients with *S. aureus* bacteremia who were admitted to hospitals in Canterbury, New Zealand (62). However, the authors did not present any estimates and again their findings may in part be explained by use of an area-based measure of SES.

Our study extends the previous studies by the use of a sequential cumulative adjustment analysis to evaluate recognized prognostic factors as potential mediators of the SES-mortality gradient after bacteremia. We found that differences in social support, pre-existing comorbidity, substance abuse, and place of acquisition and agent of infection mediated much of the socioeconomic disparities in mortality in our cohort of bacteremia patients. However, after full adjustment for all mediators we still found a residual SES-mortality gradient that we could not explain. This residual difference in mortality might be mediated by unmeasured variation in severity of infection and differences in patients' treatment and care. We are not aware of any prior studies that can support these speculations, however, in regard to cardiovascular diseases and cancer prior studies have documented socioeconomic disparities in disease severity or stage at the time of diagnosis, as well as in recommended treatment and care (174-178).

6.3. Study III

To the best of our knowledge, our study is the first to examine the relation between SES and the appropriateness of empirical antimicrobial therapy in patients with severe bacterial infection. However, several studies on bacteremia patients have examined the overall risk of receiving inappropriate antimicrobial therapy prior to the first notification of positive blood culture. In agreement with our finding of a 32% overall risk of receiving inappropriate empirical antimicrobial

therapy, Byl et al., found that 37% the bacteremia patients admitted to a teaching hospital in Bruxelles, Belgium, received inappropriate empirical therapy (140). Other studies have also reported that the proportion of bacteremia patients receiving inappropriate empirical antimicrobial therapy is up to 40%, which may vary slightly according to study settings and local antibiotic resistance patterns (139;141;179).

Different mechanisms may contribute to our finding of increased risk of receiving inappropriate antimicrobial therapy in patients of lower SES compared with patients of higher SES. Patients of lower SES may be more prone to experience infections caused by antimicrobial-resistant pathogens and pathogens unexpected by the attending physician and/or clinical practice recommendations may be less likely to be followed in patients of lower SES. We found a higher prevalence of bacteremia episodes caused by antimicrobial-resistant pathogens among patients of low SES versus high SES, although only minor differences were found. This finding is in line with previous studies suggesting that persons of low SES versus those of high SES, may be at increased risk of both carriage and infection by resistant pathogens in the community as well as in the hospital (180;181). In a US study, Huang et al. found that living in socioeconomically disadvantaged census tracts (including measures of household income, home ownership, federal poverty, unemployment, lack of plumbing, and low educational attainment) conferred from 1.7- to 2.7-fold increased risk of pneumococcal nasopharyngeal carriage, which is a precursor to invasive disease (180). In addition, the authors found that living in census tracts with low educational attainment significantly predicted carriage of a penicillin nonsusceptible strain (OR = 4.0 (95% CI: 1.3-12.7)). Furthermore, in a study of 1739 UK residents undergoing coronary artery bypass grafting, Bagger et al. examined whether postoperative infection with methicillin-resistant *S. aureus* (MRSA) was related to patients' SES (181). The authors found a graded inverse association between an area-based measure of social deprivation (Carstairs score) and risk of postoperative infection with MRSA. Patients living in the most deprived areas were seven times more likely to acquire a postoperative MRSA infection than those living in the least deprived areas.

A higher frequency of carriage and infection with antimicrobial-resistant pathogens in persons of lower socioeconomic groups may be partly explained by frequent and prophylactic prescription of antibiotics. Frequent prescription of antibiotics has repeatedly been associated with increased risk of carriage and infection with antimicrobial-resistant pathogens and there is evidence for more frequent prescription of antibiotics in persons of lower SES (182;183). A recent study from

Scotland documented that persons living in the most deprived areas had a prescription rate of antibiotics that was 36.5% higher than those living in the least deprived areas (184).

7. Main conclusions and perspectives

Recent studies from Western countries have reported an increase in the incidence of bacteremia over the last decades (5;7). At the same time large socioeconomic differences in health and life expectancy have been documented in Western countries, and are perhaps on the rise (185). In this perspective, any socioeconomic inequalities in the risk for bacteremia, the prognosis after bacteremia and/or the treatment of bacteremia are a public health concern and needs to be elucidated.

In this thesis we used data from Danish population-based medical and administrative registries to examine the association between SES and bacteremia in persons of working-age, and to examine the underlying factors that may contribute to socioeconomic differences. We found that even in a country with a universal welfare system, there are substantial socioeconomic differences in the risk of acquiring bacteremia in the community. The factors that contribute to these risk differences are likely multiple and interconnected. In our setting, differences in the prevalence of pre-existing chronic conditions and substance abuse were found to contribute to a large part of the inequalities in bacteremia risk. Thus, improvement in the prevention, treatment, and management of chronic diseases and substance abuse among persons of lower SES could reduce inequalities in bacteremia risk, abreast of reducing inequalities in overall health. However, about half of the socioeconomic differences in bacteremia risk remained unexplained by variations in the prevalence of chronic diseases and substance abuse. This finding calls for further research on the underlying mechanisms that drives socioeconomic inequalities in the risk of severe bacterial infections, in order to reduce these differences. Differences in active and passive smoking, housing conditions and crowding may play a role in explaining socioeconomic inequalities in the incidence of bacteremic pneumonia, which needs to be further investigated. In addition, the role of occupational exposures in contributing to socioeconomic differences in the incidence of bacteremia is also an important issue for further studies. Our setting with a unique opportunity to combine data from Danish population-based registers may prove especially useful in contributing to this work.

Vaccination programs have proven effective in the prevention of invasive bacterial infections (e.g., the introduction of the 23-valent pneumococcal polysaccharide vaccine has been associated with a nearly 50% reduction in the incidence of invasive pneumococcal disease among adults and

immunocompetent elderly) (186). The attention to race as a risk factor for pneumococcal disease has led to changes in vaccine recommendations in the US. Thus, the pneumococcal conjugate vaccine has been recommended specifically for African-American children (187-189). In addition, it has been discussed whether socially and economically marginalized adults should be targeted for priority vaccination (66). It is hoped that this thesis will help qualifying the discussion about this topic.

Not only do persons of lower SES have an increased risk of acquiring bacteremia in the community setting, but they also have poorer prognosis after bacteremia compared with persons of higher SES. Our research demonstrate that the mediators for socioeconomic differences in the mortality after bacteremia are diverse, including differences in social support, pre-existing comorbidity, substance abuse, and characteristics of the infection. In contrast, characteristics of the admitting hospital seemed to have a negligible role as mediator for disparities in mortality. The increased mortality among bacteremia patients of lower socioeconomic groups imply that this patient group will benefit from increased clinical attention. The treatment and management of comorbidities in bacteremia patients of lower socioeconomic groups needs special attention, as the prevalence of comorbidities among bacteremia patients of lower SES are much higher than among patients of higher SES.

We found a residual SES-mortality difference after bacteremia, which may in part be explained by unmeasured variation in the severity of bacteremia at the time of hospital admission. The lack of measures on the severity of the infection is an important limitation to our research. More information on clinical parameters would have enabled us to better characterize severity of the infection. These data may now be obtainable after the implementation of new electronic medical records, and in a future study, we would therefore like to assess any differences in severity of the infection at hospital admission across socioeconomic groups. We speculate that persons of lower socioeconomic groups may have a more severe presentation at the time of admission, which will influence their prognosis negatively. If this shows to be true, it would imply that earlier diagnosis and treatment of infections of persons in lower socioeconomic groups are needed in the primary health care sector. Early recognition and treatment of less severe bacterial infections may prevent the progression of a localized infection to systemic infection with bacteremia and even obviate the need for hospitalization.

Early appropriate antimicrobial therapy is a mainstay in the treatment of bacteremia patients (138). Therefore, it is of concern that we found a 24% greater risk of receiving inappropriate empirical antimicrobial therapy in bacteremia patients of lower SES when compared with those of higher SES. The association between SES and risk of inappropriate therapy was more pronounced in the subgroup of patients with health care-related bacteremia, than in patients with community-acquired bacteremia and nosocomial bacteremia. These findings may in part be explained by a higher prevalence of infections caused by a resistant microorganism in patients of lower SES. Recent studies have documented that persons of lower socioeconomic groups are at increased risk of both colonization and being infected by resistant microorganisms in the hospital setting as well as in the community (180;181). Still, more research is required to elucidate whether persons of lower socioeconomic groups are disproportionately affected by the recent rise in antimicrobial resistance.

Finally, this thesis may have implications for future studies on bacteremia. Although many risk and prognostic factors for bacteremia in both the community and the hospital setting have been identified much still needs to be learnt about different modifiable factors. Studies on differences in the risk for and prognosis after bacteremia across different socioeconomic groups and the underlying factors that drives any differences, may provide a new focus. Moreover, this thesis demonstrated clear evidence of an association between SES and bacteremia risk, prognosis, and treatment. This knowledge needs to be considered in future studies on bacteremia and measures of SES should therefore be obtained in all future bacteremia studies, including both observational studies and clinical trials.

8. Summary

Bacteremia has been ranked among the eight leading causes of death in Western populations. Any socioeconomic disparity in the risk of bacteremia, the prognosis after acquiring bacteremia, or in the treatment of bacteremia are therefore of public health concern. To reduce socioeconomic disparities, we need to identify the underlying mechanisms involved.

The aims of this thesis were therefore, 1) to examine the association between socioeconomic status (SES) and the risk of hospitalization with community-acquired bacteremia as well as the contribution of chronic diseases and substance abuse (alcohol- and drug-abuse) to socioeconomic differences in bacteremia risk (study I), 2) to examine the effect of SES on mortality in bacteremia patients and the underlying factors that may mediate differences in mortality (study II), and 3) to examine the association between SES and the appropriateness of empirical antimicrobial therapy in bacteremia patients (study III). In all three studies these associations were examined in adults aged 30-65 years and SES was measured on the basis of educational level and/or personal income.

The three studies were based on data from two microbiological databases (The North Denmark Bacteremia Research Database and The Danish Collaborative Bacteremia Network Database), registries of Statistics Denmark (The Danish Population's Education Register, The Income Statistics Register, and The Danish Registers on Labor Market Affiliation), The Danish National Registry of Patients, and The Civil Registration System. Linkage between these population-based registries was made possible by the use of the unique personal registry number assigned to all Danish citizens.

In study I, we investigated the association between SES and the risk of community-acquired bacteremia in a population-based case-control study that included 4,117 patients hospitalized with first-time bacteremia from January 2000 to December 2008, and 41,170 population controls matched by sex, age and region of residence. We found that persons of low SES had a substantially higher risk of bacteremia than those of high SES (odds ratio for short vs. long education = 2.30 (95% confidence interval, CI: 2.10-2.52); low income vs. high income = 2.77 (95% CI: 2.54-3.02)). Higher prevalence of chronic diseases and substance abuse in persons of low SES compared with persons of high SES explained 43-48% of the socioeconomic differences in bacteremia risk.

In study II, we conducted a cohort study of 8,653 patients with first time bacteremia from 2000 through 2008. In the 30 days of follow-up 1,374 patients died (15.9%). The 30-day mortality was higher in patients of low SES than in those of high SES (crude hazard ratio for low vs. high education = 1.38 (95% CI: 1.18–1.61); low income vs. high income = 1.58 (95% CI: 1.39–1.80)). Differences in social support, pre-existing comorbidity, substance abuse, and characteristics of the infection appeared to be important mediators for the observed SES-mortality differences. In contrast, characteristics of the admitting hospital seemed to have a negligible role in explaining disparities in mortality after bacteremia.

In study III, we performed a prevalence study of 2,253 adult bacteremia patients to examine the relation between SES and inappropriate empirical antimicrobial therapy. Compared with patients in the highest income tertile, those in the lowest income tertile had a 24% greater risk of receiving inappropriate antimicrobial therapy (low (34.6%) vs. high income (29.0%); adjusted relative risk = 1.24 (95% CI: 1.06-1.46)). This association was stronger in patients with health care-related bacteremia than in patients with community-acquired bacteremia and patients with nosocomial bacteremia.

In conclusion, we found an inverse relation between SES and the risk for community-acquired bacteremia, the 30-day mortality after bacteremia, and the appropriateness of antimicrobial therapy in bacteremia patients. The reasons for these socioeconomic disparities are most likely multifactorial and complex. We were able to identify some of the factors that contribute to these disparities (i.e. the contribution of chronic diseases to disparities in bacteremia risk). However, much still remains to be learnt about the intermediary factors that drive these disparities. Our studies showed that the use of high quality data from Danish population-based registries is a suitable source for further epidemiological studies of the association between SES and bacteremia, to obtain an understanding of these intermediary factors.

9. Danish summary

Bakteriæmi skønnes at være blandt de otte hyppigste dødsårsager i den vestlige verden. Socioøkonomiske forskelle i risiko for bakteriæmi, prognose efter bakteriæmi og behandling af bakteriæmi er derfor et folkesundhedsmæssigt problem. Kendskab til de underliggende faktorer, som medvirker til eksisterende socioøkonomiske forskelle, er afgørende for at mindske uligheden.

Formålet med afhandlingen var derfor blandt personer i alderen 30-65 år at undersøge sammenhængen mellem 1) socioøkonomisk status (SØS) og risiko for samfundserhvervet bakteriæmi, samt betydningen af forskelle i forekomsten af eksisterende kroniske sygdomme og misbrug (alkohol- og stofmisbrug) for risikoen for bakteriæmi (studie I); 2) SØS og 30-dages dødelighed efter bakteriæmi, samt hvilke faktorer, der medierede forskelle i dødelighed (studie II); og 3) SØS og dækningsgraden af empirisk antimikrobiel behandling blandt bakteriæmi-patienter (studie III). I de tre studier anvendte vi uddannelsesniveau og personlig skattepligtig indkomst som markører for SØS.

Studierne er baseret på dataudtræk fra to mikrobiologiske databaser (den Nordjyske Bakteriæmidatabase og den Danske Tværregionale Bakteriæmidatabase), registre ved Danmarks Statistik (Uddannelsesregistret, Indkomstregisteret, og Registret vedrørende Arbejdsstyrkestatistik), Landspatientregisteret og Det Centrale Personregister. Det unikke personnummer, som tildeles alle personer bosiddende i Danmark, muliggjorde kobling mellem disse befolkningsregistre.

I studie I undersøgte vi sammenhængen mellem SØS og risiko for samfundserhvervet bakteriæmi i et populationsbaseret case-kontrol studie omfattende 4117 patienter indlagt med førstegangs-bakteriæmi i perioden fra januar 2000 til december 2008, og 41170 populationskontroller matchet på køn, alder og bopælsregion. Vi fandt at personer med lav SØS havde en markant højere risiko for bakteriæmi sammenlignet med personer med høj SØS (odds ratio for kort vs. lang uddannelse = 2.30 (95% konfidensinterval (KI): 2.10-2.52); lav indkomst vs. høj indkomst = 2.77 (95% KI: 2.54-3.02)). Højere forekomst af eksisterende kroniske sygdomme og misbrug blandt personer med lav SØS sammenlignet med personer med høj SØS forklarede 43-48% af sammenhængen mellem SØS og risiko for samfundserhvervet bakteriæmi.

I studie II undersøgte vi sammenhængen mellem SØS og overlevelse efter bakteriæmi i et kohortestudie, som inkluderede 8653 patienter med førstegangs-bakteriæmi fra 2000 til 2008. I alt døde 1374 patienter (15.9%) inden for 30 dage efter bakteriæmi. Patienter med lav SØS havde en højere dødelighed sammenlignet med patienter med høj SØS (ujusteret hazard ratio for lav vs. høj uddannelse = 1.38 (95% KI: 1.18–1.61); lav indkomst vs. høj indkomst = 1.58 (KI: 1.39–1.80)). Forskelle i social support, eksisterende komorbiditet, misbrug og karakteristika relateret til infektionen var vigtige medierende faktorer for socioøkonomiske forskelle i 30-dages dødeligheden efter bakteriæmi. Derimod syntes forskelle i karakteristika for det behandlende hospital ikke at mediere den socioøkonomiske forskel i dødelighed.
I studie III undersøgte vi sammenhængen mellem SØS og risiko for ikke-dækkende empirisk antimikrobiel behandling i et prævalensstudie omfattende 2253 bakteriæmi-patienter. Vi fandt at patienter med lav indkomst havde en 24% højere risiko for at få ikke-dækkende antimikrobiel behandling sammenlignet med patienter med høj indkomst (lav (34.6%) vs. høj indkomst (29.0%); køns- og alders-justeret relativ risiko = 1.24 (95% KI: 1.06-1.46)). Denne association var mere udtalt blandt patienter med health care-related bakteriæmi end blandt patienter med samfundserhvervet bakteriæmi og nosokomiel bakteriæmi.

Sammenfattende viser vores studier en invers sammenhæng mellem SØS og risiko for samfundserhvervet bakteriæmi, død inden for 30 dage efter bakteriæmi, og risiko for ikke-dækkende empirisk antimikrobiel behandling blandt bakteriæmi-patienter. De underliggende faktorer, som medvirker til disse socioøkonomiske forskelle er mangeartede og komplekse. Vi har identificeret nogle af disse underliggende faktorer, f.eks. betydningen af forskel i prævalens af kroniske sygdomme for socioøkonomiske forskelle i risiko for bakteriæmi. Vi mangler dog stadig viden om det komplekse samspil af faktorer som medvirker til de observerede socioøkonomiske forskelle. Vores studier viser at danske befolkningsregistre er velegnede til fremtidige epidemiologiske studier af sammenhængen mellem SØS og bakteriæmi, for at opnå større viden om disse underliggende faktorer.

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11. Appendix: Study I-III

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Original Contribution

Socioeconomic Inequalities in Risk of Hospitalization for Community-Acquired Bacteremia: A Danish Population-Based Case-Control Study

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In a Danish population-based case-control study, we examined the association between socioeconomic status (SES) and risk of community-acquired bacteremia, as well as the contribution of chronic diseases and substance abuse to differences in bacteremia risk. Analyses were based on 4,117 patients aged 30–65 years who were hospitalized with first-time community-acquired bacteremia during 2000–2008 and 41,170 population controls matched by sex, age, and region of residence. Individual-level information on SES (education and income), chronic diseases, and substance abuse was retrieved from public and medical registries. Conditional logistic regression was used to compute odds ratios for bacteremia. Persons of low SES had a substantially higher risk of bacteremia than those of high SES (for short duration of education vs. long duration, odds ratio = 2.30 (95% confidence interval: 2.10, 2.52); for low income vs. high income, odds ratio = 2.77 (95% confidence interval: 2.54, 3.02)). A higher prevalence of chronic diseases and substance abuse in low-SES individuals versus high-SES individuals explained 43%–48% of the socioeconomic differences in bacteremia risk. In a country with a universal welfare system, differences in the burden of chronic diseases and substance abuse seem to have major importance in explaining inequalities in bacteremia risk.

adult; bacteremia; case-control studies; chronic disease; community-acquired infection; risk factors; socioeconomic factors; substance-related disorders

Abbreviations: CAB, community-acquired bacteremia; CI, confidence interval; DACOBAN, Danish Collaborative Bacteremia Network; PR, prevalence ratio; SES, socioeconomic status.

Community-acquired bacteremia (CAB) is a severe infection and a common cause of hospitalization in Western countries. According to recent population-based studies, the incidence of CAB has increased during the last several decades and now averages 80–90 cases per 100,000 person-years (1–3). The 30-day mortality from bacteremia remains above 15%, which places bacteremia among the top 8 causes of death in Western populations (1, 4, 5). Socioeconomic disparities in the incidence of severe bacterial infection, including bacteremia, are of public health concern and may even exist in countries with universal welfare systems (6). To reduce disparities in bacteremia risk, we need an understanding of the risk factors that contribute to these differences.

Several factors may increase the risk of infections among persons of lower socioeconomic status (SES). Crowding, poorer housing conditions, and poorer hygienic practices may increase exposure to infection in persons of lower SES (6–8). Decreased resistance to infection in lower-SES individuals may be caused by less use of vaccination programs, more smoking, and poorer nutrition (9, 10). Furthermore, several chronic diseases, including chronic heart disease (11, 12), chronic pulmonary disease (11, 13), liver disease (14), diabetes (13, 15), cancer (11, 16), human immunodeficiency virus infection (17), and conditions related to substance abuse (11, 13, 18), are associated with increased risk of bacterial infection and are more prevalent among persons

of lower SES. Thus, variations in the prevalence of chronic diseases may mediate the association between SES and risk of bacterial infection (19). However, to our knowledge, no previous study has estimated the contribution of preexisting chronic diseases to socioeconomic differences in the incidence of bacterial infection.

A few previous studies have shown an increased risk of bacteremia among persons of lower SES compared with those of higher SES. These studies were limited by either not being population-based (20, 21), using area-based measures of SES (20–23), or having a high percentage of nonresponders when using self-reported information on SES (21). Moreover, preventive efforts are hampered by uncertainty if the increased risk pertains to specific infectious agents. Previous studies have suggested increased susceptibility among persons of lower SES for pneumococcal and *Haemophilus influenzae* pneumonia (21, 22), *Staphylococcus aureus*-associated skin and soft-tissue infections (24, 25), and meningococcal and pneumococcal meningitis (26).

Therefore, we conducted a population-based case-control study, using detailed individual-level markers of SES, to examine the association between SES and risk of hospitalization for CAB, and to examine whether this association varied by type of infectious agent. Furthermore, we evaluated the extent to which the burden of chronic diseases and substance abuse contribute to socioeconomic differences in the incidence of CAB.

METHODS

Setting

We conducted this population-based case-control study in 2 regions of Denmark (North Denmark and the Capital Region) with both rural and urban areas and a population of 1.7 million people. The population was predominantly Caucasian, and fewer than 10% were immigrants or descendants of recent immigrants.

The Danish National Health Service provides tax-supported health care for all residents of Denmark, including free access to primary care and public hospitals. Only 1% of hospital beds are in the private sector, and all patients treated for severe infections are admitted to public hospitals. Since April 1, 1968, all permanent residents of Denmark have been assigned a unique civil registration number. These civil registration numbers are included in all Danish medical and public registries, which allowed us to perform electronic linkage between registries (27).

Identification of bacteremia cases

We obtained data from the population-based bacteremia research database established by the Danish Collaborative Bacteremia Network (DACOBAN). DACOBAN was formed to allow coordinated surveillance of bacteremia cases and to study risk factors and prognostic factors for bacteremia. The DACOBAN research database has been described in detail elsewhere (28, 29). All patients with a first-time hospitalization for CAB during the period 2000–2008 were identified in the database. All bacteremia episodes were physician-diagnosed, and blood culture isolates regarded as contaminants were excluded. We did not include patients with blood cultures obtained more than 48 hours after hospital admission, because we considered these infections to have been hospital-acquired. Patients who had been discharged from a hospital within 30 days before the bacteremia episode were also excluded, since these episodes were considered to be health-care-associated.

Selection of population controls

The Danish Civil Registration System is updated daily. It contains civil registration numbers, data on changes in residence, migration, and vital status (dead or alive), and dates of death for all Danish residents from 1968 to the present (27). We used the Civil Registration System to randomly select 10 population controls for each bacteremia case. We matched population controls by age, sex, and region of residence. Controls were selected through incidence density sampling (i.e., eligible population controls had to be alive and at risk of a first hospitalization for CAB on the date of sampling).

Data on SES

Registries administered by the government agency Statistics Denmark are updated yearly and contain detailed individual-level socioeconomic information on all Danish citizens (30–32). We obtained information on educational attainment and annual personal income from these registries as markers of SES. These 2 markers of SES were selected to measure different aspects of socioeconomic stratification. Education is generally acquired in young adulthood and will to some extent measure early-life SES. In contrast, income can change over the life course but may better capture adult SES (33, 34).

Because we used education and income as markers of SES, we restricted the study to adults aged 30–65 years, assuming that most persons in this age group had completed their education and were in their earning years. During the study period, optional retirement with a public pension was possible from the age of 65 onward. The study was restricted to persons below this age, because education and income are considered to be less reliable markers of SES in older, retired persons (33, 35).

Information on highest completed level of education was drawn from the Population Education Register, which consists of data generated from administrative records of educational institutions and from surveys (31). We categorized education into primary/lower secondary education (short), upper secondary education (medium), and tertiary education (long) according to the *International Standard Classification of Education 1997* (36).

Personal annual income was drawn from the Income Statistics Register and was defined as all income subject to income taxation (wages, salaries, and all types of benefits and pensions). The income data are primarily supplied by tax authorities and are assumed to reflect real income (32). We adjusted income for inflation according to the year 2000 value of the Danish krone and grouped it into tertiles: low income (first tertile), middle income (second tertile), and high income (third tertile).

Additionally, we obtained information on employment status, immigrant status, cohabitation status, and marital status. Employment status was grouped into 3 categories: employed/self-employed; unemployed/employment subsidized by labor market arrangement; and early retirement pensioner. Cohabitation status was categorized as living either alone or in a relationship. For all variables, we used data from the year preceding the index date of the bacteremia diagnosis.

Identification of chronic diseases

In order to evaluate the contribution of chronic diseases and substance abuse to the association between SES and CAB risk, we obtained data from the Danish National Registry of Patients on any previous hospital diagnosis prior to current admission. The registry contains data on all nonpsychiatric hospitalizations that have taken place since 1977 and all visits to emergency departments and outpatient clinics that have occurred since 1995 (37). The following conditions were considered to be associated with increased risk of CAB: cardiovascular disease, including previous myocardial infarction or congestive cardiac insufficiency; peripheral vascular disease; cerebrovascular disease; dementia; hemiplegia; chronic pulmonary disease; connective tissue disease; peptic ulcer disease; liver disease; diabetes mellitus; moderate or severe chronic kidney disease; solid cancer; leukemia; lymphoma; human immunodeficiency virus infection/acquired immunodeficiency syndrome; and disorders related to alcohol and drug abuse. Associated *International Classification of Diseases* codes are provided in Appendix Table 1.

Statistical analysis

We calculated frequencies and proportions of cases and controls within categories of SES and for sex, immigrant status, employment status, cohabitation status, marital status, and each chronic disease. Log-binomial regression analysis was used to calculate age- and sex-adjusted prevalence ratios and 95% confidence intervals for the association between SES and chronic diseases and substance abuse. Odds ratios for risk of CAB hospitalization according to each marker of SES were calculated using conditional logistic regression. Because we used incidence density sampling of population controls, the odds ratios estimated incidence rate ratios for CAB in the underlying population (38). We calculated odds ratios with and without adjustment for chronic diseases and substance abuse. To determine the contribution of chronic diseases and substance abuse to the association between SES and bacteremia risk, we calculated the percentage reduction in the β coefficient after adjustment, using the formula $100 \times (\beta_{unadjusted} - \beta_{adjusted})/(\beta_{unadjusted})$. This method has been used previously by Stringhini et al. (39). We calculated 95% confidence intervals for the percentage of attenuation using a bootstrap method with 1,000 resamplings. To examine whether the association between SES and risk of CAB was consistent in different subgroups, we performed stratified analyses according to age group, sex, and number of chronic diseases. We also performed stratified analyses according to infectious agent. To examine the association between income and risk of CAB independently of educational attainment, we also performed analyses in subgroups of persons with different levels of education.

All statistical analyses were performed with Stata statistical software, version 11.2 (StataCorp LP, College Station, Texas). The study was approved by the Danish Data Protection Agency.

RESULTS

Descriptive data

We identified 4,117 persons aged 30–65 years with a first hospitalization for CAB and 41,170 matched population controls (Table 1). The overall number of bacteremia cases corresponded to an incidence of 55 per 100,000 person-years in our middle-aged study population. The median age of the bacteremia cases and population controls was 54 years (interquartile range, 44–60 years), and 52.8% were males. The proportion of immigrants was 10% among both cases and controls.

On average, substantially more bacteremia cases than matched controls had a short education (40.1% vs. 27.3%) or a low income (50.4% vs. 31.6%). In addition, cases were more likely to be out of the workforce, to live alone, and be unmarried. The prevalence of chronic disease was also substantially higher among cases than among controls. Among the cases, 51.2% had been diagnosed with 1 or more chronic diseases, compared with 17.5% of the controls. Among the cases, there was also a greater prevalence of alcohol abuse (16.4% vs. 2.5%) and drug abuse (6.6% vs. 0.7%).

Table 2 shows age- and sex-adjusted prevalence ratios for the association between SES and preexisting chronic diseases and substance abuse. Cases with short education and cases in the lowest income tertile were more likely to have 1 or more preexisting chronic diseases than those with long education and those in the highest income tertile (for short education vs. long education, adjusted prevalence ratio (PR) = 1.39 (95% confidence interval (CI): 1.27, 1.53); for low income vs. high income, PR = 1.52 (95% CI: 1.39, 1.66)). They were also much more likely to be substance abusers (short education vs. long: PR = 2.58 (95% CI: 2.07, 3.22); low income vs. high: PR = 5.41 (95% CI: 4.14, 7.05)). The same patterns were observed among population controls, where the prevalence ratio for 1 or more preexisting chronic diseases was 1.50 (95% CI: 1.42, 1.59) for short education versus long education and 1.59 (95% CI: 1.51, 1.68) for low income versus high income. Compared with controls with the highest SES, those with the lowest SES were also much more likely to be substance abusers (short education vs. long: PR = 2.99 (95% CI: 2.52, 3.56); low income vs. high: PR = 6.33 (95% CI: 5.31, 7.54)).

Risk of CAB hospitalization according to SES

The risk of CAB hospitalization increased gradually with decreasing SES (Table 3). This finding was consistent for both markers of SES, with unadjusted odds ratios of 2.30 (95% CI: 2.10, 2.52) for short education versus long education and 2.77 (95% CI: 2.54, 3.02) for low income versus high income. Adjustment for preexisting chronic diseases and conditions related to alcohol and drug abuse greatly

Table 1. Characteristics of Cases With a First-Time Hospitalization for Community-Acquired Bacteremia and Population Controls, Denmark, 2000–2008

	CAB Cases ($n = 4,117$)		Population Controls ($n = 41,170$)	
	No.	%	No.	%
Demographic Characteristics				
Male sex	2,173	52.8	21,730	52.8
Immigration status[a]				
Danish-born	3,706	90.0	37,186	90.3
Immigrant from Western country	136	3.3	1,681	4.1
Immigrant from non-Western country	275	6.7	2,303	5.6
Socioeconomic Markers				
Educational attainment[b]				
Short	1,650	40.1	11,246	27.3
Medium	1,548	37.6	17,151	41.7
Long	785	19.1	11,967	29.1
Missing data	134	3.3	806	2.0
Income category[c]				
Low (first tertile)	2,074	50.4	12,992	31.6
Middle (second tertile)	1,159	28.2	13,907	33.8
High (third tertile)	874	21.2	14,192	34.5
Missing data	10	0.2	79	0.2
Employment status[a]				
Employed/self-employed	1,882	45.7	29,311	71.2
Unemployed/labor market arrangement	975	23.7	7,867	19.1
Early retirement pension	1,238	30.1	3,862	9.4
Missing data	22	0.5	130	0.3
Cohabitation status[a]				
Living alone	1,856	45.1	12,055	29.3
Living in a relationship[d]	2,261	54.9	29,115	70.7
Marital status[a]				
Married	2,024	49.2	26,023	63.2
Divorced or widowed	1,038	25.2	7,467	18.1
Never married	1,033	25.1	7,550	18.3
Missing data	22	0.5	130	0.3
Chronic disease				
Cardiovascular disease[e]	318	7.7	909	2.2
Peripheral vascular disease	191	4.6	474	1.2
Cerebrovascular disease	295	7.2	1,101	2.7
Dementia	39	1.0	56	0.1
Hemiplegia	42	1.0	63	0.2
Chronic pulmonary disease	410	10.0	1,463	3.6
Connective tissue disease	153	3.7	595	1.5
Peptic ulcer disease	349	8.5	846	2.1
Liver disease	421	10.2	442	1.1
Diabetes mellitus	513	12.5	1,144	2.8
Chronic kidney disease	209	5.1	245	0.6
Cancer	403	9.8	1,544	3.8
Leukemia	26	0.6	40	0.1
Lymphoma	71	1.7	88	0.2
HIV/AIDS	71	1.7	35	0.1
No. of chronic diseases				
0 (low)	2,008	48.8	33,962	82.5
1 (medium)	1,202	29.2	5,778	14.0
≥2 (high)	907	22.0	1,430	3.5
Conditions related to substance abuse				
Alcohol abuse	677	16.4	1,031	2.5
Drug abuse	270	6.6	271	0.7

Abbreviations: AIDS, acquired immunodeficiency syndrome; CAB, community-acquired bacteremia; HIV, human immunodeficiency virus.

[a] Data are presented for descriptive purposes only.

[b] Educational attainment was defined in accordance with the *International Standard Classification of Education 1997* (36): short (primary/lower secondary education), medium (upper secondary education), or long (tertiary education).

[c] Income categories were based on tertiles.

[d] Persons living in a relationship included married couples, persons of the same sex living in a registered partnership, unmarried couples with children who were living at the same address, and unmarried couples without children who were living at the same address and had a maximum age difference of 15 years.

[e] Includes previous myocardial infarction or congestive cardiac insufficiency.

attenuated this association. A higher prevalence of chronic diseases and substance abuse in low-SES individuals compared with high-SES individuals could explain approximately half (43%–48%) of the association between SES and risk of CAB. Nonetheless, after adjustment for chronic diseases and substance abuse, the risk of CAB was still 1.6- to 1.7-fold higher for persons of low SES compared with persons of high SES.

Stratified analyses showed that the increased risk of CAB in persons of low SES was a robust finding across age groups, sex, and number of chronic diseases. More pronounced associations between the 2 markers of SES and risk of CAB were found for persons aged 40–49 years (short education vs. long: unadjusted odds ratio = 3.12 (95% CI: 2.58, 3.77); low income vs. high: unadjusted odds ratio = 4.14 (95% CI: 3.48, 4.93)). Furthermore, income remained a predictor of CAB risk independently of educational level (Table 4).

Analyses stratified by infectious agent

Escherichia coli was the most commonly isolated bacterium, identified in 1,167 (28%) of the cases, followed by

Table 2. Association Between Socioeconomic Status and Prevalence of Chronic Diseases and Substance Abuse in Community-Acquired Bacteremia Cases and Population Controls, Denmark, 2000–2008

Socioeconomic Marker	Chronic Diseases[a]		Substance Abuse[b]	
	PR[c]	95% CI	PR[c]	95% CI
Community-Acquired Bacteremia Cases (n = 4,117)				
Educational attainment[d]				
Short	1.39	1.27, 1.53	2.58	2.07, 3.22
Medium	1.22	1.11, 1.34	1.68	1.33, 2.12
Long	1.00	Referent	1.00	Referent
Income category[e]				
Low (first tertile)	1.52	1.39, 1.66	5.41	4.14, 7.05
Middle (second tertile)	1.26	1.14, 1.39	2.20	1.63, 2.96
High (third tertile)	1.00	Referent	1.00	Referent
Population Controls (n = 41,170)				
Educational attainment[d]				
Short	1.50	1.42, 1.59	2.99	2.52, 3.56
Medium	1.23	1.16, 1.30	1.79	1.51, 2.13
Long	1.00	Referent	1.00	Referent
Income category[e]				
Low (first tertile)	1.59	1.51, 1.68	6.33	5.31, 7.54
Middle (second tertile)	1.19	1.13, 1.26	2.45	2.02, 2.97
High (third tertile)	1.00	Referent	1.00	Referent

Abbreviations: CI, confidence interval; PR, prevalence ratio.
[a] One or more chronic diseases versus none.
[b] Included alcohol abuse and drug abuse.
[c] Prevalence ratios were adjusted for age and sex.
[d] Educational attainment was defined in accordance with the *International Standard Classification of Education 1997* (36): short (primary/lower secondary education), medium (upper secondary education), or long (tertiary education).
[e] Income categories were based on tertiles.

Streptococcus pneumoniae ($n = 799$; 19%) and *S. aureus* ($n = 426$; 10%). Figures 1 and 2 show that the inverse association between SES and CAB was evident for all types of infective agents and both markers of SES.

DISCUSSION

In this large, population-based case-control study, low SES inferred on the basis of educational attainment and income was strongly associated with increased risk of hospitalization for CAB. This inverse association was consistent for all infective agents. Furthermore, in our setting within a country with a universal welfare system, much of the association between SES and CAB risk was explained by differences in the prevalence of chronic diseases and substance abuse. Nonetheless, about half of the socioeconomic difference in CAB risk remained unexplained by variations in the prevalence of chronic diseases and substance abuse.

Our findings of a higher incidence of bacteremia among persons of lower SES are consistent with previous studies. A population-based New Zealand study of 779 incident cases of *S. aureus* bacteremia revealed a lower incidence of bacteremia among persons living in nondeprived areas compared with those living in the most deprived areas (age- and sex-adjusted rate ratio = 0.74, 95% CI: 0.56, 0.98) (23). Two recent US studies found an increased risk of bacteremic pneumonia among persons of lower SES and persons living in impoverished areas (21, 22). Flory et al. (21) used self-reported information on individual-level SES and found that persons without a high school education were 2.7 (95% CI: 2.0, 3.7) times more likely to be admitted to a hospital with bacteremic pneumococcal pneumonia than persons who had attained a college degree. Moreover, persons with an annual income less than $6,000 had a 10-fold increased risk of bacteremic pneumococcal pneumonia compared with those with an income higher than $50,000. The study was hampered by a high percentage of nonresponders to educational (54% missing) and income (67% missing) questions among the 609 individuals with pneumonia. In the second US study, Burton et al. (22) used area-based socioeconomic measures to examine disparities in the incidence of microbiologically verified bacteremic pneumonia among 4,870 adults in 9 states. They found that the incidence of bacteremic pneumonia was more than 2-fold higher (incidence rate ratio = 2.39, 95% CI: 2.16, 2.64) among residents of the most impoverished census tracts (≥20% of residents living in poverty) than among residents of the least impoverished census tracts (<5% of residents living in poverty) (22).

Our study supports previous findings of increased susceptibility to infections caused by *S. aureus*, pneumococci, meningococci, and *H. influenzae* among persons of lower SES, which may be partly mediated by overcrowding, poor housing conditions, poor hygienic practices, and smoking (21, 22, 24–26). Evidence is limited, however, with regard to an association between SES and an increased risk of invasive infections caused by enterobacteria, which often originate in the urinary tract. Previous studies have found an increased prevalence of bacteriuria, which is a risk factor for development of acute pyelonephritis, in lower-SES women (40, 41). Furthermore, diabetes is associated with increased risk of enterobacterial bacteremia (42) and is more prevalent in persons of lower SES; this may partly explain our finding of an inverse association between SES and risk of enterobacterial bacteremia.

Several factors may contribute to the association between SES and CAB risk that remained after accounting for differences in chronic diseases and substance abuse. We lacked information on vaccination status at the individual level. However, overall coverage for pneumococcal and meningococcal vaccines is extremely low in our working-age study population compared with other Western populations, including the US population (43). The polysaccharide pneumococcal vaccine is recommended only for persons aged 65 years or older and for persons aged 2–64 years with certain chronic conditions (44). The estimated coverage for pneumococcal vaccine was less than 0.1% in persons aged 30–65 years during our study period (15). The meningococcal group C vaccine and the meningococcal conjugate vaccine

Table 3. Association Between Socioeconomic Status and Risk of Hospitalization for Community-Acquired Bacteremia, Before and After Adjustment for Chronic Diseases and Substance Abuse, Denmark, 2000–2008

Socioeconomic Marker	Unadjusted		Adjusted[a,b]		% of Attenuation[c]	95% CI
	OR	95% CI	OR	95% CI		
Educational attainment[d]						
Short	2.30	2.10, 2.52	1.60	1.45, 1.77	43	36, 50
Medium	1.39	1.27, 1.52	1.18	1.07, 1.29	51	31, 70
Long	1.00	Referent	1.00	Referent		
Income category[e]						
Low (first tertile)	2.77	2.54, 3.02	1.69	1.54, 1.86	48	42, 54
Middle (second tertile)	1.41	1.28, 1.55	1.20	1.09, 1.32	47	29, 66
High (third tertile)	1.00	Referent	1.00	Referent		

Abbreviations: CI, confidence interval; OR, odds ratio.

[a] Odds ratios were adjusted for preexisting chronic diseases and for conditions related to alcohol and drug abuse (see Table 1).

[b] *P*-trend < 0.001 for both socioeconomic status markers.

[c] Percentage of attenuation = $100 \times (\beta_{unadjusted} - \beta_{adjusted})/(\beta_{unadjusted})$.

[d] Educational attainment was defined in accordance with the *International Standard Classification of Education 1997* (36): short (primary/lower secondary education), medium (upper secondary education), or long (tertiary education). Information on educational attainment was available for 96.7% of the cases; therefore, only 3,983 cases were included in the analysis.

[e] Income categories were based on tertiles. Information on income was available for 99.8% of the cases; therefore, only 4,107 cases were included in the analysis.

against serogroups A, C, W-135, and Y are only recommended for travelers to high-risk countries. It is therefore unlikely that socioeconomic differences in vaccination coverage explain the observed disparities in the incidence of pneumococcal and meningococcal bacteremia. Furthermore, the *H. influenzae* type b vaccine was introduced for routine childhood vaccination in 1993, with a coverage rate that has reached almost 90%. After introduction of the vaccine, there was near-elimination of invasive *H. influenzae* type b disease in Denmark (45).

Several lifestyle factors are associated with SES. Persons of lower SES tend to smoke more and to eat more unhealthy foods (46). Previous studies have suggested that both smoking and poor nutrition are risk factors for severe bacterial infection, particularly lower respiratory tract infection (47, 48). We adjusted for several chronic diseases related to unhealthy lifestyles, including chronic obstructive pulmonary disease, diabetes, and cardiovascular disease. Still, we find it likely that the residual association between SES and risk of CAB could be partly related to differences in lifestyle factors. Overcrowding and poor housing conditions may also mediate some of the risk differences in our setting (7, 49), and further studies should assess the potential role of these factors. Finally, studies by Cohen et al. (9, 50) have also suggested that physiological responses to chronic stress associated with lower SES can impair immune function. The observed disparities in the risk of bacterial infection may therefore be partly explained by differences in exposure to psychosocial stress (9, 50).

Our study had 2 major strengths. First, our study design, within the setting of a free tax-supported universal health-care

Table 4. Association Between Income and Risk of Hospitalization for Community-Acquired Bacteremia, by Educational Attainment, Denmark, 2000–2008

Income Category[a]	Educational Attainment[b]											
	Short Education				Medium Education				Long Education			
	Unadjusted		Adjusted[c]		Unadjusted		Adjusted[c]		Unadjusted		Adjusted[c]	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Low (first tertile)	2.66	2.15, 3.29	1.59	1.26, 2.01	2.36	2.02, 2.76	1.55	1.30, 1.84	1.81	1.46, 2.25	1.39	1.08, 1.78
Middle (second tertile)	1.42	1.14, 1.78	1.23	0.96, 1.57	1.35	1.16, 1.58	1.16	0.99, 1.38	1.04	0.84, 1.29	0.87	0.69, 1.10
High (third tertile)	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent

Abbreviations: CI, confidence interval; OR, odds ratio.

[a] Income categories were based on tertiles.

[b] Educational attainment was defined in accordance with the *International Standard Classification of Education 1997* (36): short (primary/lower secondary education), medium (upper secondary education), or long (tertiary education).

[c] Odds ratios were adjusted for preexisting chronic diseases and for conditions related to alcohol and drug abuse (see Table 1).

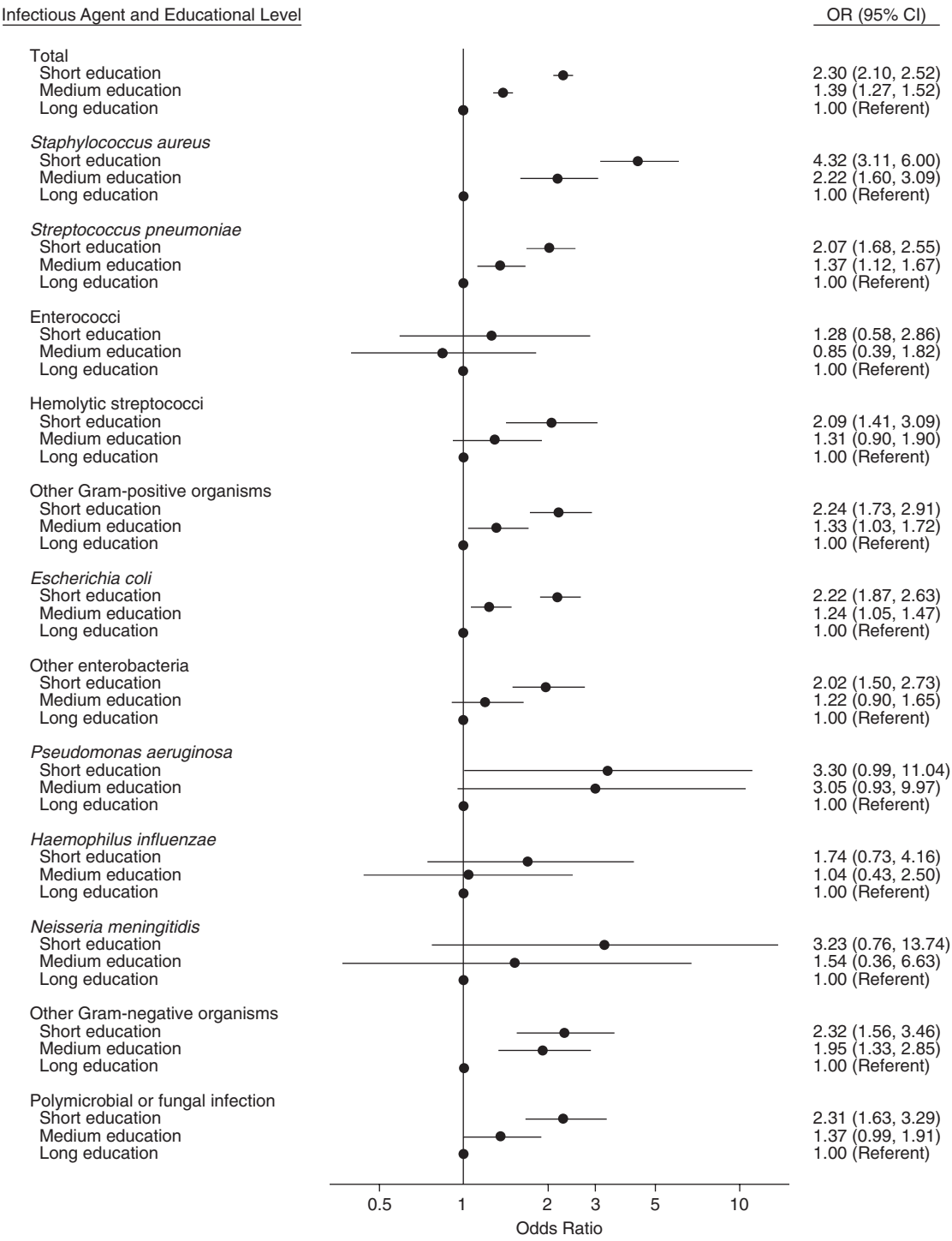

Figure 1. Odds ratios (ORs) for hospitalization for community-acquired bacteremia according to educational level, by infectious agent, Denmark, 2000–2008. Educational level was defined in accordance with the *International Standard Classification of Education 1997* (36): short (primary/lower secondary education), medium (upper secondary education), or long (tertiary education). Bars, 95% confidence intervals (CIs).

system, allowed us to conduct a population-based study with little concern about selection bias. Second, we were able to obtain individual-level SES data of high validity and on almost all study subjects (31, 32). Moreover, SES data were collected independently of our study; thus, our study had no influence on the validity of the SES data.

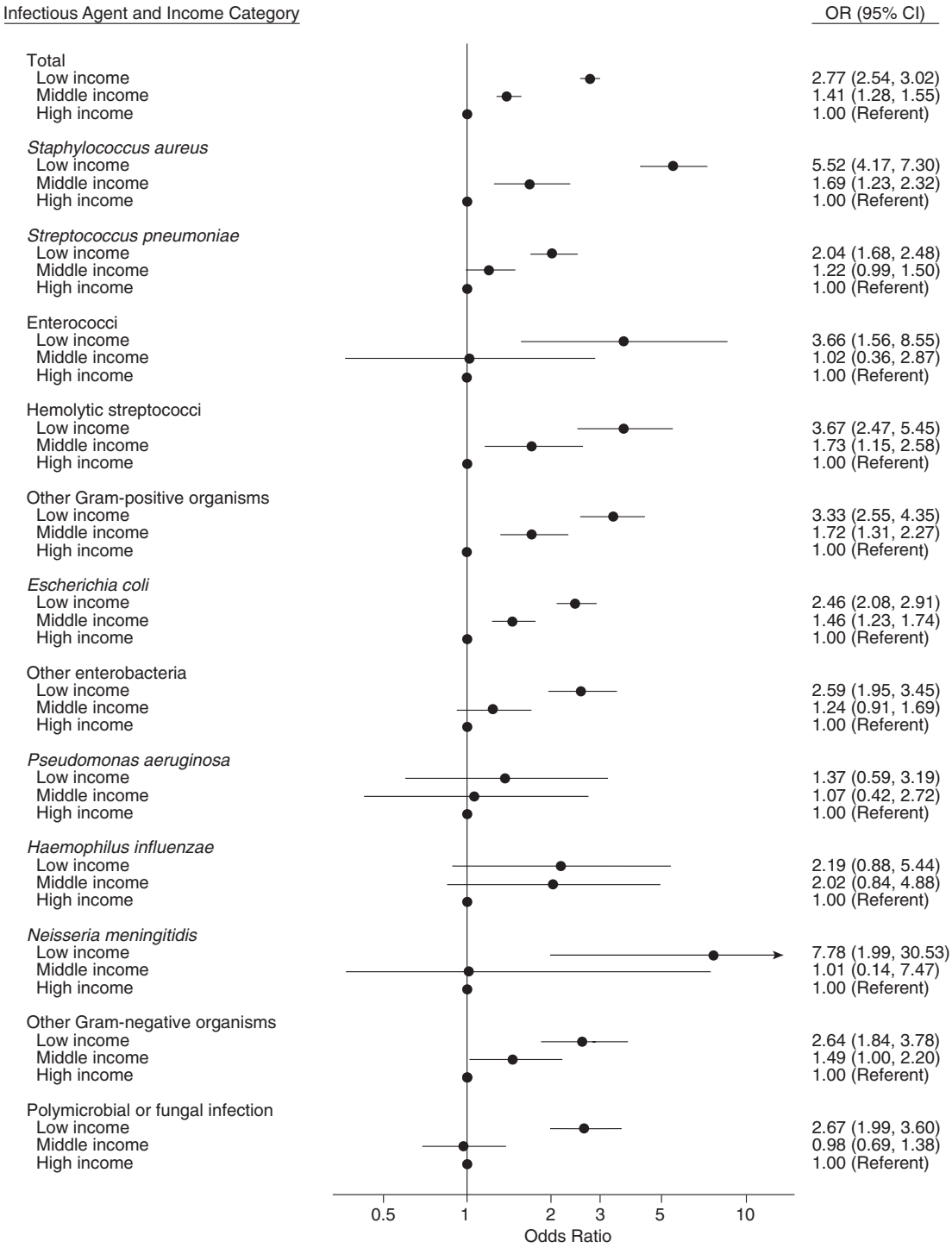

Figure 2. Odds ratios (ORs) for hospitalization for community-acquired bacteremia according to income category, by infectious agent, Denmark, 2000–2008. Income categories were based on tertiles: low (first tertile), middle (second tertile), and high (third tertile). Bars, 95% confidence intervals (CIs).

There were certain limitations of our study that also merit comment. Even though we studied more than 4,000 cases of CAB, analyses stratified by bacteremia type still had low precision. Furthermore, we included only hospitalized patients and did not know the percentage of CAB cases that was captured in our study population. We assume that most

cases of bacteremia in the age group studied here would result in hospitalization, because of the severity of the symptoms. Still, physicians may be more likely to hospitalize persons of low SES versus persons of high SES, including those with less severe bacteremia, because of concerns about poor self-care, treatment compliance, and lack of social support. The possible surveillance bias could have led to overestimation of the risk of CAB in persons of lower SES compared with persons of higher SES. In addition, physicians probably have a lower threshold for admitting persons with the coexisting chronic diseases that were associated with low SES in our study. However, our finding of a consistent inverse association between SES and CAB risk in subgroups of persons with different levels of chronic disease suggests a lack of major bias.

An important step in the prevention of severe infections is the identification of persons at increased risk. In this study, we found that persons of lower SES were at increased risk of hospitalization for CAB compared with those of higher SES. The mediating factors that contribute to this increased risk of severe infection among lower-SES individuals are complex and interwoven. In our setting within a universal welfare system, we found that differences in the prevalence of preexisting chronic conditions and substance abuse had a major role in explaining inequalities in bacteremia risk. Therefore, improvement in prevention, treatment, and management of chronic diseases among persons of lower SES could reduce inequalities in risk of CAB, along with reducing inequalities in overall health. Still, about 50% of the inequalities in CAB risk in this population remained unexplained. Therefore, the role of other potential mediating factors, including smoking, poor nutrition, overcrowding, and housing conditions, needs further investigation.

The inverse association between SES and CAB risk was consistent for all infective agents. Nonetheless, efforts targeted toward prevention of the most prevalent agents, including *E. coli* and *S. pneumoniae*, would have the largest impact on reducing inequalities in the incidence of CAB.

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Appendix Table 1. Diagnosis codes for chronic disease conditions included in a study of socioeconomic status and risk of community-acquired bacteremia, Denmark, 2000–2008[a]

Condition	ICD Version and Code(s)	
	ICD-8	ICD-10
Cardiovascular disease[b]	410, 427.09, 427.10, 427.11, 427.19, 428.99, and 782.49	I11.0, I13.0, I13.2, I21–I23, and I50
Peripheral vascular disease	440–445	I70–I74 and I77
Cerebrovascular disease	430–438	I60–I69, G45, and G46
Dementia	290.09–290.19 and 293.09	F00–F03, F05.1, and G30
Hemiplegia	344	G81 and G82
Chronic pulmonary disease	491–493 and 515–518	J41–J47, J60–J67, J68.4, J70.1, J70.3, J84.1, J92.0, J96.1, J98.2, and J98.3
Connective tissue disease	135.99, 446, 712, 716, and 734	M05, M06, M08, M09, M30–M36, and D86
Peptic ulcer disease	530.91, 530.98, and 531–534	K22.1 and K25–K28
Liver disease	070.00, 070.02, 070.04, 070.06, 070.08, 456.00–456.09, 571, 573.00, 573.01, and 573.04	B15.0, B16.0, B16.2, B18, B19.0, K70.0–K70.4, K70.09, K71–K74, K76.0, K76.6, I85
Diabetes mellitus	249 and 250	E10, E11, and E14
Moderate or severe chronic kidney disease	403, 404, 580–584, 590.09, 593.19, 753.10–753.19, and 792	I12, I13, N00–N05, N07, N11, N14, N17–N19, and Q61
Solid cancer	140–199	C00–C80
Leukemia	204–207	C91–C95
Lymphoma	200–203 and 275.59	C81–C85, C88, C90, and C96
HIV/AIDS	079.83	B20–B24
Disorders related to alcohol abuse	291, 303.19, 303.20, 303.28, 303.29, 303.91, 979, and 577.10	F10.2–F10.9, G31.2, G62.1, G72.1, I42.6, K29.2, and K86.0
Disorders related to drug abuse	294.39 and 304	F11–F16, F18, F19, and T40

Abbreviations: AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus; ICD, *International Classification of Diseases*.
[a] The Danish version of the Eighth Revision of the ICD (ICD-8) was used until the end of 1993; the Tenth Revision (ICD-10) was used thereafter.
[b] Includes previous myocardial infarction or congestive cardiac insufficiency.

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Effect of Socioeconomic Status on Mortality after Bacteremia in Working-Age Patients. A Danish Population-Based Cohort Study

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Abstract

Objectives: To examine the effect of socioeconomic status (SES) on mortality in patients with bacteremia and the underlying factors that may mediate differences in mortality.

Methods: We conducted a population-based cohort study in two Danish regions. All patients 30 to 65 years of age with first time bacteremia from 2000 through 2008 were identified in a population-based microbiological bacteremia database (n = 8,653). Individual-level data on patients' SES (educational level and personal income) and comorbid conditions were obtained from public and medical registries. We used Cox regression to examine mortality within 30 days after bacteremia with and without cumulative adjustment for potential mediators.

Results: Bacteremia patients of low SES were more likely to live alone and be unmarried than patients of high SES. They also had more pre-existing comorbidity, more substance abuse, more Staphylococcus aureus and nosocomial infections, and more admissions to small nonteaching hospitals. Overall, 1,374 patients (15.9%) died within 30 days of follow-up. Patients of low SES had consistently higher mortality after bacteremia than those of high SES crude hazard ratio for low vs. high education, 1.38 [95% confidence interval (CI), 1.18–1.61]; crude hazard ratio for low-income vs. high-income tertile, 1.58 [CI, 1.39–1.80]. Adjustment for differences in social support, pre-existing comorbidity, substance abuse, place of acquisition of the infection, and microbial agent substantially attenuated the effect of SES on mortality (adjusted hazard ratio for low vs. high education, 1.15 [95% CI, 0.98–1.36]; adjusted hazard ratio for low-income vs. high-income tertile, 1.29 [CI, 1.12–1.49]). Further adjustment for characteristics of the admitting hospital had minimal effect on observed mortality differences.

Conclusions: Low SES was strongly associated with increased 30-day mortality after bacteremia. Less social support, more pre-existing comorbidity, more substance abuse, and differences in place of acquisition and agent of infection appeared to mediate much of the observed disparities in mortality.

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Introduction

Bacteremia is an increasingly prevalent and life-threatening condition with a reported 30-day mortality above 15% in studies from industrialized countries [1,2]. In addition to increased risk of infections, low socioeconomic status (SES) may also worsen infection outcomes [3–5]. However, few studies have examined the association between SES and mortality after a severe infection, including after bacteremia.

A recent US study of patients hospitalized for sepsis adjusted for demographic factors and pre-existing comorbidity and found that, compared with married patients, widowed, single, and legally separated patients had greater odds of in-hospital death [6]. In another US study, Mendu et al. found an unadjusted relationship between neighborhood poverty rate and mortality within 1 year after bacteremia in patients admitted to intensive care units [7]. In contrast, in a population-based study from New Zealand, Huggan et al. found no relationship between an area-based measure of SES and mortality after *Staphylococcus aureus* bacteremia [8]. Thus, these previous studies have reached conflicting conclusions and used marital status as a proxy for SES or area-based measures of SES, with no data on detailed individual-level measures of SES. Moreover, none of them examined which prognostic factors may mediate socioeconomic disparities in mortality.

Compared with patients of higher SES, patients of lower SES tend to experience less social support, which may lead to more severe infection at admission and a more severe prognosis [6,9,10]. Several studies have documented the adverse impact of pre-existing comorbidity and conditions related to substance abuse on

survival after bacteremia [11–13]. Furthermore, treatment in hospitals with high patient volume and teaching status may be associated with improved outcome and patients of high SES may have a better chance of being admitted to large university hospitals [14,15].

To examine the effect of SES on mortality after bacteremia, we designed a population-based cohort study. We used two different individual-level indicators of SES, educational level and personal income, to capture different aspects of socioeconomic stratification. We further evaluated if differences in social support, pre-existing comorbidity, substance abuse, infection characteristics, and characteristics of the admitting hospital could explain socioeconomic differences in mortality after bacteremia.

Methods

Study Design

We conducted this study as a population-based cohort study. The geographic area included two Danish regions (North Denmark Region and Capital Region) with a total population of 1.7 million persons. All hospitalized patients aged 30 to 65 years with first time bacteremia from 2000 through 2008 were included in the cohort.

Setting

The Danish tax-funded welfare system provides free access to health care, education, and benefits such as pensions and unemployment coverage. All citizens are granted free services at general practitioners and public hospitals. Only 1% of hospital beds are in the private sector.

Since April 1, 1968, all citizens in Denmark have been registered in the Civil Registration System. A unique personal identification number (civil registration number) allows accurate linkage of information among national registries, including medical registries.

Identification of Patients with Bacteremia

We obtained data from the Danish Collaborative Bacteremia Network (DACOBAN). This network includes the Departments of Clinical Microbiology in the North Denmark Region (Aalborg Hospital) and the greater Copenhagen area (Hvidovre Hospital and Herlev Hospital). DACOBAN was established to enable coordinated surveillance of all cases of bacteremia in the two regions and to study risk factors and prognostic factors for bacteremia [16]. The three departments that serve these regions record data on all microbiological specimens, including blood cultures, in an electronic laboratory information system (ADBakt, Autonik, Ramsta, Sweden). A research database that consists of all patients with a first-time diagnosis of bacteremia between January 1, 2000 and December 31, 2008 has been established from data from these laboratory information systems. Bacteremia was defined as bacterial or fungal growth in blood cultures where contamination had been ruled out. Coagulase-negative staphylococci, Corynebacterium spp., Bacillus spp. and Propionibacterium acnes were regarded as contaminants unless they were isolated from two or more separate blood culture sets within a 5-day period [17].

We only included patients in the age group of 30 to 65 years because we assumed that most of them had completed their education and were of working age. The civil registration number, age, sex, the date on which the first positive blood culture was drawn (date of bacteremia diagnosis), hospital and specialty, microbial agent, and place of acquisition of infection (community-acquired or nosocomial) were included in the database for all patients. Bacteremia was defined as community-acquired if the first positive blood culture was obtained within 48 hours after hospital admission and as nosocomial if it was drawn more than 48 hours after hospital admission.

Socioeconomic Status

SES was based on patients' educational level and personal income. Although the two indicators are related they measure different aspects of socioeconomic stratification. Formal education is normally completed in young adulthood and will therefore to some extent measure early life SES. In contrast, income can change over a life course, but may better capture aspects of SES later in life [18,19]. To assess the effect of both early life SES and later life SES on mortality after bacteremia, we examined both SES indicators.

SES data were obtained for all patients through registries maintained by the government agency Statistics Denmark [20–22]. These registries contain detailed individual-level socioeconomic data, updated yearly, for all Danish citizens. Information on patients' highest completed education was obtained from the Population's Education Register, which consists of data generated from surveys and from the administrative records of educational institutions. In 2008 the register contained valid information on education for 97% of the Danish population born from 1945 to 1990 [20]. We categorized educational level into primary/lower secondary education (low), upper secondary education (medium), and tertiary education (high) according to the International Standard Classification of Education (1997) [23].

Patients' personal annual income was all income subject to income taxation (wages and salaries, and all types of benefits and pensions). Income data was obtained from the Income Statistics Register. Data in the register are primarily supplied by tax authorities and the income data are assumed to equal the real income [21]. Personal annual income was adjusted for inflation according to the year 2000 value of the Danish crown (DKK) and was grouped into tertiles: low-income (1st tertile), middle-income (2nd tertile) and high-income (3rd tertile).

We also obtained data on patients' employment status, nationality, cohabitation status, and marital status. Employment status was grouped into employed/self-employed, unemployed/employment subsidized by labor market arrangement and early retirement pensioners. We used cohabitation status and marital status as markers for social support. For all variables, we used data from the year preceding the index date of the bacteremia diagnosis.

Pre-existing Comorbidity

We obtained data from the Danish National Patient Registry for all diagnoses recorded from the start of the registry until the date of bacteremia diagnosis. The registry contains information for almost 100% of all inpatient admissions to public and private non-psychiatric hospitals in Denmark since 1977 and from outpatient and emergency room visits since 1995. Each record includes one primary diagnosis and up to 20 secondary diagnoses, which have been classified according to the International Classification of Diseases [24].

Pre-existing comorbidity was summarized according to the Charlson Comorbidity Index, which was originally developed to predict 1-year mortality in hospitalized medical patients [25]. Since then, the index has been adapted and validated for use with hospital diagnoses and has been used in previous studies of the association between comorbidity and survival after bacteremia [13,26,27]. The index consists of 19 disease groups and each disease group is assigned a specific weight depending on the

severity of the pre-existing condition. Based on the Charlson index scores three levels of comorbidity were defined: 0 (low), corresponding to patients with no recorded pre-existing comorbidity; 1–2 (medium), and >2 (high).

Diagnoses related to substance abuse (alcohol and drug abuse) are not included in the Charlson index and may influence prognosis after bacteremia. Therefore, we also collected data on previous alcohol- and drug-abuse-related diagnoses from the National Patient Registry.

Hospital Characteristics

Patients were treated in 1 of 16 public hospitals. We characterized these hospitals according to number of hospital beds, hospital volume, and medical school affiliation. We categorized hospital beds, setup and staffed for use, as less than 300 beds or 300 beds or more. Hospital volume was defined as the annual number of bacteremia patients treated at the institution and categorized as low-volume (≤99 bacteremia patients treated per year), medium-volume (100–299 per year), and high-volume (≥300 per year) hospitals. Teaching hospitals were defined as hospitals directly affiliated with a medical school.

Follow-up and Mortality

Our outcome was all-cause mortality within 30 days after the bacteremia diagnosis. We obtained data on each patient's vital status from the Danish Civil Registration System [28]. This registry contains daily updated information on all changes in vital status and migration for all Danish citizens. Patients were followed from the date of their diagnosis to the time of death, date of emigration, or completion of 30 days of follow-up, whichever occurred first.

Statistical Analysis

We first constructed contingency tables to provide information on baseline characteristics and crude outcomes according to SES, which were inferred on the basis of patients' educational level and personal income. Using Kaplan-Meier plots we examined mortality within 30 days after bacteremia according to SES.

A Cox proportional hazards model was constructed to determine the association between SES and 30-day mortality. We performed a sequential cumulative adjustment analysis to assess whether differences in social support (cohabitation and marital status), pre-existing comorbidity (comorbidity included in the Charlson Comorbidity Index and conditions related to substance abuse), infection characteristics (place of acquisition, microbial agent, and admitting specialty) or hospital characteristics (number of hospital beds, hospital volume, and medical school affiliation) accounted for socioeconomic differences in mortality. We included the potential mediators in our analyses in a sequence that reflected the temporal relation of the potential mediators (e.g., we assumed that SES would normally precede comorbidity existing at the time of the bacteremia diagnosis).

Log-minus-log plots were used to confirm that the proportional hazards assumption was not violated [29]. All analyses were performed with Stata statistical software, version 11.2 (StataCorp, College Station, TX). The study was approved by the Danish Data Protection Agency (Record no. 2010-41-5650). Informed consent was not required by Danish law.

Results

Patient Characteristics

The cohort consisted of 8,653 hospitalized patients aged 30 to 65 years with a first time diagnosis of bacteremia, which corresponded to an incidence of 114 episodes per 100,000 person-years in our study population. The median age of the cohort was 55 years (interquartile range, 47 to 61), and 3,853 (44.5%) were women. Table 1 shows baseline characteristics according to educational level. Only small differences with respect to age and gender were seen. Patients with higher education were slightly younger. The medium-educated patients were more likely to be male. On average, patients with lower education were much less affluent than those with higher education (i.e., 44.7% vs. 17.4% in the lowest income tertile). They were more likely to live alone and be unmarried, and were substantially more likely to be out of the workforce (70.6%) than the patients with higher education (34.6%). Virtually all pre-existing comorbidities were more prevalent among patients with lower education. Only solid cancer, leukaemia, and lymphoma were more prevalent among those with a higher education. Similarly, the prevalence of conditions related to alcohol and drug abuse were substantially increased among those with lower education. Patients with lower education were also more likely to have *Staphylococcus aureus* bacteremia, to have a nosocomial infection, and to receive intensive care. In addition, patients with lower education were more likely to be admitted to small, low-volume, and nonteaching hospitals.

A similar but more extreme pattern of differences was seen for income categories: bacteremia patients with low versus high income were 1.5 times more likely to live alone and be unmarried, had a 1.5 to 4 times higher prevalence of many comorbidities, and had a more than 4-fold higher risk of substance abuse (Table 2).

Mortality

Overall, 1,374 patients (15.9%) died within 30 days of follow-up. There was a substantial gradient in mortality according to both educational level and income categories. Survival curves for the different levels of education and income diverged early after the bacteremia diagnosis and the differences in mortality persisted throughout the 30 days of follow-up (Figure 1). The 30-day mortality among the lower educated patients was 17.4% compared with 13.0% for those with higher education, which was an absolute difference in 30-day mortality of 4.5% [95% confidence interval (CI): 2.4–6.5%] and corresponded to a crude hazard ratio of 1.38 [95% CI: 1.18–1.61]. The difference in 30-day mortality was 6.7% [95% CI: 4.8–8.6%] when patients in the low-income tertile (30-day mortality, 19.7%) were compared with patients in the high-income tertile (30-day mortality, 12.9%). This corresponded to a crude hazard ratio of 1.58 [95% CI: 1.39–1.80].

Sequential adjustment for social support, pre-existing comorbidity, substance abuse, and infection characteristics attenuated the effect of SES on mortality (Table 3 and 4). Further adjustment for differences in characteristics of the admitting hospital had only a marginal impact on the adjusted 30-day mortality hazard ratios. The fully adjusted risk estimates showed that there was still a residual difference in mortality according to both educational level (low vs. high education, 1.14 [95% CI: 0.97–1.35] and income categories (low vs. high income, 1.30 [95% CI: 1.13–1.49] after adjustment for a range of known prognostic factors.

To examine whether income mediated the effect of education, we also included income as a covariate in our statistical model examining the effect of education on mortality. The effect of education on mortality after bacteremia was further attenuated after inclusion of income as a covariate (low vs. high education, 1.08 [95% CI: 0.91–1.28]), showing that income in part mediated the effect of education.

Table 1. Baseline characteristics of 8,382 patients with bacteremia, aged 30 to 65 years, categorized according to educational level.

	Educational level					
	Low		Medium		High	
Variable	**(n = 3,457; 41.2%)**		**(n = 3,312; 39.5%)**		**(n = 1,613; 19.2%)**	
Demographic charateristic						
Median age, *y*	56		56		54	
Men, n (%)	1,770	(51.2)	2,041	(61.6)	841	(52.1)
Nationality, n (%)						
Danish	3,187	(92.2)	3,057	(92.3)	1,448	(89.8)
Immigrants from Western countries	72	(2.1)	102	(3.1)	67	(4.2)
Immigrants from non-Western countries	198	(5.7)	153	(4.6)	98	(6.1)
Socioeconomic indicators, n (%)						
Income category						
Low (1st tertile)	1,544	(44.7)	965	(29.1)	281	(17.4)
Middle (2nd tertile)	1,309	(37.9)	1,145	(34.6)	335	(20.8)
High (3rd tertile)	600	(17.4)	1,194	(36.1)	995	(61.7)
Data missing	4	(0.1)	8	(0.2)	2	(0.1)
Employment						
Employed/self-employed	1,007	(29.1)	1,693	(51.1)	1,049	(65.0)
Unemployed/labor market arrangement	910	(26.3)	793	(23.9)	309	(19.2)
Early retirement pension	1,530	(44.3)	812	(24.5)	249	(15.4)
Data missing	10	(0.3)	14	(0.4)	6	(0.4)
Social support, n (%)						
Living alone						
Yes	1,788	(51.7)	1,325	(40.0)	581	(36.0)
No	1,669	(48.3)	1,987	(60.0)	1,032	(64.0)
Marital status						
Married	1,458	(42.2)	1,826	(55.1)	971	(60.2)
Divorced or widowed	1,006	(29.1)	833	(25.2)	317	(19.7)
Never married	983	(28.4)	639	(19.3)	319	(19.8)
Data missing	10	(0.3)	14	(0.4)	6	(0.4)
Pre-existing comorbidity, n (%)						
Clinical conditions included in the CCI						
Previous myocardial infarction	207	(6.0)	185	(5.6)	64	(4.0)
Congestive cardiac insufficiency	213	(6.2)	157	(4.7)	53	(3.3)
Peripheral vascular disease	236	(6.8)	192	(5.8)	62	(3.8)
Cerebrovascular disease	332	(9.6)	330	(10.0)	113	(7.0)
Dementia	36	(1.0)	44	(1.3)	13	(0.8)
Hemiplegia	49	(1.4)	28	(0.9)	11	(0.7)
Chronic pulmonary disease	475	(13.7)	297	(9.0)	98	(6.1)
Connective tissue disease	146	(4.2)	142	(4.3)	58	(3.6)
Peptic ulcer disease	450	(13.0)	333	(10.1)	81	(5.0)
Mild liver disease	454	(13.1)	364	(11.0)	99	(6.1)
Moderate or severe liver disease	212	(6.1)	166	(5.0)	53	(3.3)
Diabetes, without complications	488	(14.1)	398	(12.0)	140	(8.7)
Diabetes with complications	311	(9.0)	248	(7.5)	86	(5.3)
Moderate or severe kidney disease	264	(7.6)	282	(8.5)	91	(5.6)
Solid cancer	590	(17.1)	628	(19.0)	312	(19.3)
Metastatic solid cancer	135	(3.9)	171	(5.2)	97	(6.0)
Leukemia	47	(1.4)	74	(2.2)	37	(2.3)

Table 1. Cont.

	Educational level					
	Low		Medium		High	
Variable	(n = 3,457; 41.2%)		(n = 3,312; 39.5%)		(n = 1,613; 19.2%)	
Lymphoma	102	(3.0)	160	(4.8)	98	(6.1)
HIV/AIDS	67	(1.9)	24	(0.7)	6	(0.4)
Charlson comorbidity index score						
Low (0)	1,103	(31.9)	1,182	(35.7)	733	(45.4)
Medium (1–2)	1,291	(37.3)	1,182	(35.7)	507	(31.4)
High (>2)	1,063	(30.8)	948	(28.6)	373	(23.1)
Substance abuse, n (%)						
Alcohol abuse	719	(20.8)	624	(18.8)	192	(11.9)
Drug abuse	344	(10.0)	115	(3.5)	38	(2.4)
Characteristics of infection, n (%)						
Microbial agent						
Staphylococcus aureus	565	(16.3)	546	(16.5)	226	(14.0)
Streptococcus pneumoniae	394	(11.4)	375	(11.3)	190	(11.8)
Other gram-positive organisms	645	(18.7)	641	(19.4)	356	(22.1)
Escherichia coli	866	(25.1)	803	(24.3)	411	(25.5)
Other enterobacteria	1,302	(37.7)	1,206	(36.4)	609	(37.8)
Other gram-negative organisms	268	(7.8)	295	(8.9)	126	(7.8)
Polymicrobial or fungal	396	(11.5)	384	(11.6)	172	(10.7)
Acquisition						
Community-acquired	2,175	(62.9)	2,089	(63.1)	1,054	(65.3)
Nosocomial	1,266	(36.6)	1,207	(36.4)	550	(34.1)
Data missing	16	(0.5)	16	(0.5)	9	(0.6)
Specialty						
Internal medicine	2,269	(65.6)	2,110	(63.7)	996	(61.8)
Surgery	847	(24.5)	899	(27.1)	495	(30.7)
Intensive care	327	(9.5)	286	(8.6)	108	(6.7)
Data missing	14	(0.4)	17	(0.5)	14	(0.9)
Hospital characteristics, n (%)						
Bed size						
Low (<300 beds)	725	(21.0)	601	(18.2)	242	(15.0)
High (>300 beds)	2,732	(79.0)	2,711	(81.9)	1,371	(85.0)
Hospital volume[a]						
Low (≤99/year)	678	(19.6)	561	(16.9)	271	(16.8)
Medium (100–299/year)	517	(15.0)	492	(14.9)	190	(11.8)
High (≥300/year)	2,262	(65.4)	2,259	(68.2)	1,152	(71.4)
Teaching hospital[b]						
No	497	(14.4)	404	(12.2)	177	(11.0)
Yes	2,960	(85.6)	2,908	(87.8)	1,436	(89.0)
Mortality, n (%)						
30-day	602	(17.4)	529	(16.0)	209	(13.0)

Abbreviation: CCI, Charlson comorbidity index.
[a]Hospital volume was defined as the annual number of bacteremia patients treated at the institution.
[b]Teaching hospitals were defined as hospitals directly affiliated with a medical school.
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Table 2. Baseline characteristics of 8,633 patients with bacteremia, aged 30 to 65 years, categorized according to income.

	Income category					
	Low		Middle		High	
Variable	(1st tertile; n = 2,878)		(2nd tertile; n = 2,878)		(3rd tertile; n = 2,877)	
Demographic charateristic						
Median age, *y*	55		55		55	
Men, n (%)	1,450	(50.4)	1,481	(51.5)	1,858	(64.6)
Nationality, n (%)						
Danish	2,524	(87.7)	2,633	(91.5)	2,713	(94.3)
Immigrants from Western countries	109	(3.8)	78	(2.7)	84	(2.9)
Immigrants from non-Western countries	245	(8.5)	167	(5.8)	80	(2.8)
Socioeconomic indicators, n (%)						
Educational level						
Low	1,515	(52.6)	1,320	(45.9)	618	(21.5)
Medium	943	(32.8)	1,138	(39.5)	1,223	(42.5)
High	274	(9.5)	337	(11.7)	1,000	(34.8)
Data missing	146	(5.1)	83	(2.9)	36	(1.3)
Employment						
Employed/self-employed	412	(14.3)	1,023	(35.6)	2,367	(82.3)
Unemployed/labor market arrangement	843	(29.3)	995	(34.6)	260	(9.0)
Early retirement pension	1,605	(55.8)	858	(29.8)	248	(8.6)
Data missing	18	(0.6)	2	(0.1)	2	(0.1)
Social support, n (%)						
Living alone						
Yes	1,513	(52.6)	1,428	(49.6)	923	(32.1)
No	1,365	(47.4)	1,450	(50.4)	1,954	(67.9)
Marital status						
Married	1,239	(43.1)	1,315	(45.7)	1,789	(62.2)
Divorced or widowed	883	(30.7)	775	(26.9)	578	(20.1)
Never married	738	(25.6)	786	(27.3)	508	(17.7)
Data missing	18	(0.6)	2	(0.1)	2	(0.1)
Pre-existing comorbidity, n (%)						
Clinical conditions included in the CCI						
Previous myocardial infarction	170	(5.9)	161	(5.6)	135	(4.7)
Congestive cardiac insufficiency	167	(5.8)	157	(5.5)	115	(4.0)
Peripheral vascular disease	207	(7.2)	178	(6.2)	117	(4.1)
Cerebrovascular disease	310	(10.8)	284	(9.9)	207	(7.2)
Dementia	40	(1.4)	39	(1.4)	14	(0.5)
Hemiplegia	21	(0.7)	48	(1.7)	24	(0.8)
Chronic pulmonary disease	397	(13.8)	328	(11.4)	175	(6.1)
Connective tissue disease	138	(4.8)	128	(4.5)	93	(3.2)
Peptic ulcer disease	406	(14.1)	323	(11.2)	167	(5.8)
Mild liver disease	498	(17.3)	321	(11.2)	135	(4.7)
Moderate or severe liver disease	227	(7.9)	160	(5.6)	61	(2.1)
Diabetes, without complications	436	(15.2)	378	(13.1)	238	(8.3)
Diabetes with complications	285	(9.9)	238	(8.3)	136	(4.7)
Moderate or severe kidney disease	235	(8.2)	238	(8.3)	180	(6.3)
Solid cancer	430	(14.9)	500	(17.4)	624	(21.7)
Metastatic solid cancer	100	(3.5)	138	(4.8)	169	(5.9)
Leukemia	40	(1.4)	55	(1.9)	66	(2.3)
Lymphoma	70	(2.4)	114	(4.0)	177	(6.2)

Table 2. Cont.

	Income category					
	Low		Middle		High	
Variable	(1st tertile; n = 2,878)		(2nd tertile; n = 2,878)		(3rd tertile; n = 2,877)	
HIV/AIDS	62	(2.2)	32	(1.1)	13	(0.5)
Charlson comorbidity index score						
Low (0)	872	(30.3)	981	(34.1)	1,259	(43.8)
Medium (1–2)	1,064	(37.0)	1,035	(36.0)	976	(33.9)
High (>2)	942	(32.7)	862	(30.0)	642	(22.3)
Substance abuse, n (%)						
Alcohol abuse	829	(28.8)	526	(18.3)	235	(8.2)
Drug abuse	338	(11.7)	148	(5.1)	45	(1.6)
Characteristics of infection, n (%)						
Microbial agent						
Staphylococcus aureus	513	(17.8)	463	(16.1)	409	(14.2)
Streptococcus pneumoniae	308	(10.7)	295	(10.3)	384	(13.4)
Other gram-positive organisms	556	(19.3)	547	(19.0)	582	(20.2)
Escherichia coli	694	(24.1)	749	(26.0)	693	(24.1)
Other enterobacteria	1,031	(35.8)	1,108	(38.5)	1,066	(37.1)
Other gram-negative organisms	223	(7.8)	253	(8.8)	230	(8.0)
Polymicrobial or fungal	345	(12.0)	318	(11.1)	322	(11.2)
Acquisition						
Community-acquired	1,766	(61.4)	1,831	(63.6)	1,880	(65.4)
Nosocomial	1,096	(38.1)	1,036	(36.0)	983	(34.2)
Data missing	16	(0.6)	11	(0.4)	14	(0.5)
Specialty						
Internal medicine	1,857	(64.5)	1,862	(64.7)	1,830	(63.6)
Surgery	719	(25.0)	745	(25.9)	835	(29.0)
Intensive care	289	(10.0)	254	(8.8)	196	(6.8)
Data missing	13	(0.5)	17	(0.6)	16	(0.6)
Hospital characteristics, n (%)						
Bed size						
Low (<300 beds)	575	(20.0)	607	(21.1)	443	(15.4)
High (>300 beds)	2,303	(80.0)	2,271	(78.9)	2,434	(84.6)
Hospital volume[a]						
Low (≤99/year)	552	(19.2)	559	(19.4)	457	(15.9)
Medium (100–299/year)	417	(14.5)	434	(15.1)	383	(13.3)
High (≥300/year)	1,909	(66.3)	1,885	(65.5)	2,037	(70.8)
Teaching hospital[b]						
No	377	(13.1)	437	(15.2)	291	(10.1)
Yes	2,501	(86.9)	2,441	(84.8)	2,586	(89.9)
Mortality, n (%)						
30-day	566	(19.7)	433	(15.1)	371	(12.9)

Abbreviation: CCI, Charlson comorbidity index.
[a]Hospital volume was defined as the annual number of bacteremia patients treated at the institution.
[b]Teaching hospitals were defined as hospitals directly affiliated with a medical school.
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Discussion

In this population-based cohort study we found that patients of lower SES, inferred on the basis of educational level and income, had higher 30-day mortality after bacteremia than those of higher SES. The association between SES and mortality was most pronounced when we used income as SES indicator. More than half of the socioeconomic differences in mortality could be explained by differences in social support, pre-existing comorbidity, alcohol and drug abuse, and characteristics of the infection. In

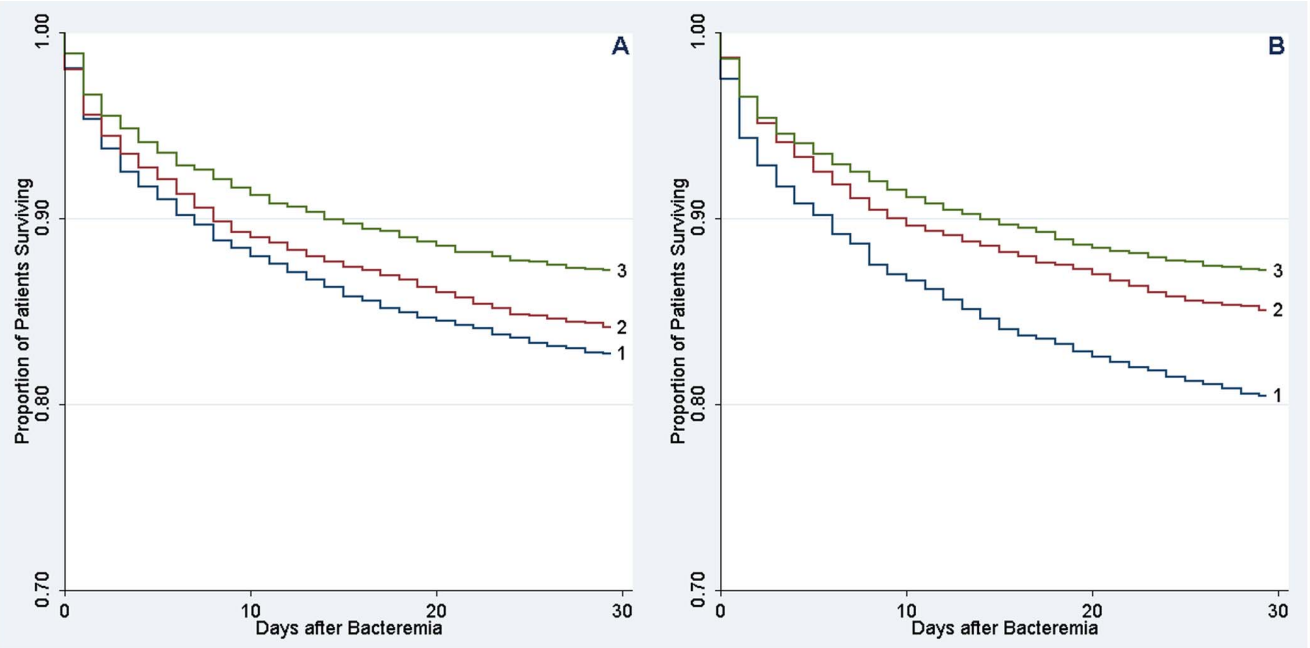

Figure 1. Crude Kaplan-Meier survival curves according to socioeconomic status. A) Educational level (low 1, medium 2, high 3), B) Income (low 1, middle 2, high 3).
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contrast, characteristics of the admitting hospital had only a marginal explanatory effect on the socioeconomic mortality differences. Our findings thus suggest that socioeconomic disparities in mortality after bacteremia are to a large extent explained by a range of adverse prognostic factors that are present before hospital admission and include severe pre-existing comorbidity, unhealthy lifestyle, and lack of social support.

Table 3. 30-day mortality risk after first time diagnosis of bacteremia according to educational level and effect of adjustment for social support, pre-existing comorbidity, substance abuse, characteristics of infection, and hospital characteristics.

	Educational level		
	Low	**Medium**	**High**
Unadjusted	1.38 (1.18–1.61)	1.25 (1.07–1.47)	1.00 (reference)
Adjusted			
Demographic characteristics[a]	1.33 (1.14–1.56)	1.17 (0.99–1.37)	1.00 (reference)
+ social support[b]	1.27 (1.08–1.49)	1.15 (0.98–1.35)	1.00 (reference)
+ pre-existing comorbidity[c]	1.20 (1.02–1.41)	1.08 (0.92–1.28)	1.00 (reference)
+ characteristics of infection[d]	1.15 (0.98–1.36)	1.04 (0.88–1.22)	1.00 (reference)
+ hospital characteristics[e]	1.14 (0.97–1.35)	1.03 (0.88–1.22)	1.00 (reference)

[a]Age, sex, and nationality.
[b]Cohabitation and marital status.
[c]Comorbidities included in the Charlson comorbidity index and conditions related to substance abuse.
[d]Microbial agent, place of acquisition, and admitting specialty.
[e]Number of hospital beds, hospital volume, and medical school affiliation.
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For the clinician it is important to know if certain groups of patients with severe infection have a poorer prognosis than others and our study therefore has clinical implications. Worse prognosis among bacteremia patients of lower SES imply that these patients would benefit from increased clinical attention. Our findings of a much higher prevalence of comorbidities among bacteremia patients of lower SES suggest that special attention should be paid to improved management of these patients' comorbidities, which may reduce their excess mortality risk.

We are aware of only three studies that have examined socioeconomic disparities in mortality in cohorts of patients with sepsis or bacteremia. Seymour et al. conducted a population-based cohort study of 37,524 hospitalizations for sepsis in New Jersey, US [6]. After adjusting for demographic factors and comorbid conditions, they found that single and divorced men and single women had greater odds of in-hospital mortality than married persons. In contrast to our study, this study used marital status as a proxy for social factors and did not include data on more precise measures of SES, such as educational level and income. Furthermore, identification of patients with infections was based on administrative ICD-9-CM codes and the infections were not microbiologically verified. Mendu et al. analyzed data from 2,435 patients with bacteremia who were admitted to intensive care units at two hospitals in Boston, Massachusetts, US [7]. This study reported an unadjusted 'dose-response' relationship between neighborhood poverty rate and mortality within one year after bacteremia among patients receiving critical care. Adjustment for demographic factors, patient type, comorbidity, laboratory data, and severity of illness attenuated this association substantially and the authors concluded that neighborhood poverty was not associated with mortality after bacteremia. However, their use of an aggregate area-based measure of SES may have led to some inaccuracy due to misclassification of individual SES. A third study

Table 4. 30-day mortality risk after first time diagnosis of bacteremia according to income and effect of adjustment for social support, pre-existing comorbidity, substance abuse, characteristics of infection, and hospital characteristics.

	Income Category		
	Low (1st tertile)	Middle (2nd tertile)	High (3rd tertile)
Unadjusted	1.58 (1.39–1.80)	1.18 (1.02–1.35)	1.00 (reference)
Adjusted			
Demographic characteristics[a]	1.69 (1.48–1.93)	1.22 (1.07–1.41)	1.00 (reference)
+ social support[b]	1.58 (1.38–1.81)	1.16 (1.01–1.33)	1.00 (reference)
+ pre-existing comorbidity[c]	1.37 (1.19–1.57)	1.08 (0.92–1.22)	1.00 (reference)
+ characteristics of infection[d]	1.29 (1.12–1.49)	1.03 (0.89–1.18)	1.00 (reference)
+ hospital characteristics[e]	1.30 (1.13–1.49)	1.03 (0.89–1.19)	1.00 (reference)

[a]Age, sex, and nationality.
[b]Cohabitation and marital status.
[c]Comorbidities included in the Charlson comorbidity index and conditions related to substance abuse.
[d]Microbial agent, place of acquisition, and admitting specialty.
[e]Number of hospital beds, hospital volume, and medical school affiliation.
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by Huggan et al. included 779 patients with *Staphylococcus aureus* bacteremia admitted to hospitals in Canterbury, New Zealand [8]. The authors reported that there was no relationship between an address-based measure of deprivation and mortality but did not present any estimates. This study also used an area-based measure of SES, which may have resulted in misclassification of individual SES [30].

In contrast with previous studies we used a sequential cumulative adjustment analysis to evaluate a range of recognized prognostic factors as potential mediators of the socioeconomic mortality differences. Even after full adjustment for all the potential mediators included in our study, we still found a residual difference in mortality. It is likely that the residual difference may be explained partly by greater levels of undiagnosed comorbidity among patients of lower SES, which again may be due to poor self-care and late presentation of clinical disease. However, we speculate that unmeasured variation in severity of infection at admission may also explain some of the residual mortality differences. Furthermore, since we did not have precise data on bacteremia patients' care and treatment, we cannot rule out that difference in the quality of care contributed to the residual mortality differences.

Our study has several important limitations. First, we used information collected during routine clinical work and data from administrative registries, which limited clinical detail in our study. More information on clinical parameters would have enabled us to better characterize severity of the infection and to assess any differences in severity according to SES. On the other hand, the use of routinely collected microbiological data and accurate linkage of high-quality registries enabled us to avoid some major methodological problems, such as selection and surveillance bias. Use of prospectively recorded individual data on SES indicators, which were collected independently, also reduced misclassification of patients SES. Second, our outcome measure was all-cause mortality, and we did not have any data on other important outcomes, such as recovery and functional status. When interpreting all-cause mortality, it must be considered that patients may have died from causes unrelated to their infection. Nevertheless, by including only deaths that occurred within 30 days after the date of bacteremia diagnosis we assume that most deaths would be at least to some extent related to the infection. Third, even though we studied a large cohort of bacteremia patients statistical precision was still limited. Fourth, we included bacteremia patients with a microbiologically confirmed infection, which allowed us to assess the mediating effect of the microbial agent on the association between SES and mortality. We can assume that the vast majority of the bacteremia patients in our cohort fulfilled the criteria for sepsis [31,32]. However, since less than 50% of patients with sepsis have documented bacteremia, our findings cannot necessarily be generalised to sepsis patients [33,34].

In conclusion, we found that patients of low SES had higher mortality within 30 days after bacteremia than those of high SES. Differences in social support, pre-existing comorbidity, substance abuse, and characteristics of the infection were important explanatory factors for these SES-mortality gradients. In contrast, characteristics of the admitting hospital seemed to have a negligible role in explaining disparities in mortality. The residual impact of SES on mortality might be explained by differences in bacteremia severity and treatment of the infection. Future studies should assess the importance of potential differences in severity of illness and quality of care in explaining socioeconomic mortality differences after bacteremia.

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Author Contributions

Conceived and designed the experiments: KK MN HCS MS. Performed the experiments: KK MN HCS RWT MS. Analyzed the data: KK. Contributed reagents/materials/analysis tools: KK MN HCS RWT MS. Wrote the paper: KK. Data management: KK. Critical revision of the manuscript: KK MN HCS RWT MS. Final approval of the submitted manuscript: KK MN HCS RWT MS.

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Relation between socioeconomic status and inappropriate empirical antimicrobial therapy in bacteremia patients

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Abstract

Background: Early administration of appropriate antimicrobial therapy is associated with increased survival in patients with severe infections. Little is known about the relationship between socioeconomic status and the risk of receiving inappropriate empirical antimicrobial therapy in patients with bacteremia.

Methods: We performed a prevalence study of adult bacteremia patients (30-65 years of age) in Northern Denmark. All patients with a first time bacteremia between 1 January 2000 and 31 December 2008 were identified in a population-based bacteremia database. Individual-level information on patients' income was obtained from Statistics Denmark and used as marker of socioeconomic status. We computed sex- and age-adjusted risk estimates for receiving inappropriate therapy according to tertile income groups, using log-binomial regression analysis.

Results: Among 2,253 patients diagnosed with bacteremia during the study period, 31.8% received inappropriate empirical antimicrobial therapy. Compared with patients in the highest income group, those in the lowest income group had a 24% greater risk of receiving inappropriate antimicrobial therapy (low [34.6%] vs. high income [29.0%]; adjusted relative risk, RR: 1.24 [95% confidence interval, CI: 1.06-1.46]). The association between income and risk of inappropriate therapy was more pronounced in patients with health care-related bacteremia (33.8% vs. 24.5%; adjusted RR: 1.42 [95% CI: 0.98-2.06]), than in patients with community-acquired bacteremia (25.5% vs. 20.8%; adjusted RR: 1.28, 95% CI: 0.96-1.71), and patients with nosocomial bacteremia (48.4% vs. 42.7%; adjusted RR: 1.13, 95% CI: 0.92-1.39).

Conclusions: Less affluent bacteremia patients are more likely to receive inappropriate empirical antimicrobial therapy than more affluent patients.

Introduction

Bacteremia is a severe infection and associated with considerable morbidity and mortality [1]. Extrapolating from existing population-based studies, Goto and Al-Hasan recently estimated that bacteremia accounts for more than 250.000 deaths each year in North America and Europe combined [2]. These estimates place bacteremia among the top eight causes of death in Western populations [3]. Despite the use of evidence-based treatment strategies and availability of antibiotics that secure coverage of the most prevalent microorganisms, the average in-hospital, or 30-day mortality from bacteremia remains above 15% in adults [1].

A large body of literature have documented that early administration of appropriate antimicrobial therapy is associated with increased survival in bacteremia patients [4-6]. Still, up to 40% of patients with bacteremia receive inappropriate empirical antimicrobial therapy [7-9].

We have recently documented notable socioeconomic disparities in mortality among bacteremia patients in Denmark [10]. In patients with low income the 30-day mortality after bacteremia was 19.7% compared with 12.9% in patients with high income (sex- and age-adjusted hazard ratio 1.69; 95% confidence interval, CI: 1.48-1.93). It is important to know if patients of lower socioeconomic status (SES) are less likely to receive appropriate antimicrobial therapy. Any socioeconomic differences in the therapy received may, in part, explain disparities in mortality and will emphasize the need for improved care in this segment of the patient population. However, to our knowledge, no previous study has examined if the appropriateness of empirical antimicrobial therapy varies across socioeconomic groups.

Compared with persons of higher SES, persons of lower SES may be more prone to experience infections caused by antimicrobial-resistant pathogens and pathogens unexpected by the attending physician [11-13]. Furthermore, previous studies have documented that clinical practice

recommendations are less likely to be followed in patients of lower SES [14-16]. Therefore, we hypothesized that bacteremia patients of lower SES are at increased risk of receiving inappropriate antimicrobial therapy compared with those of higher SES. We tested this hypothesis in a population based prevalence study, using personal income as a marker of SES, to examine socioeconomic differences in the appropriateness of empirical antimicrobial therapy.

Methods

Design and setting

We conducted a population-based prevalence study of bacteremia patients hospitalized from 1 January 2000 to 31 December 2008 in the North Denmark Region. The population covered was stable at nearly 500,000 inhabitants throughout the study period despite administrative reforms in 2007. All inhabitants are provided with free, tax-supported access to health care, including free services at general practitioners and public hospitals. Patients with severe infections, including bacteremia, were treated at one of seven public hospitals. The largest hospital is Aalborg University Hospital, which serves as a district hospital for the city of Aalborg and as a referral hospital in the region. The seven hospitals are provided with clinical microbiology services, blood cultures included, by the Department of Clinical Microbiology at Aalborg University Hospital. Details on blood culture methodology have been provided elsewhere [17].

Regional clinical guidelines included recommendations for choice of empirical antimicrobial therapy for severe infections. During the study period, the recommended empirical treatment of sepsis patients included a combination of penicillin and gentamicin, supplemented with metronidazole if an anaerobic infection was considered likely. Low levels of antimicrobial resistance in the region compared with other Western countries allowed this conservative approach to empirical antimicrobial therapy of sepsis patients [18].

Bacteremia patients

We included patients of working age (30 to 65 years) with a first time episode of bacteremia. All bacteremia patients were identified in the North Jutland Bacteremia Research Database maintained by the Department of Clinical Microbiology, Aalborg [17]. Information in the database was prospectively collected on a daily basis. A physician with expertise in clinical microbiology reviewed all Gram stain reports and susceptibility tests of the isolated organism(s). On the basis of preliminary results, including microscopy results, a first notification of positive blood culture was made by telephone to the attending physician. A second notification was undertaken, normally within 24 hours, when a definite or working diagnosis and susceptibility to relevant antibiotics had been obtained. At all contacts with the attending physician microbiological data, clinical information, information on department and hospital, appropriateness of empirical antimicrobial therapy, and any advice given on adjustment of antimicrobial therapy were routinely recoded. These data were subsequently reviewed by a senior physician and entered into the bacteremia database.

Data on SES

We used income as marker of SES, because it has been shown to be a useful measure of socioeconomic stratification in adulthood [19]. Unique personal identification numbers, given to all Danish citizens at birth, made it possible to link the bacteremia database to the Income Statistics Register at Statistics Denmark [20, 21]. Information in this register is provided primarily by tax-authorities and includes income subject to taxation (wages and salaries, and all types of benefits and pensions). The register has a nearly 100% coverage and the income data are assumed to equal the real income [21]. We obtained information on all bacteremia patients' personal annual income from

the year preceding the index date of bacteremia. Income was adjusted for inflation according to the year 2000 value of the Danish crown (DKK) and categorized into three income groups: low (1st tertile), medium (2nd tertile), and high (3rd tertile).

Definitions

Bacteremia was defined as a clinical episode with one or more positive blood cultures given significance by evaluation of all available microbiological and clinical data. The focus of infection was determined based on clinical and microbiological findings, including cultures of other body fluids and sites (e.g. urine, respiratory tract secretions or pus) and categorized as urinary tract, gastrointestinal tract, respiratory tract, other, or unknown. Clinical speciality and admission to intensive care was determined at the time when the first positive blood culture was obtained. Community-acquired bacteremia was defined as an episode of bacteremia present or incubating at admission to hospital. An episode of bacteremia acquired in hospital or evident after hospital discharge was defined as nosocomial. Patients with a recent hospital admission (≤30 days from discharge) or frequent hospital contacts (e.g. for chemotherapy or haemodialysis) were defined as having health-care related bacteremia [17].

Empiric antimicrobial therapy was defined as antibiotics administered prior to the first notification of a positive blood culture. Antimicrobial therapy was defined as inappropriate if it was found inactive against the isolated organism(s) on the basis of in vitro susceptibility data and not consistent with current clinical practice recommendations (adequate doses and by adequate route of administration), as previously defined by McGregor and colleagues [22]. All susceptibility tests were performed by use of tablet diffusion (Neo-Sensitabs®; Rosco, Taastrup, Denmark) and each

plate was reviewed by a senior physician. Susceptibility assessment was in accordance with the breakpoints provided by the Swedish Reference Group for Anitibiotics (SRGA) [23].

Patients' status at first notification of positive blood culture was categorized as either dead, treatment ceased, appropriate empirical antimicrobial therapy received, or inappropriate empirical therapy received.

Information on pre-existing comorbid conditions was obtained from the Danish National Patient Registry and defined on the basis of codes according to the International Classification of Diseases (ICD), as described in detail elsewhere [24].

Statistical analysis

First, we calculated frequencies and prevalence proportions within income groups for patient characteristics (age, sex, immigrant status, and comorbid conditions). Next, differences in infection characteristics, characteristics of the admitting hospital and status at first notification of positive blood culture were examined across income groups. Subsequently, we used log-binomial regression analysis to examine the relationship between income and inappropriateness of the received empirical antimicrobial therapy [25]. We calculated age- and sex-adjusted relative risk (RR) estimates with 95% CIs for receiving inappropriate antimicrobial therapy according to income overall and for subgroups of patients according to acquisition of infection, focus of infection, and microbial agent.

Statistical analysis was performed using Stata statistical software, version 11.2 (StataCorp. LP, College Station, Texas). The study was approved by the Danish Data Protection Agency (Record no. 2010-41-5650). The study was not subject to approval by ethics committee because data collection did not involve direct patient contact.

Results

A total of 2,300 eligible patients with a first time diagnosis of bacteremia were included. Information on personal income was missing for three patients and 44 patients (1.9%) had incomplete data on empirical antimicrobial therapy. Analyses were therefore based on the remaining 2,253 patients.

Patients with community-acquired bacteremia accounted for 1,041 (46.2%), while 749 (33.2%) had nosocomial bacteremia, and 463 (20.6%) had health-care related bacteremia. The majority of patients (62.7%) were hospitalized in medical wards, 27.8% in surgical wards and 9.5% in intensive care units. The most frequent focus of infection was the urinary tract (22.2%) followed by the gastrointestinal tract (16.8%), and the respiratory tract (13.8%). Overall, 31.8% (667/2,100) of patients received inappropriate empirical antimicrobial therapy.

Patient characteristics, infection characteristics, and status at first notification of positive blood culture across income groups

Table 1 shows demographic and clinical characteristics of bacteremia patients according to income. The median age at diagnosis was 55 years (interquartile range 47-61 years), and 1,198 (53%) were men. Patients in the lowest income group were slightly older and more likely to be women, or immigrants from non-Western countries compared with patients in the highest income group. Compared with patients with higher incomes, those with lower incomes were also more likely to have pre-existing comorbidities (66.4% in the lowest income group had one or more comorbid conditions versus 57.3% in the highest income group), in particular chronic pulmonary disease, peripheral vascular disease, liver disease, diabetes, and HIV were more prevalent among patients

with low income. Notably, solid cancer, leukaemia, and lymphoma were more prevalent among those with high income.

Furthermore, patients with low income were more often admitted to an intensive care unit (10.4% versus 8.0%) and less often to a surgical ward (25.3% versus 31.2%) than patients with high income (Table 2). They were also more likely to have *Staphylococcus aureus* (16.4% versus 12.9%) and fungal infections (3.6% versus 1.6%) while place of acquisition and primary focus of infection differed little across income groups. Substantially more bacteremia patients in the low income group were treated at small (42.2% versus 34.6%), low-volume (24.5% versus 20.9%), and non-teaching hospitals (42.2% versus 34.6%) compared with patients in the high income group.

At the time of positive blood culture notification, mortality was 50% higher in patients with low income (5.7%) than those with high income (3.9%). The proportion of patients in whom treatment was ceased was also slightly higher among patients with low income versus high income (2.7% versus 2.3%).

Association between income and inappropriate empirical antimicrobial therapy

Absolute and relative risk estimates of the association between SES and inappropriate empirical therapy are presented in Table 3. Overall, 34.6% of patients in the low income group received inappropriate therapy at the time of notification of positive blood culture compared with 29.0% of patients in the high income group. This corresponded to a sex- and age-adjusted risk difference of 6.8% (95% CI: 1.9-11.8) and a relative risk of 1.24 (95% CI: 1.06-1.46) for receiving inappropriate therapy. The risk of inappropriate therapy gradually increased with decreasing income.

Analyses according to acquisition of infection, focus of infection, and microbial agent, revealed the similar pattern for patients in the lowest income group being more likely to receive inappropriate

therapy than those in the high income group. These stratified analyses rendered imprecise risk estimates, but estimates tended to be highest among patients with health care-related bacteremia (RR: 1.42 [95% CI: 0.98-2.06] for low vs. high income), *Streptococcus pneumoniae* bacteremia (RR: 3.63 [95% CI: 0.92-14.30]), and with a respiratory tract focus (RR: 3.55 [95% CI: 1.19-10.53]).

Antimicrobial susceptibility according to income

Bacteria resistant to antimicrobial drugs were more frequently isolated from patients with low income than those with high income. Yet, differences in antimicrobial resistance across income groups were small. In the low income group 6 patients (22.2% [6/27]) had Enterococci resistant to ampicillin compared with 4 patients (17.4% [4/23]) in the high income group. Enterobacteriaceae resistant to antimicrobials were also isolated more frequently in patients with low income than in those with high income (sulphonamide: 29.9% [86/288] versus 23.5% [66/281]), ciprofloxacin: 4.9% [14/288] versus 4.3% [12/281], piperacillin/tazobactam: 3.5% [10/288] versus 2.5% [7/281]). However, gentamicin resistant Enterobacteriaceae were less frequently isolated from patients in the low income group compared with the high income group (2.1% [6/288] versus 3.6% [10/281]). Resistance of Enterobacteriaceae to third-generation cephalosporins (ceftazidime, cefotaxime, and/or ceftriaxon) occurred in 17 patients with low income versus 13 patients with high income (5.9% [17/288] versus 4.6% [13/281]). Two patients, one in the low income group and one in the high income group, had bacteremia with methicillin-resistant *Staphylococcus aureus*. Only one patient had bacteremia with penicillin-non-susceptible *Streptococcus pneumoniae*, this patient was in the middle income group.

Discussion

In this population-based prevalence study of bacteremia patients, we found that economically disadvantaged patients were more likely to receive inappropriate empirical antimicrobial therapy compared with more affluent patients. These differences across income groups tended to be greatest in patients with health care-related infections and patients with respiratory tract foci. In addition, we found a higher prevalence of antimicrobial-resistant pathogens among patients with low income, although differences across income groups were small. Our finding of a 32% overall risk of receiving inappropriate empirical antimicrobial therapy is in accordance with the relatively high risk of up to 40% reported in previously published studies [7-9]. However, none of these studies examined differences in the appropriateness of empirical antimicrobial therapy across socioeconomic groups.

Previous studies have identified several risk factors for the administration of inappropriate antimicrobial therapy. Leibovici and coworkers found that prior antibiotic therapy, presence of a central catheter and bacteremia caused by specific types of pathogens, including *Candida* species, *Acinetobacter* species, *Enterococcus* species and *Pseudomonas* species are associated with inappropriate antimicrobial therapy [26]. Recent studies have also documented that lack of infectious diseases consultation and bacteremia with antimicrobial-resistant pathogens are associated with increased risk of receiving inappropriate antimicrobial therapy [7, 27]. Several of these risk factors were more prevalent in bacteremia patients with low incomes than those with high incomes. More patients in the low income group had *Candida* infections, had bacteremia with antibiotic-resistant pathogens and were admitted to small non-teaching hospitals without infectious diseases specialists and on-site consultation, which may in part have contributed to the differences in the appropriateness of antimicrobial therapy across income groups.

Different mechanisms may explain the higher frequency of antimicrobial-resistant pathogens in patients with low income compared with patients with high income. Frequent and prophylactic prescription of antibiotics has repeatedly been associated with increased risk of carriage and infection with antimicrobial-resistant pathogens [28-30]. Higher prevalence of chronic medical conditions and unhealthy behaviours may have lead to more antibiotic prescriptions and probably also more frequent prescribing of broad-spectrum antibiotics to persons of lower SES than those of higher SES. For example, both chronic obstructive pulmonary diseases and patients' smoking habits have independently been associated with the prescription of broad-spectrum antibiotics [31, 32]. The higher frequency of antimicrobial-resistant pathogens isolated in bacteremia patients of lower SES may therefore in part be caused by more frequent prescription of antibiotics to this segment of the patient population [33]. Another explanation for our findings may be that low SES patients are more susceptible to health-care related and nosocomially acquired bacteremia with resistant pathogens [11].

A noteworthy finding is our finding of a 50% higher mortality in patients with low income compared with patients with high income at the time of positive blood culture notification. This finding is comparable with the socioeconomic differences in 30-day mortality that we have recently reported, but also reveals that socioeconomic disparities in mortality exits even at a very early stage after bacteremia. Differences in initial empirical antimicrobial therapy may contribute to these socioeconomic disparities in early mortality as well as 30-day mortality [10].

Our study has several strengths. Our use of a population-based bacteremia research database allowed us to identify all hospitalized patients with a first time diagnosis of bacteremia with little concern over selection bias. Furthermore, linkage with the Income Statistics Register that contains information on personal income collected for administrative purposes and therefore independent of

our study, reduced concern over information bias. Data in the register are considered to have a very high validity and coverage [21].

There are also a number of limitations to the results of this study. At the time of first notification 97 patients were dead and in another 56 patients the treatment was ceased because of terminal illness. The majority of these patients were in the lowest income group. We lacked information on antimicrobial therapy administered to these patients, and were therefore unable to determine the appropriateness of any administered antimicrobial therapy in these patients. Furthermore, despite analyzing data from more than 2000 bacteremia patients with a total of 667 patients receiving inappropriate therapy, our study was still underpowered to detect the relatively modest differences in the inappropriateness of antimicrobial therapy across income groups in stratified analyses. However, despite our lack of statistical precision the general pattern of increased risk for receiving inappropriate antimicrobial therapy among the less affluent patients in our subgroup analysis is of concern.

In conclusion, we found that bacteremia patients with low income had an increased risk of receiving inappropriate empirical antimicrobial therapy compared with those with high income. Proper empirical antimicrobial therapy for serious infections, including bacteremia, can be life saving. Therefore, special efforts should be made to improve the administration of effective antimicrobial treatment in this segment of the patient population which may improve their outcomes.

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Table 1. Characteristics of patients hospitalized with first time bacteremia (n=2,253) according to income group, Northern Denmark, 2000-2008. Values are numbers (percentages) unless stated otherwise

Characteristics	Income group					
	Low (1st tertile, n=751)		Middle (2nd tertile, n=751)		High (3rd tertile, n=751)	
Demographic charateristics						
Age, median, years (IQR)	56.2		55.7		55.1	
Men	326	(43.4)	369	(49.1)	503	(67.0)
Female	425	(56.6)	382	(50.9)	248	(33.0)
Immigrant status						
Danish	704	(93.7)	718	(95.6)	728	(96.9)
Immigrants from Western countries	19	(2.5)	17	(2.3)	12	(1.6)
Immigrants from non-Western countries	28	(3.7)	16	(2.1)	11	(1.5)
Comorbid conditions						
Cardiovascular disease	72	(9.6)	77	(10.3)	56	(7.5)
Peripheral vascular disease	66	(8.8)	49	(6.5)	27	(3.6)
Cerebrovascular disease	66	(8.8)	72	(9.6)	45	(6.0)
Chronic obstructive pulmonary disease	109	(14.5)	97	(12.9)	48	(6.4)
Connective tissue disease	41	(5.5)	31	(4.1)	21	(2.8)
Liver disease	80	(10.7)	50	(6.7)	23	(3.1)
Diabetes mellitus	120	(16.0)	94	(12.5)	67	(8.9)
Chronic kidney disease	70	(9.3)	64	(8.5)	43	(5.7)
Solid cancer	123	(16.4)	146	(19.4)	175	(23.3)
Leukaemia	11	(1.5)	25	(3.3)	32	(4.3)
Lymphoma	22	(2.9)	35	(4.7)	51	(6.8)
HIV/AIDS	5	(0.7)	1	(0.1)	1	(0.1)
Number of comorbid conditions						
Low (0)	252	(33.6)	266	(35.4)	321	(42.7)
Medium (1)	246	(32.8)	269	(35.8)	285	(38.0)
High (≥2)	253	(33.7)	216	(28.8)	145	(19.3)

Table 2. Infection characteristics and status at positive blood culture notification according to income group, Northern Denmark, 2000-2008. Values are numbers (percentages)

	Income group					
	Low (1st tertile, n=751)		Middle (2nd tertile, n=751)		High (3rd tertile, n=751)	
Infection characteristics						
Acquisition						
Community-acquired	361	(48.1)	344	(45.8)	336	(44.7)
Health-care associated	144	(19.2)	160	(21.3)	159	(21.2)
Nosocomial	246	(32.8)	247	(32.9)	256	(34.1)
Microbial agent						
Staphylococcus aureus	123	(16.4)	106	(14.1)	97	(12.9)
Streptococcus pneumoniae	96	(12.8)	94	(12.5)	104	(13.9)
Other gram-positive organisms	103	(13.7)	119	(15.9)	133	(17.7)
Escherichia coli	200	(26.6)	208	(27.7)	181	(24.1)
Other gram-negative organisms	142	(18.9)	137	(18.2)	148	(19.7)
Fungal	27	(3.6)	24	(3.2)	12	(1.6)
Polymicrobial	60	(8.0)	63	(8.4)	76	(10.1)
Focus of infection						
Urinary tract	173	(23.0)	169	(22.5)	159	(21.2)
Respiratory tract	104	(13.9)	111	(14.8)	96	(12.8)
Gastrointestinal tract	125	(16.6)	116	(15.5)	137	(18.2)
Other	148	(19.7)	165	(22.0)	164	(21.8)
Unknown	201	(26.8)	190	(25.3)	195	(26.0)
Type of hospitalization unit						
Intensive care	78	(10.4)	73	(9.7)	60	(8.0)
Internal medicine	481	(64.1)	474	(63.1)	452	(60.2)
Surgical	190	(25.3)	199	(26.5)	234	(31.2)
Characteristics of the admitting hospital						
Bed size						
Low (<300 beds)	317	(42.2)	300	(40.0)	260	(34.6)
High (>300 beds)	434	(57.8)	451	(60.1)	491	(65.4)
Hospital volume[a]						
Low (≤99/year)	184	(24.5)	168	(22.4)	157	(20.9)

Medium (100-299/year)	133	(17.7)	132	(17.6)	103	(13.7)
High (≥300/year)	434	(57.8)	451	(60.1)	491	(65.4)
Teaching hospital[b]						
No	317	(42.2)	300	(40.0)	260	(34.6)
Yes	434	(57.8)	451	(60.1)	491	(65.4)
Status at notification of positive blood culture						
All treatment ceased	20	(2.7)	19	(2.5)	17	(2.3)
Dead	43	(5.7)	25	(3.3)	29	(3.9)
Initial empirical antimicrobial therapy						
Appropriate	449	(65.3)	482	(68.2)	502	(71.2)
Inappropriate	238	(34.6)	224	(31.7)	205	(29.1)

[a]Hospital volume was defined as the annual number of bacteremia patients treated at the institution
[b]Teaching hospitals were defined as hospitals directly affiliated with a medical school

Table 3. Risk difference and relative risk for inappropriate empirical antimicrobial therapy at the time of positive blood culture notification according to income group, Northern Denmark, 2000-2008

	Income group						Risk difference[a], % (95% CI)				Relative risk[a] (95% CI)			
	Low		Middle		High		Low vs. high income		Middle vs. high income		Low vs. high income		Middle vs. high income	
All patients	238/687	(34.6)	224/706	(31.7)	205/707	(29.0)	6.8	(1.9 to 11.8)	4.0	(-0.9 to 8.9)	1.24	(1.06 to 1.46)	1.14	(0.97 to 1.34)
Acquisition														
Community-acquired	84/329	(25.5)	62/325	(19.1)	66/317	(20.8)	5.4	(-1.3 to 12.0)	-1.2	(-7.5 to 5.0)	1.28	(0.96 to 1.71)	0.95	(0.69 to 1.30)
Nosocomial	109/225	(48.4)	115/232	(49.6)	102/239	(42.7)	6.0	(-3.2 to 15.2)	8.4	(-0.6 to 17.5)	1.13	(0.92 to 1.39)	1.19	(0.98 to 1.45)
Health care-related	45/133	(33.8)	47/149	(31.5)	37/151	(24.5)	11.8	(1.1 to 22.6)	9.0	(-1.3 to 19.3)	1.42	(0.98 to 2.06)	1.34	(0.92 to 1.95)
Microbial agent														
Staphylococcus aureus	37/115	(32.2)	36/102	(35.3)	24/93	(25.8)	6.3	(-5.9 to 18.5)	10.3	(-2.6 to 23.3)	1.31	(0.85 to 2.02)	1.42	(0.92 to 2.20)
Streptococcus pneumoniae	6/89	(6.7)	5/88	(5.7)	3/103	(2.9)	*	*	*	*	3.63	(0.92 to 14.30)	2.88	(0.67 to 12.34)
Other Gram-pos.	38/97	(39.2)	42/112	(37.5)	48/125	(38.4)	-0.5	(-13.7 to 12.7)	-2.2	(-14.6 to 10.2)	1.01	(0.72 to 1.41)	0.98	(0.71 to 1.37)
Escherichia coli	52/184	(28.3)	44/198	(22.2)	41/175	(23.4)	4.7	(-4.3 to 13.7)	-2.7	(-10.4 to 4.9)	1.22	(0.84 to 1.75)	0.95	(0.65 to 1.39)

Other Gram-neg.	58/124	(46.8)	46/127	(36.2)	50/132	(37.9)	12.3	(0.0 to 24.6)	1.0	(-10.9 to 13.0)	1.34	(1.00 to 1.80)	0.98	(0.71 to 1.36)
Fungal	21/24	(87.5)	19/20	(95.0)	7/11	(7.0)	*	*	*	*	*	*	1.42	(1.17 to 1.73)
Polymicrobial	26/54	(48.2)	33/59	(55.9)	31/67	(46.3)	3.9	(-14.8 to 22.7)	12.8	(-4.8 to 30.5)	1.01	(0.68 to 1.49)	1.21	(0.87 to 1.71)
Focus of infection														
Urinary tract	55/166	(33.1)	50/167	(29.9)	48/155	(31.0)	4.2	(-6.2 to 14.6)	1.7	(-8.5 to 11.8)	1.20	(0.86 to 1.66)	1.07	(0.76 to 1.49)
Respiratory tract	12/99	(12.1)	14/106	(13.2)	4/93	(4.3)	*	*	*	*	3.55	(1.19 to 10.53)	3.67	(1.26 to 10.64)
Abdomen	51/110	(46.4)	34/100	(34.0)	45/130	(34.6)	12.5	(-0.2 to 25.3)	0.0	(-12.7 to 12.8)	1.40	(1.02 to 1.92)	0.99	(0.68 to 1.44)
Miscellaneous foci	47/142	(33.1)	57/164	(34.8)	49/160	(30.6)	3.6	(-6.9 to 14.2)	5.1	(-5.0 to 15.3)	1.08	(0.78 to 1.50)	1.13	(0.83 to 1.55)
Unknown	73/170	(42.9)	69/169	(40.8)	59/169	(34.9)	9.8	(-0.7 to 20.4)	7.8	(-2.8 to 18.4)	1.31	(0.99 to 1.73)	1.28	(0.97 to 1.70)

[a]Sex- and age-adjusted risk estimates

* Estimates not calculated because of failure of convergence in the log-binomial regression