

Haematological malignancies and bacteraemia:

Risk and prognosis

PhD thesis
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Introduction

Bacteraemia is one of the most serious complications encountered by patients with haematological malignancies. Bacteraemia causes hospitalisations, use of major resources, dose reductions and delays of chemotherapeutic treatments, and increased mortality. The incidence of haematological malignancies is increasing (1); at the same time, the proportion of patients achieving a complete remission and longer survival has likewise increased during the last three decades (2;3). Therefore, bacteraemia in this group of patients will pose an increased burden in the future. To improve prevention and treatment of bacteraemia among haematological patients, we need better understanding of the disease, including its risk and prognostic factors. Randomised controlled trials (RCTs) cannot provide all necessary information since they are usually conducted within small samples that often under-represent vulnerable patient groups (4). In addition, not all outcomes of haematological diseases are suitable for an experimental study. In order to study the entire spectrum of patients, we need large and valid sources of information with prospective data collection and complete follow-up. This thesis used population-based registries to examine risk factors and prognosis of bacteraemia in patients with haematological malignancies.

Registry data in the study of haematological malignancies

Haematological malignancies are a group of neoplasms arising through malignant transformation of bone marrow-derived cells. The great diversity of these disorders reflects the complexity of normal haematopoiesis and the immune system. Over the past 100 years, several classifications have been devised attempting to provide clinically and biologically relevant subdivisions of haematological malignancies. These classifications have been instrumental for keeping records in databases, such as hospital discharge registries, pathology registries, and dedicated cancer registries.

RCTs cannot address many important clinical questions about haematological malignancies for reasons that range from logistics (e.g., a very short opportunity for enrolment, precluding informed consent), to lack of long-term follow-up, to ethical aspects. Several properties of population-based databases make them potentially suitable for answering a wide spectrum of research questions. In particular, registry data 1) have a longitudinal perspective, 2) allow the study of rare events owing to the large

number of observations, 3) represent routine clinical care enabling the study of “real-world” effectiveness of treatments, 4) represent patient subpopulations that are often excluded from RCTs, such as patients with coexisting diseases (comorbidity), and 5) are quickly accessible at relatively low cost, aiding study efficiency (4). Before population-based registries can be used to study haematological malignancies, it is essential to evaluate the quality of haematological diagnoses in these registries.

The burden of haematological malignancies

Incidence

In the recent years, approximately 2000 new cases of a haematological malignancy annually are diagnosed in Denmark (5). A challenging aspect of the epidemiology of haematological malignancies lies in the apparent changes in their occurrence, noted over the last few decades (6). Non-Hodgkin’s lymphoma has one of the most rapidly increasing incidences among malignant disease (7). Conversely, the trend in Hodgkin’s disease and acute myeloid leukaemia is a steady decline, which may, however, be a registrational artefact (6). With the exception of Hodgkin’s disease and acute lymphoblastic leukaemia, the incidence rates of haematological malignancies increase with advancing age (8). More than 50% of the patients with incident leukaemia or non-Hodgkin’s lymphoma are aged 65 or older (9). Over the next decades, with the expected dramatic increase in the size of elderly population, the prevalence of haematological malignancies is also likely to increase.

Prognosis

Haematological malignancies, like most diseases, progress orderly from the biologic onset, to the point when early diagnosis is possible, to the time of usual diagnosis, and ultimately to the outcome (10). This progression is called the *natural history* of a disease. Of special interest to clinicians is the *clinical course* – the part of the natural history that begins after disease is diagnosed. Prognosis is a qualitative or quantitative prediction of the outcome of a disease (11). From the patient point of view prognosis is the probability that he will develop each of the alternative outcomes of the natural history of his disease (10).

The determinants of the outcome of an illness

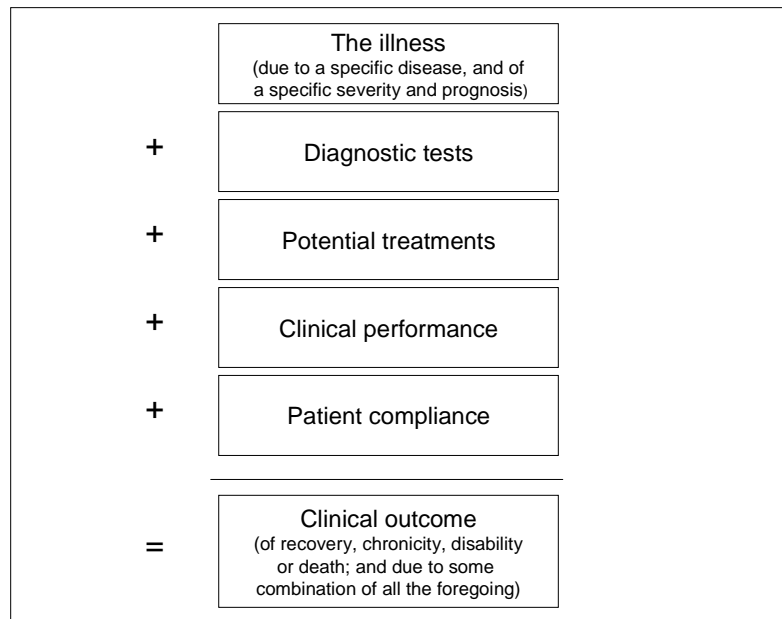


Figure 1. Determinants of the outcome of an illness (10). This model applies to an outcome-oriented review of the performance with a specific disease but is not suitable when dealing with symptoms.

Several factors influence the outcome of a disease (figure 1). The specific disease and the patients' general condition, which can be influenced by age and comorbidity, are examples of factors that have been examined in relation to outcome of haematological malignancies. For example, 5-year survival among adult patients with acute myeloid leukaemia has improved since the 1970s from approximately 10% to >50% in patients younger than 55 to 60 years of age (2). However, an improvement among patients older than 55 years of age is barely seen (from 5% to 15%) (2;12). Hodgkin's disease today is one of the most curable forms of cancer with an overall survival dramatically improved from about 50% in the 1960s to more than 80% in the 1990s (3). In non-Hodgkin's lymphoma whose course may vary from aggressive causing death within weeks to indolent with no therapy, the relative overall survival rate improved from about 30% in the 1960s to about 50% in the early 1990s (1). Elderly non-Hodgkin's lymphoma patients are shown to have a poorer outcome than younger and middle-aged patients, even with matched clinical characteristics (remission rates decline from 68% in the young to 45% in the elderly) (13).

Improved treatment of haematological malignancies may explain some of the improvement in prognosis seen over the last four decades. Treatment options include

chemotherapy, immunotherapy, radiotherapy, bone marrow transplantation, and stem cell transplantation in combination with supportive care (i.e., blood product transfusions, growth factors, such as granulocyte colony-stimulating factor, and antimicrobials) (2). However, it is also likely that diagnostic tests have improved over time allowing more accurate and perhaps earlier diagnosis leading to earlier and more targeted treatment. Little information exists on patients' clinical performance, however, it is reasonable to expect that it should differ between elderly and younger haematological patients.

Haematological malignancies and infections in a historical view

According to Jean Klastersky, fever and infections as a consequence of neutropenia mainly in acute leukaemia or agranulocytosis, were first described about 100 years ago (14). However, little attention was paid to this syndrome.

In the 1960s, the attention to severe infections among patients with haematological or other malignancies increased, due to better antineoplastic treatment. GP Bodey and co-workers were among the first researchers to target febrile neutropenia and specific pathogens, such as *Pseudomonas aeruginosa* and *Serratia marcescens*, as challenges in oncologic treatment (15;16). At that time, mortality following *P. aeruginosa* bacteraemia was approximately 90%, in spite of the availability of antibiotics active *in vitro* (17;14).

In the 1970s According to PubMed, the term "empiric antibiotic therapy" was used for the first time in 1971 by Schimpff *et al* in a paper on febrile patients with cancer and granulocytopenia (18). The authors launched the concept that a combination of antibiotics active against *P. aeruginosa* and other Gram-negative bacilli should be given empirically as soon as neutropenic patients become febrile. In 1973 in Europe, the group of Klastersky at Jules Bordet Institute in Brussels initiated a series of randomised controlled multicenter trials under the auspices of The International Antimicrobial Therapy Cooperative Group of the European Organization for Research and Treatment of Cancer (EORTC) (19-23). These trials focused on finding the most superior antibiotic combination for empirical treatment. In the EORTC trials, the results were

primarily evaluated based on patients with positive microbiological findings, which further focused the attention to patients with bacteraemia.

Bacteraemia

Focal infections, such as pneumonia, acute cystitis, or perianal abscesses, occur in patients with haematological malignancies (24-26). However, because of the compromised inflammatory response in these patients, the classic signs and symptoms of infection may be masked (27;28). An elevated temperature may be its only clinical sign; thus, the results of blood cultures play a pivotal diagnostic role.

Definition

Bacteraemia is defined as the presence of viable bacteria circulating in the bloodstream and is evidenced by blood culture on the condition that contamination is effectively ruled out (29-32). Coagulase-negative staphylococci, *Corynebacterium* spp., *Bacillus* spp and *Propionibacterium acnes* can be regarded as contaminants unless isolated from two or more separate blood culture sets. By convention, candidaemia is included in the collective term bacteraemia, and in the daily clinical setting bacteraemia is defined as bacterial or fungal growth in blood cultures, in situations in which the isolated pathogen is given etiological significance based on clinical and microbiological assessment.

Bacteraemia can be categorized according to the bacterial isolate(s), the presumed focus of infection, and/or the origin of the bacteraemia. In the following, we will focus on aspects of categorization of bacteraemia that are pertinent to patients with haematological malignancies.

Bacterial isolates

Bacteraemias are conventionally grouped together based on similarity of microbial agents (*e.g.*, Gram-negative rods). We refer to these groups as types of bacteraemia throughout this thesis. Whereas Gram-negative bacteria (*Escherichia coli*, *Klebsiella* spp, and *P. aeruginosa*) were predominant in neutropenic cancer patients in the 1970s and early 1980s (33), Gram-positive bacteria (coagulase-negative staphylococci and viridans streptococci) became progressively prevalent in the late 1980s and early 1990s

(figure 2) (34). Some of the factors implicated in the increasing number of Gram-positive bacteraemias are the administration of aggressive chemotherapy and radiotherapy regimens that produce severe mucositis, increased use of indwelling catheters, the widespread use of fluoroquinolones as prophylactic agents, and empirical antibiotic treatment with high activity against Gram-negative infections (35). The fact that there is no discrimination between first and following episodes of bacteraemia in most studies may also have influenced these findings.

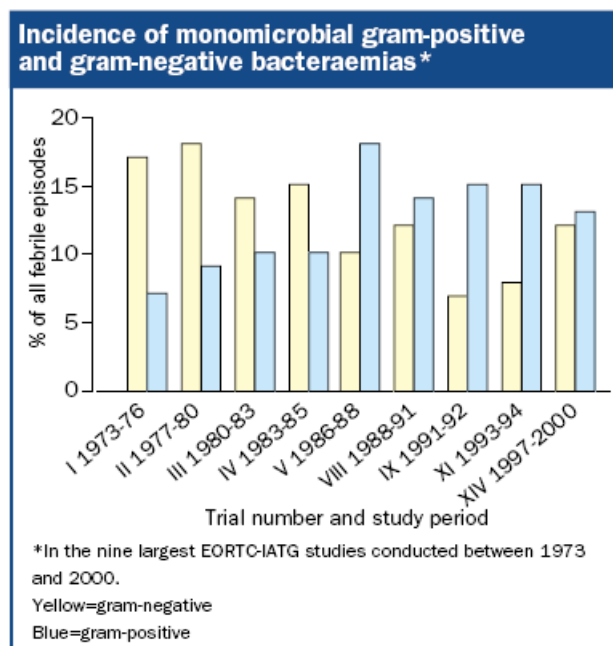


Figure 2. Incidence of monomicrobial Gram-positive and Gram-negative bacteraemias in nine EORTC-IATG studies, *Lancet* 2002; 359:723-725.

The change in spectrum of microorganisms causing bacteraemia has been more unequivocal in studies including non-neutropenic haematological patients as well (36-38). A Danish study found differences in the distribution of bacteraemia-causing microorganisms between two Danish regions, suggesting that local surveillance is of importance (39).

Origin of bacteraemia

The Centers for Disease Control and Prevention (CDC) surveillance definitions of bacteraemia include only nosocomial infections (40). Infections that are not acquired in

hospital are considered community-acquired by default (41). Patients with haematological malignancies are often cared for in outpatient settings, and it may not always be appropriate to categorize their infections as merely community-acquired. Thus, a separate category, “health-care related infections”, is justified for recently hospitalised patients or those with regular contact to hospitals (41).

Focus of bacteraemia

The focus of bacteraemia (the organ or tissue infected at the time when the bacteraemia becomes clinically apparent) can be determined based on clinical symptoms, signs of local infection, imaging techniques, and microbiological confirmation through relevant samples. As patients with haematological malignancies may have an impaired inflammatory response, signs of localised infections such as purulence, fluctuation, or lung infiltrates may not develop and the focus of bacteraemia will often remain unknown. Failure to determine the source of infection is associated with increased mortality in patients with community-acquired bacteraemia (42). At the same time, Pittet *et al* found that pneumonia as a source of infection was associated with increased mortality in nosocomial bloodstream infections (43). Likewise, Gonzales-Barca *et al* found that pneumonia – defined as the presence of acute respiratory illness and pulmonary infiltrate – as the focus of bacteraemia was associated with a higher risk of mortality among neutropenic patients (OR, 4.4 (95% CI: 1.9-10)) (44). In the latter study, however, the authors did not address the impact of an unknown focus.

Neutropenia

Neutrophils make up over 90% of the circulating granulocytes in a normal individual and serve as the body’s primary defence against infections (45;46). Neutropenia is characterised by an abnormally low number of neutrophil granulocytes and can be expressed as absolute neutrophil count (ANC) measured in cells x 10⁹ per L of blood.

In a seminal study from 1965, Bodey *et al* (47) followed 52 patients aged 1-77 years with a newly diagnosed acute leukaemia. Survival time was on average 329 days (range 6 to 791 days) and white blood cell counts were recorded every 1 to 4 weeks. The authors found that the incidence of infectious episodes decreased with increasing levels

of circulating granulocytes and lymphocytes. At a critical concentration of granulocytes (1.5×10^9 per L of blood), no further decrease in infection incidence was observed. Mortality was likewise related to the granulocyte level. The highest mortality occurred among patients with persistent severe granulocytopenia (table I).

Granulocyte level		Episodes	
Initial	Change	Total	Fatal
/L		no.	%
$<0.1 \times 10^9$	None	15	80
$<1 \times 10^9$	None, or fall	44	59
$<1 \times 10^9$	Rise, but still $< 1 \times 10^9$	15	40
$<1 \times 10^9$	Rise to $> 1 \times 10^9$	26	27
$>1 \times 10^9$	Rise	44	32

Table I. Case fatality rate of severe infections related to change in granulocyte level during first week of infection (47). Survival ranged from 6 to 791 days and the author gives no time dimension for the case fatality rate.

On the initiative of the World Health Organization, two meetings (in 1977 and 1979) were held on standardization of reporting results in cancer treatment; at these meetings, the following recommendation for grading of neutropenia was made (48):

- Grade 0 (ANC $\geq 2 \times 10^9$ per L of blood)
- Grade 1 (ANC $1.5 - 1.9 \times 10^9$ per L of blood)
- Grade 2 (ANC $1.0 - 1.4 \times 10^9$ per L of blood)
- Grade 3 (ANC $0.5 - 0.9 \times 10^9$ per L of blood)
- Grade 4 (ANC $< 0.5 \times 10^9$ per L of blood)

Empirical antibiotic treatment

Between July 1968 and July 1969, eleven out of the 22 neutropenic patients admitted at the Baltimore Cancer Research Center with *P. aeruginosa* bacteraemia died within 72 hours of the initial positive blood culture and all but two patients eventually died of

their infection. As a consequence, empirical antibiotic treatment, i.e., a combination of carbenicillin and gentamycin was instituted without waiting for microbiological and/or further clinical documentation of an infection (18). Schimpff *et al* reported, that after this concept was instituted, there were fewer deaths secondary to *P. aeruginosa* infection (four deaths in 13 episodes of bacteraemia), the rate of complete or temporary improvement for *P. aeruginosa* infection was 80%, and there was prolonged life span in all patients (18). This concept became widely accepted, although empirical use of antibiotics for fever makes the microbiological documentation of infection more difficult. Since the introduction of empirical antibiotic treatment, a dramatic improvement in prognosis of Gram-negative bacteraemia was noticed (49): in 1962, the mortality from Gram-negative rod bacteraemia in neutropenic patients approached 90% (17), while in the first EORTC-IATCG study in 1978, mortality after Gram-negative rod bacteraemia was just above 20% (33). Early and appropriate empirical antibiotic treatment is likewise associated with increased survival in patients with septic shock or bacteraemia in general (50;51). Several factors, however, influence the decision of which antibiotics to administer. The “best” empirical regimen for use at one hospital may be inadequate for use in another hospital due to local variations in the frequency of isolation of particular pathogens and in prevalence of antibiotic resistance (52).

Haematological malignancies and incidence of bacteraemia

For patients with haematological malignancies bacteraemia is widely regarded as a major risk factor for mortality (27;49;53) However, little formal epidemiological evidence exists on the magnitude of the incidence of bacteraemia among patients with haematological malignancies. We searched the MEDLINE database and used the terms “incidence”, “bacteraemia”, and “haematological malignancies”, limiting the search to include only studies in adults. This search strategy yielded 55 studies. Only one of these studies, reported in Spanish by Teira *et al.*, computed incidence rates of bacteraemia among haematological patients admitted at one haematological department (54). Of the 244 newly diagnosed cases of acute myeloid leukaemia or lymphoma 53 admitted patients were lost to follow-up. In the remaining 191 patients, 684 blood cultures were obtained and 155 of which were positive. The incidence rate of bacteraemia, expressed as cases per 1000 patient-days, was 5.8 for AML and 0.21 for high-grade malignant lymphoma. However, this study did not distinguish between first and following

episodes of bacteraemia in the same patient. To the best of our knowledge, no prior study has addressed incidence rates of bacteraemia among patients with haematological malignancies in a population-based setting.

Risk factors for bacteraemia in patients with haematological malignancies

Characteristics associated with an increased risk of becoming diseased are called risk factors (55). The term risk factor is rather loosely used and is not necessarily a causal factor (56). We searched MEDLINE using the terms “haematological malignancy”, “bacteraemia”, and “risk factors” and limited the search to include only studies in adults. This search strategy yielded 20 studies. However, only few relative risk estimates were provided in these studies. In a case-control study by Pagano *et al*, use of central venous catheter (OR 6.1(95% CI: 1.3-12.3)) and neutropenia for more than six days (OR 3.0 (95% CI: 1.7-9.5)) were found to be risk factors for bacteraemia in patients with haematological malignancies (57). Ruescher *et al* conducted a case-control study among recipients of autologous bone marrow transplantation (58). In a randomised controlled trial among neutropenic cancer patients Bucaneve *et al* found prophylactic use of flourquinolones to be associated with an absolute decrease in risk of bacteraemia, risk difference -0.16 (95% CI: -0.22 to -0.09) (59). Age above 40 years did not seem to be a risk factor for bacteraemia after allogeneic stem cell transplantation (RR 0.82 (95% CI: 0.44 – 1.51) (60). Similarly, in a study of 131 consecutive episodes of fever and chemotherapy-induced neutropenia in 85 adults with haematological malignancies Garcia-Suarez *et al* found similar rates of infection in elderly and in younger haematological cancer patients with febrile neutropenia (61).

Neither comorbidity nor the underlying type of malignancy has been well examined as a potential risk factor for bacteraemia in cancer patients. Among 365,014 American patients hospitalised with haematological malignancies in 1999, 64,684 developed severe sepsis (62). The relative risks (RR) of severe sepsis, however, showed large variation between the different types of haematological malignancies, with Hodgkin’s disease having the smallest (RR=4.1), and acute myeloid leukaemia the largest (RR=65.2). association with severe sepsis.

Haematological malignancies and prognosis of bacteraemia

The inability to distinguish patients with bacteraemia from those without, led to the practice of admitting all febrile neutropenic patients to a hospital and giving them intravenously empiric antibiotic treatment (63). This strategy became a significant burden in health care and economic terms. Developments of risk-assessment models to accurately differentiate febrile patients with neutropenia at low risk for mortality has now led to newer concepts of risk-based therapy treatment.

Clinical epidemiological studies can be grossly categorized into clinical prediction studies and explanatory studies, although both aims can be combined in a single study. The clinical importance of information on prognostic studies is summarised in Box 1 (64). These issues are relevant to both prediction studies and explanatory studies. In prediction studies, as those are used in risk-based therapy, the aim is to identify factors associated with the outcome and therefore can be used to predict this outcome. The only measures of interest in prediction studies are absolute risks. Thus, clinical prediction studies are usually cohort studies since absolute risks cannot be estimated in case-control studies. (64;65).

- To guide clinical decision-making, including treatment selection and patient counselling
- To improve understanding of the disease process
- To improve the design and analysis of clinical trials (for example, risk stratification)
- To assist in comparing outcome between treatment groups in non-randomised studies by allowing adjustment for case mix
- To define risk groups based on prognosis
- To predict disease outcome more accurately or parsimoniously

Box 1 —Purpose of studies of prognostic factors (adapted from Altman and Lyman) (64)

In explanatory studies of bacteraemia in haematological malignancies the aim is to explain, rather than merely describe, biology and cause of bacteraemia by isolating the effects of specific variables and understanding the mechanisms of action (56).

Explanatory studies focus is on the effect of a single variable in terms of the relative risk comparing groups of subjects defined by different levels of this variable (65). All other included variables are considered to be potential covariates. The choice of statistical model depends on the scientific question being asked. It will rarely be necessary to include a large number of covariates in the model, because only few exposures are of genuine scientific interest, and there are usually only a few variables of sufficient *a priori* importance to be considered as potential confounders (65).

Through regular search in MEDLINE using the terms “haematological malignancy”, “bacteraemia”, and “mortality” combined with manual searches, we identified several studies that examined the outcome of bacteraemia among haematological and/or neutropenic patients. Tables II and III shows the most important of these studies, some of which are purely predictive. Whereas predictive models may be able to accurately predict the risk of a future complication, they are not designed to provide insight in causality. The good predictive models are constructed based on information available at a given time, but not necessarily by the predictors’ causal role in the chain leading to the outcome. Therefore we do not consider that predictive model reflect biologic mechanism of disease.

Few studies have aimed to explain the clinical cause of bacteraemia in patients with haematological malignancies. In the present thesis we have focused on the effects of the type of underlying malignancy and type of bacteraemia (studies II and III), and on the effects of increasing age and comorbidity (Study IV).

<i>Haematological malignancy patients with and without neutropenia</i>								
Authors	Country	Study period	Design	Type of infection	Number	Adjustment	Risk estimates	Results
E. Rintala (71)	Finland	1985-90	Cohort	Sepsis, bacteraemia, and unexplained fever	554 febrile episodes in 126 patients 104 episodes of bacteraemia	No	No	23% of episodes of positive blood culture had sepsis related death (death within 7 days of the latest positive blood culture)
F. Rossini (74)	Italy	1989-94	Cohort	Infectious episodes including unexplained fever	554 <65 year, 27% bacteraemia 211 ≥65 year 19% had bacteraemia	No, but stratification	No, but OR can be computed	Death 22% for patients below 65 years vs. 28% above 65 years.
Hovgaard <i>et al</i> (70)	Denmark	1981-85	Cohort	Bacteraemia	171 episodes in 142 patients	No	No, correlations	Overall 7-day mortality 20%. Poor disease prognosis (39%), penicillin >6 days (30%) or hypotension (49%)
Gunther <i>et al</i> (72)	Sweden	1980-86	Cohort	Bacteraemia	198 episodes in 129 patients	No	No	Bacteraemia related death 26%
Cherif <i>et al</i> (69)	Sweden	1988-2001	Cohort	Bacteraemia	1402 episodes in 927 patients	No	No	7-day mortality 6.3% 30-day mortality 15.6%
Velasco <i>et al</i> (73)	Brazil	2000-01	Cohort	Bacteraemia	110 episodes in 82 patients in	Yes	Yes	Overall mortality 24.5% low performance OR 5.1, ventilatory support OR 3.7, Recent weight loss OR 3.1 and relapsed leukaemia OR 2.7
Williams <i>et al</i> (62)	USA	1999	Cohort	Severe sepsis	34684 cases of severe sepsis in 365, 014 patients	Yes, for age and gender	RR severe sepsis, not for mortality	In-hospital mortality for haematological patients 36.1% Mortality became independent of age above 40-44 years

Table II. Studies of bacteraemia in patients with haematological malignancies

<i>Haematological patients with neutropenia</i>								
Authors	Country	Study period	Design	Type of infection	Number	Adjustment	Risk estimates	Results
Garcia-Suarez <i>et al</i> (61)	Spain	2000-01	Cohort	Infectious episodes including unexplained fever	131 episodes in 85 adults – bacteraemia in 40% < 60 year and 35.7% above 60 years	No, but stratification into high risk or low risk	No	Mortality in high risk group: 12.5% in elderly vs. 20% in non-elderly. Low risk group: 0% vs. 0% no separate analyses among bacteraemic patients
<i>Haematological and other cancer patients with neutropenia</i>								
Authors	Country	Study period	Design	Type of infection	Number	Adjustment	Risk estimates	Results
Elting <i>et al</i> (36)	Multicenter	1980-93	Pooled data from 10 RCT	Bacteraemia	909 episodes in 799 patients 74% haematological malignancies	Yes	OR for ultimate outcome	OR>1 for Complex bacteraemia, presence of shock, Ps. aer or clostridium, and low albumin. ANC recovery was protective
Gonzales-Barca (44)	Spain	1986-96	Cohort	Bacteraemia	438 episodes 83% had a haematological malignancy	Yes	OR for mortality	Overall 30-d mortality: 24.4% OR shock 10 (4-23) OR pneumonia 4 (2-10) OR uncontrolled cancer 4 (1.5-13), absence of prophylaxis 2.4
EORTC-group (21-23)	International from 24 inst.	1990	RCTs	Patients with fever; 25% had monomicrobial bacteraemia	1074/872	Yes	Multivariate coefficient	Gram-positive bacteraemias: mortality 4% (death within 9 days) significantly associated with outcome: age: 1.05, CVC: 1.3, susceptibility: -1.62
Johansson <i>et al</i> (68)	Sweden	1982-88	Cohort 1975-1981 as control	Bacteraemia	269 /78 with granulocytopenia 33/ 22 with bacteraemia	No	No	Mortality within 4 weeks 34%/ 45%
Wisplinghoff <i>et al</i> (109)	Germany	1995-2001	Cohort	Nosocomial bloodstream infection	2340 patients 30% neutropenic unknown % haematological malignancies	No, but stratification by pathogen and by neutropenia	Yes, crude mortality ratio	Crude mortality 36% among neutropenic patients 31% among non-neutropenic patients.

Table III. Studies of bacteraemia in neutropenic patients with haematological malignancies or other cancers

Considerations for planning an observational study of bacteraemia in patients with haematological malignancies

The first priority of any researcher embarking on an observational study is to state the objectives of the study clearly and quantitatively so that the parameter to be measured is certain (66). The overall goal is accuracy in measurements, which means estimating the sought parameter with little error.

Choice of source population

A good choice of study subjects ensures that the parameter estimated in the study is an accurate estimate of that parameter in the population of interest. The study sample should be obtainable at acceptable time and monetary expense, yet it should be large enough to allow for control of random error (67). The outcome of bacteraemia in patients with haematological malignancies has been studied in different types of populations (figure 3). Several studies, including the EORTC studies, were conducted among neutropenic cancer patients with over 80% prevalence of haematological malignancies (23;44;68). Other studies were conducted strictly among patients with haematological malignancies with and without neutropenia (69-71). Some of the studies included only patients with bacteraemia (36;44;68;69;72;73), whereas other studies have examined all “infectious episodes”, including other infections such as pneumonia and unexplained fever (23;61;71;74). In most studies, the authors did not distinguish between first and following infectious episodes.

Most studies have identified their study population at a single haematological department, with few studies being population-based. As discussed above, population-based registries have several advantages as data sources (4) and the use in Denmark of the unique civil registration number allows complete and long-term follow-up of study subjects identified in administrative databases.

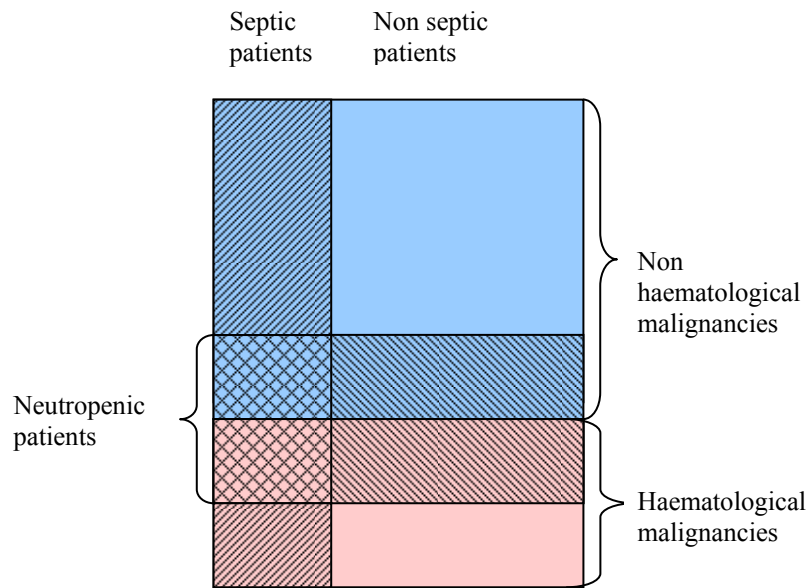


Figure 3. Different populations of cancer patients with bacteraemia

Choice of exposure

The definition of exposure can be somewhat confusing. Exposure means proximity and/or contact with a source of disease agent in such a manner that transmission of the agent or harmful effect of the agent may occur (56). Exposure is, however, used in a more broad sense about all traits potentially capable of affecting the outcome, including, for instance, genetic factors (75). The term *predictor* can be used instead of *exposure* to indicate uncertainty of whether an association is causal. Choice of predictors/exposures depends solely on the hypothesis. Examples in the existing literature of predictors of mortality in patients with a haematological malignancy and bacteraemia are uncontrolled underlying cancer, and use of antibiotic prophylaxis (44).

Choice of outcome

When describing the prognosis of patients with infectious diseases one should ideally include the full range of manifestations that would be considered important to the patients (55). However, in patients with a haematological malignancy and bacteraemia the single most important outcome is death. Death may, however, be measured in several ways. We have chosen to use the term mortality rate, which is defined as the number of deaths that occur in the study population divided by the total time at risk

experienced by this study population (11). The term case-fatality, which is almost exclusively used in infectious diseases, means the proportion of people who will die of a certain disease out of those who contract it (76). This measurement is, however, not useful in patients with underlying diseases because it can be difficult to distinguish between deaths due to the infection and deaths due to the underlying disease. The time period for measuring case-fatality rate is often unstated and if so, presumably there is a short period of increased risk (66). Time periods commonly used when studying bacteraemia are 7 and 30 days (44; 69-71). Some studies have measured in-hospital mortality, which is the proportion of patients with bacteraemia that dies during hospitalisation (62). In most of the investigations the follow-up was short, less than 30 days.

One may argue that the question of interest is how many deaths would have been avoided, had the patients not contracted an episode of bacteraemia and thus the most appropriate way of measuring death is to measure the proportion of deaths directly attributable to the bacteraemia. Weinstein et al. (1983) distinguished between deaths directly related to sepsis, indirectly related to sepsis, or unrelated to sepsis (30). We disagree with this classification for several reasons. Through our registries it is difficult to obtain valid information about cause-specific death (77) and it is difficult to distinguish between the contribution of the septic process and that of the underlying disorders when examining 30- and 90-day mortality. Therefore, we believe overall mortality to be the most robust and relevant measure of outcome in the analyses presented in this thesis.

Confounding factors

Confounding literally means mixing together, and in explanatory bacteraemia studies this implies that the effect of one factor under study (*e.g.*, comorbidity) is mixed with or masked by the effect of another factor (*e.g.*, age) on the outcome of bacteraemia. To act as a confounder in a study of mortality in patients with bacteraemia, a factor must 1) itself be a risk factor for mortality, 2) be unevenly distributed between the comparison groups, and 3) not be a consequence of the infection. Some of the predictors of mortality identified in previous studies (36;44;73) (*i.e.*, presence of shock and use of

ventilatory support) occur due to bacteraemia and should thus not be considered confounders. Possible confounding factors are the underlying type of haematological malignancy, age, and comorbidity. It is also likely, as shown by Bodey *et al* (47), that mortality of bacteraemia is related to the presence and duration of neutropenia. Type of microorganism and focus of bacteraemia are other possible factors related to mortality. Few of the existing studies have taken potential confounding factors into consideration.

Conclusion

Administrative hospital data are potentially important sources for cancer and infectious disease research; yet, data quality regarding haematological diseases in the discharge registries is not well known. Little data likewise exist on the incidence of bacteraemia among patients with haematological malignancies in general. Although several studies have evaluated the outcome of bacteraemia in patients with haematological malignancies (see table II and III), many important uncertainties remain. Advanced underlying cancer is a poor prognostic factor (44), but little is known on how the different types of cancer affect the outcome. None of the existing studies included bacteraemic patients without haematological malignancies as a control group, and few have assessed the outcome in relation to the origin (hospital or community) or type of bacteraemia. Several aspects of the association between age and outcome of bacteraemia in haematological patients are likewise poorly understood, in particular, the impact of comorbidity. Furthermore, we were unable to identify a study with more than 30 days of follow-up.

Properly designed epidemiological studies are needed based on validated data sources. We used population-based registries which, in combination with the existence of the unique civil registration number, allowed a relatively large sample size and complete long-term follow-up of the patients.

Aims of the thesis

- a. To evaluate the quality of data on haematological malignancy diagnoses in a hospital discharge registry, and to quantify the impact of any misclassification of diagnoses on survival estimates. (Study I) Since a hospital discharge registry may serve as the study base in studies among patients with haematological malignancies.
- b. To compare the type and the origin of the first episode of bacteraemia in patients with and without a diagnosis of a haematological malignancy, and to examine 30- and 90-day mortality rates.(Study II)
- c. To estimate the incidence rate of bacteraemia, to examine whether there was a variation in mortality following bacteraemia in patients with different haematological malignancies, and to examine whether the type of bacteraemia had any impact on the mortality rates. (Study III)
- d. To compare the outcome of bacteraemia according to age of patients with haematological malignancies, taking neutropenia into consideration, to examine the shape of the relation between age and bacteraemia, and to evaluate the impact of comorbidity on the association between age and bacteraemia. (Study IV)

Subjects and methods

Data sources

The studies in this thesis are cohort studies conducted in North Jutland County, Denmark, within a population of approximately 500,000 inhabitants. As in all of Denmark, the entire population in the county was provided with free, tax-supported health care. Haematologic patients with bacteraemia were treated in one of seven public hospitals, of which one (Aalborg Hospital) served as both district and referral hospital. Stem cell transplantation or bone marrow transplantation was not performed within the county. Thus, if the treatment included transplantation, the patient was transferred to a hospital outside the county. Antibiotic, antiviral, or antifungal prophylaxis in neutropenic patients was not used during the study period. Bacteriological service for the entire county was provided by the Department of Clinical Microbiology, Aalborg Hospital.

The studies are based on data from the following data sources:

The North Jutland Hospital Discharge Registry

Since 1977, Danish counties have developed administrative information systems and used them routinely to monitor hospital admissions, waiting lists, operations, and treatment. Data from these systems are transferred to the national Danish Hospital Discharge Registry (HDR). This registry comprises data on 99.4% of all discharges from Danish non-psychiatric hospitals and includes civil personal registration number (CPR), dates of admission and discharge, the surgical procedure(s) performed, and up to 20 discharge diagnoses classified according to the Danish version of the International Classification of Diseases (ICD). The 8th revision was used until the end of 1993 and 10th revision was used thereafter (78). The discharge diagnoses are given by the physicians.

The Danish Cancer Registry

The Danish Cancer Registry (DCR) is a population-based nationwide registry with data on incident cases of cancer in Denmark since 1943 (79). Reporting to this system by medical doctors became mandatory in 1987. Data kept on each individual includes personal identification number, method of verification of the cancer, clinical stage, and residence at date of cancer diagnosis. All available data are reclassified to the modified ICD-7. The registry receives notifications from hospital departments (including departments of pathology and forensic medicine), general practitioners, and practising specialists. Annual links to HDR and the National Death Certificate Files ensure that cases that have not been reported to the DCR are subsequently included (79). However, this procedure causes years of delay and the registry lacks information about the exact date of diagnosis, and the specific department.

North Jutland County Bacteraemia Registry

Since 1981, all episodes of bacteraemia in North Jutland County have been registered in the microbiologic County Bacteraemia Registry (79;80). This registry is maintained by the Department of Clinical Microbiology at the Aalborg Hospital, which provides bacteriological service nationwide. In case of a positive blood culture, the physician in charge at the Department of Clinical Microbiology notifies the attending physician by telephone and both physicians jointly assess the patient (the general condition, underlying comorbidity, portals of entry of the infecting microorganism, likely focus of infection, and appropriateness of ongoing antibiotic therapy). The clinical information obtained and the advice given has, since 1992, been routinely registered on a paper form concurrently with the clinical episode as part of standard working practice in the department. On this paper form, follow-up contacts have been registered, too. The forms are the basis of registrations of bacteraemia cases in the database. The registry contains data on bacterial isolates and susceptibility patterns, and on patients' age, gender, date of admission, presumed focus of infections, empirical antibiotic treatment, and civil registration number.

The County Pathology Registry (Study I)

The Department of Pathology, Aalborg Hospital, keeps computerized records of bone marrow and histopathology findings, including date of diagnosis. In study I, a manual search of individual electronic files was done to confirm the histopathological diagnoses for 251 patients identified either only in HDR or only in DCR.

The County Clinical Biochemistry Registry, LABKA (Studies III and IV)

Computerized clinical biochemistry data have been kept for all patients in North Jutland County since 1997. For the period 1992-1997, the data are kept as consecutively numbered printouts in the medical records and can therefore be retrieved through review of the medical records. From the LABKA database, maintained by the Department of Clinical Biochemistry, we retrieved information about leukocyte count within one week prior to a positive blood culture (Ref: Christiansen JU, Maruard CD, Nielsen HC. LABKA. A real-time computer system for the clinical laboratory. Scand J Clin Lab Invest Suppl. 1989;194:57-61.).

The Civil Registration system

In order to link data from the different registries, we used a unique 10-digit personal identification number that is assigned by the Central Office of Civil Registration to permanent and temporary Danish residents since 1968. From the Civil Registration system we also obtained information on vital status (dead or alive), date of death, and residence of the study population members.

Definition of source population, exposure, and outcomes

Table V gives an overview over the structure of the studies II-IV. The classifications of the different variables used are described in details below.

Haematological malignancies

Data on haematological malignancies in all four studies were obtained from the Hospital Discharge Registry and/or the Danish Cancer Registry. All patients aged 15 years or older were included in the studies. Children under 15 years of age were excluded because they are considered a special entity and are treated in close collaboration with the national reference centre at Aarhus University Hospital. Furthermore, in contrast to adults are children with acute lymphoblastic leukaemia given prophylactic antibiotic treatment in relation to induction treatment (82).

We chose to categorize haematological malignancies into: acute myeloid leukaemia, Hodgkin's disease, Non-Hodgkin's lymphoma or chronic lymphocytic leukaemia, and multiple myeloma or other malignant plasma cell neoplasms. All remaining haematological malignancies, including chronic myeloid leukaemia, were classified as "Other". The diagnoses were based on ICD-8 and ICD-10 codes in HDR and modified ICD-7 codes in DCR (See table IV)

	The Hospital Discharge Registry		The Danish Cancer Registry
	ICD-8	ICD-10	ICD-7
Overall	200.09-207.99	C81.0-C96.9.	198.0-205.0, 740.1-799.9
Acute myeloid leukaemia	205.09	C92.0	214.1,
Hodgkin's disease	201.99	C81.0-9	201.0-1
Non-Hodgkin lymphoma and chronic lymphocytic leukaemia	200.09-19, 202.09-29, 204.19, 275.59, 275.90	C82.0-85.9, C88.0-9, C91.1, C96.0-9	198.0, 200-202.0, 205.0, 740.1-799.9, 204.0
Multiple myeloma and other malignant plasma cell neoplasms	203.99	C90.0-2	203.0-2

Table IV. ICD-codes used to identify patients with haematological malignancies in the Hospital Discharge Registry and the Danish Cancer Registry.

In study I, we compared patients registered in HDR with patients registered in DCR. For validation we further obtained histopathological diagnoses for all patients identified only in one of the registries.

In study II, haematological malignancies were the exposure in a study population comprising all patients with bacteraemia; in studies III and IV, haematological malignancies defined the study population.

Bacteraemia

We used the County Bacteraemia Registry to identify episodes of bacteraemia. Three different systems for blood culture were being used during the study period. In 1992, a “12-tube” system was used whereby blood samples were drawn into Vacutainer® tubes and transported to the laboratory where each sample was inoculated into a set with 12 tubes of bacteriological media (four tubes of nutrient broth, four tubes of semisolid nutrient agar, and four tubes of semisolid thioglycollate agar) (83). During 1992-1995, the Colorbact® system (Statens Serum Institut, Copenhagen, Denmark) was used, in which blood was sampled directly into two aerobic and one anaerobic (84) bottles with culture broth. From 1996 on, the BacT/Alert system (bioMérieux sa, Marcy l’Etoile, France) was used and blood was likewise sampled directly into two aerobic and one anaerobic culture bottles. For adult patients, the nominal volume per blood culture for the three systems was 16–18, 20–22, and 28–32 mL, respectively (85).

The sample volume generally recommended for blood cultures is 30 mL (86;87) and the local practice with three broth culture bottles per set instead of two was implemented in order to obviate a need for two independent venipunctures (88). With two bottles per set the sample volume may be critically low if the second set is actually not drawn due to logistic or technical difficulties or because instituting antibiotic treatment is given priority. The drawback is that the significance of some opportunistic pathogens cannot be confirmed by independent samples.

The bacteraemia episodes were characterised based on the isolated pathogen and further categorized into Gram-positive bacteraemia, Gram-negative bacteraemia, and

polymicrobial bacteraemia or fungaemia. Polymicrobial bacteraemia was defined as more than one pathogen isolated within 24 hours (30).

Focus of infection was defined as the organ or tissue infected at the time when the bacteraemia became clinically apparent (89). Cultures of other body fluids and sites (*e.g.*, pus, urine, and respiratory secretions) were obtained when considered clinically relevant. Thus, determining the focus of infection was based on microbiological and clinical findings (42). In studies II-IV, we categorized the focus as known or unknown.

Table V summarises the structure of the studies II-IV. The population of study II included all adult (≥ 15 years old) county residents diagnosed with their first episode of bacteraemia during the study period. Study III evaluated both risk with bacteraemia as the outcome (a), and prognosis (b). In the prognostic section of study II and in studies III and IV, entry in the studies was defined as the date of the first positive blood culture draw.

Mortality

The main outcomes in the prognostic studies were the mortality rate and cumulative all-cause mortality after 7, 30, or 90 days of follow-up from the date of the first positive blood culture. We refer to the cumulative mortality at for instance day 7 as 7-day mortality.

Predictors (exposure)

As mentioned above, haematological malignancies were used as a predictor in study II. In that study, we also included all other cancer diagnoses as a predictor variable. In study III, the predictors were the different categories of haematological malignancies and type of bacteraemia. Age was the predictor in study IV; we used three age categories: 15-59 years, 60-79 years, and 80 years or older.

Study	Period	Source population	Predictors	Outcome(s)
II	1992- 2002	All patients with a first episode of bacteraemia	Haematological malignancies and other cancers	30-day and 90-day mortality
III a	1992- 2002	All patients with an incident haematological malignancy	Different types of haematological malignancies	Bacteraemia
III b	1992- 2002	All patients with an incident haematological malignancy and bacteraemia	Different types of haematological malignancies, and type of bacteraemia	30-day and 90-day mortality
IV	1992- 2002	All patients with an incident haematological malignancy and bacteraemia	Age	7-day and 30-day mortality

Table V. Characteristics of studies II-IV.

Definition of other variables

Comorbidity

In order to adjust for confounding by comorbidity, we computed the Charlson index based on ICD codes for all previous hospitalisations recorded in the Hospital Discharge Registry. Within this index, malignant diseases are categorised in the following four groups: solid tumour, lymphoma, leukaemia, or metastatic cancer. We excluded the diagnoses of leukaemia and lymphoma when calculating the index, because these were our predictor diseases. In the analyses in study II, we likewise excluded all malignant diagnoses when calculating the index.

Three levels of comorbidity were defined: 0 (“low”), corresponding to patients with no recorded underlying disease (other than leukaemia or lymphoma); 1–2 (“medium”); and >2 (“high”).

Empirical antibiotic treatment

We adjusted the analyses for appropriateness of the empirical antibiotic treatment. The empirical antibiotic therapy given to the patient at first notification of the positive blood culture was recorded in the Bacteraemia Registry. Therapy was considered appropriate if given intravenously (with the exceptions of fluoroquinolones and metronidazole) and if the blood isolate(s) were susceptible to one or more of the antibiotic drugs administered. The empirical treatment was considered inappropriate if isolates were found resistant or if doses or the form of administration were insufficient (90;91).

Presence of neutropenia

Information regarding neutrophil count was retrieved from the LABKA database. Patients were considered neutropenic if their neutrophil count at the date of the positive blood culture was $<0.5 \times 10^9/L$ or, for cases in which no neutrophil count was recorded, if the total leukocyte count was $<0.5 \times 10^9/L$. If no white blood count was available from the date of the positive blood culture, we recorded the latest blood count within one week before the positive blood culture.

Statistical analyses

In Study I, we estimated the completeness of registration in HDR as the proportion of patients registered with a haematological malignancy in DCR who were also found with such a diagnosis in HDR, *i.e.*, the numerator was the number of patients registered in both registries and the denominator was the number of all patients registered in DCR (92). We defined PPV as the proportion of patients registered with a haematological malignancy in HDR who also had a haematological malignancy diagnosis in DCR, *i.e.*, the numerator was the number of patients registered in both registries and the denominator was the number of all patients registered in HDR. To compare survival estimates for patients registered in HDR with survival estimates for patients registered in DCR, we constructed Kaplan-Meier survival curves for each of the two groups and used Cox's regression to estimate the mortality rate ratios (MRR) and associated 95% Confidence Interval (CI).

In studies II and III, we computed mortality rates and cumulative mortality after 30 and 90 days from Kaplan-Meier estimates with follow-up starting on the date of the first positive blood culture. We constructed contingency tables for the main study variables and the cumulative mortality. Cox's regression was used to compare mortality among different groups of patients.

Moreover, in study III we computed the incidence rate of bacteraemia and summarized risk over time based on Kaplan-Meier analysis using the date of admittance with the first haematological malignancy as time of entry. The patients were followed until their first episode of bacteraemia, death, or 31 December 2002, whichever came first. We used Cox's regression analysis to estimate the incidence rate ratios after one year of follow-up for the different types of haematological malignancies. In these analyses, we adjusted for age, gender, and comorbidity.

In study IV, we constructed Kaplan-Meier survival curves, based on the date of the patients' first positive blood culture, and estimated the mortality rate and cumulative risk of death after 7 and 30 days of follow-up. We computed standardized 7- and 30-day mortality rates using direct standardization in the age groups to the distribution of comorbidity and malignancy type in the youngest age group. We further used Cox's

proportional hazards analysis to estimate the mortality rate ratio (MRR) for 7- and 30-days mortality. These analyses were stratified according to the presence of neutropenia at the onset of the bacteraemia. To obtain a clearer picture of the shape of the relation between age and outcome of bacteraemia in patients with haematological malignancies, we used quadratic splines to smooth the age-mortality curve with linear restrictions imposed on both tails (93).

In the Cox's proportional hazards analysis, we graphically assessed the proportionality of hazards assumption for the model.

All estimates were presented with 95% confidence intervals (CI). The analyses were performed in Stata Statistical Software (Release 8.0. College Station, TX: Stata Corporation).

Results

Below follows a summary of the main results obtained in the four studies.

Study I. The data quality of haematological malignancy

ICD-10 diagnoses in a population-based Hospital Discharge Registry

We identified a total of 1,159 patients registered with their first haematological malignancy diagnosis in either HDR or DCR in 1994-1999. Of these, 908 (78.3%) were found in both registries, 167 (14.4%) were found only in the HDR, and 84 (7.3%) were found only in DCR.

Completeness and positive predictive value

Using DCR as the reference standard, the overall completeness of haematological malignancies in HDR was 91.5% (95% CI: 89.6–93.1), and PPV was 84.5% (95% CI: 82.2–86.5).

For the specific types of malignancies, completeness values were similar, whereas PPV varied among the four groups of diseases (see table VI).

	Total n	Degree of completeness % (95% CI)	PPV % (95% CI)
All haematological malignancies	1,159	91.5 (89.6 – 93.1)	84.5 (82.2 – 86.5)
Acute myeloid leukaemia	117	89.0 (80.4 – 94.1)	67.6 (58.3 – 75.7)
Hodgkin’s disease	84	88.7 (78.5 – 94.4)	71.4 (60.5 – 80.3)
Non-Hodgkin lymphoma, or chronic lymphocytic leukaemia	683	88.2 (85.3 – 90.6)	85.3 (82.3 – 87.9)
Multiple myeloma	171	90.9 (85.1 – 94.6)	82.3 (75.6 – 87.4)

Table VI. Total number of patients with a first-time diagnosis of a haematological malignancy. Degree of completeness and positive predictive value (PPV) are given as percent.

Validity of the diagnoses

We reviewed the histopathological diagnoses for all patients identified only in HDR or only in DCR by manually searching individual electronic files in the County Pathology Registry. For patients registered only in DCR, 73.8% of the diagnoses were confirmed as correct or most likely correct; for patients registered only in HDR, 42.5% were correct based on histopathological findings or peripheral blood smears. Patients registered in both registries were considered as correctly diagnosed. Thus, diagnosis could not be confirmed for 96 (8.9%) patients registered in HDR, and 62 patients with confirmed diagnoses in DCR were missing in HDR. Among patients registered only in HDR, 71 actually had a haematological malignancy. Overall, 992 patients were registered with a haematological malignancy in DCR. Thus, 71 patients correspond to an under-reporting to the DCR by approximately 7%.

Mortality

MRR for all haematological malignancies registered in the Hospital Discharge Registry compared with those registered in the Danish Cancer Registry, was 0.98 (95% CI: 0.88–1.09). Table VII shows the mortality rate ratios for the specific types of malignancies.

	MRR	95% CI
All haematological malignancies	0.98	0.88 - 1.09
Acute myeloid leukaemia	0.91	0.67 – 1.24
Hodgkin’s disease	1.33	0.77 – 2.38
Non-Hodgkin’s lymphoma or chronic lymphocytic leukaemia	0.98	0.84 – 1.14
Multiple myeloma	0.87	0.68 – 1.12

Table VII. Mortality rate ratio (MRR) and 95% confidence interval (CI) for patients registered in the Hospital Discharge Registry (HDR) in North Jutland County, Denmark, compared with patients registered in the Danish Cancer Registry.

Study II. Haematological malignancies

- a predictor of a poor outcome in patients with bacteraemia

We identified 7,456 patients diagnosed with a first episode of bacteraemia during the study period. Of these, 444 (6%) had been diagnosed with a haematological malignancy, 1,726 (23%) had a non-haematological malignancy diagnosis, and 64 (< 1%) had both.

The bacteraemia was less likely to be community-acquired (18% vs. 48%), and the focus of the bacteraemia was more often unknown (55% vs. 20%) in patients with haematological malignancies compared with patients without a haematological malignancy. Bacteraemia in patients with haematological malignancies less frequently involved isolates of *E. coli* (23% vs. 31%) and more frequently included *P. aeruginosa* (9% vs. 2%) than bacteraemia in patients without haematological malignancies. The two groups had very similar proportions of Gram-negative (49% vs. 50%) and Gram-positive (37% vs. 39%) bacteraemias (figure 4).

Mortality

Kaplan-Meier curves over 90 days of follow-up are shown in figure 5.

The 7-day cumulative mortality in bacteraemic patients with haematological malignancies was 17%, versus 12% for those with no malignant diagnosis, yielding an adjusted MRR of 1.2 (95% CI 0.9-1.6). Bacteraemic patients with other types of malignant diseases had a 7-day cumulative mortality of 15% yielding an adjusted MRR of 1.3 (95% CI 1.1-1.5) compared with bacteraemic patients without any malignancy. Thirty-day mortality of the bacteraemic patients with haematological malignancies was 32% compared with 20% for bacteraemic patients with no malignant diagnosis. The adjusted MRR was 1.6 (95% CI 1.3-2.0) for patients with a haematological malignancy, and 1.5 (95% CI 1.4-1.7) for patients with non-haematological malignancies.

After 90 days of follow-up, the cumulative mortalities were 49% in patients with haematological malignancies, and 25% in patients without any malignancy diagnosis, resulting in an adjusted MRR of 2.1 (95% CI 1.8-2.5). Among patients with non-haematological malignancies the adjusted 90-day MRR was 1.7 (95% CI 1.6-1.9).

Other variables

Compared with Gram-positive bacteraemia, Gram-negative bacteraemia conferred an adjusted MRR of 0.9 (95% CI 0.8-1.0) for 30-day mortality; for polymicrobial bacteraemia or fungaemia, the adjusted MRR was 1.3 (95% CI 1.1-1.5). We found community-acquired infections to have a slightly better prognosis than those with the other origins. Patients with an unknown focus of bacteraemia had a worse prognosis than patients with a known focus (30-day adjusted MRR 1.4 (95% CI 1.3-1.6)). Inappropriate empirical treatment was likewise associated with a slightly worse prognosis (30-day adjusted MRR 1.2 (95% CI 1.1-1.4)).

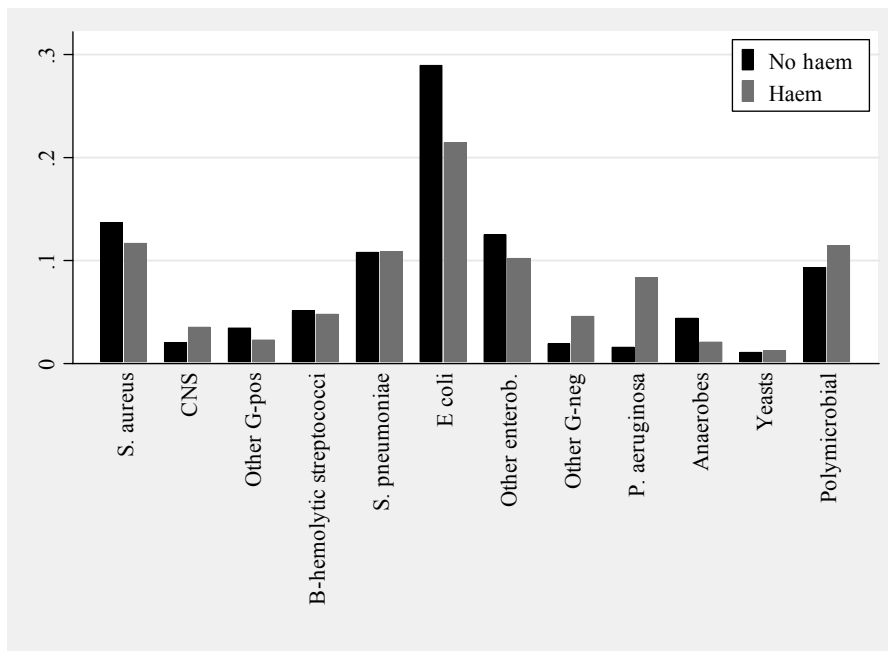


Figure 4. Distribution of the microbial agents isolated in the first episode of bacteraemia among patients with (Haem) and without (No haem) a haematological malignancy.

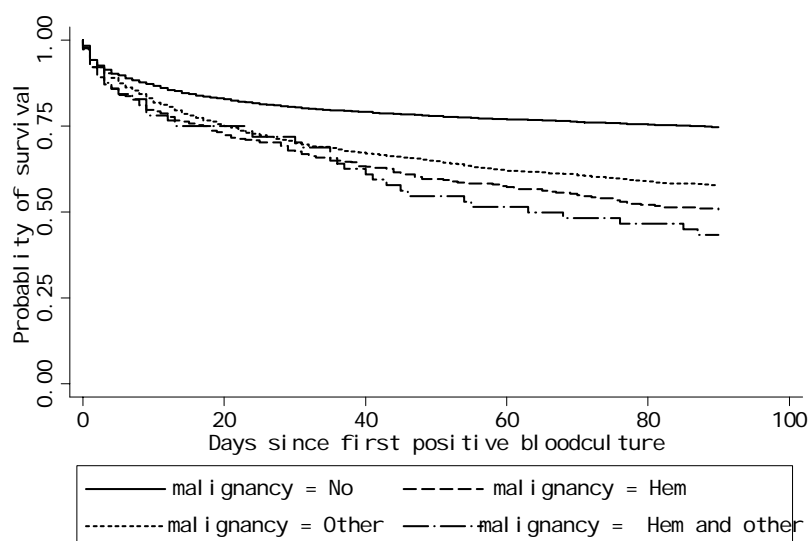


Figure 5. Kaplan-Meier curves for bacteraemia patients without any malignancy (solid line), with haematological malignancies (dashed line), with other types malignant diseases (dotted line), and with both a haematological and another type of malignancy (mixed line).

Study III. Risk and mortality of bacteraemia in different haematological malignancies

We identified 1,666 patients with an incident haematological malignancy: 926 (56%) men and 740 (44%) women. Acute myeloid leukaemia was diagnosed in 169 (10%), Hodgkin’s disease in 111 (7%), multiple myeloma in 245 (15%), and non-Hodgkin’s lymphoma or chronic lymphatic leukaemia, in 943 (57%) of the cases. The remaining 198 patients were categorized as “other”.

Among the 358 (21%) patients included, median time from the date of the haematological diagnosis to the first episode of bacteraemia was 1.1 years (interquartile range 0.2-3.4 years), yielding an incidence rate of 96 per 1000 person-years. Figure 6 shows the cumulative incidence for the different types of haematological malignancies within the first year of follow-up.

When compared with Hodgkin’s disease patients, the incidence rate ratios [IRRs] for bacteraemia were 23.3 (95% CI: 10.0-54.5) for acute myeloid leukaemia, 3.8 (95% CI: 1.5-9.3) for multiple myeloma, 2.2 (95% CI: 0.9-5.1) for non-Hodgkin lymphoma or

chronic lymphatic leukaemia, and 8.3 (95% CI: 3.5-19.6) for others, all adjusted for age, gender, and comorbidity.

Mortality

The crude 7-day mortality of patients with bacteraemia was 17% (95% CI: 13%-21%); the 30-day mortality rate was 32% (95% CI: 27%-37%); and the 90-day mortality 50% (95% CI: 44%-55%). Table VIII shows crude and adjusted MRR for 30 and 90 days of follow-up, according to the type of haematological malignancy and type of bacteraemia. Adjusted MRRs for the different malignancies all approximated unity.

Gram-positive organisms caused 35% and Gram-negative organisms caused 50% of the bacteraemias. In 14% of the cases, the first episode of bacteraemia was polymicrobial and only 1% was caused by yeasts. Patients with polymicrobial bacteraemia or fungaemia had increased mortality when compared with patients who had Gram-positive bacteraemia (adjusted 30-day MRR 1.9 (95%CI: 1.1-3.3)). Conversely, Gram-negative bacteraemia did not have a substantially increased mortality compared with Gram-positive bacteraemia (adjusted 30-day MRR 1.0 (95% CI: 0.6-1.5)).

Neutropenia at onset of bacteraemia was present in 31% of the patients and was associated with an increased mortality (adjusted 30-day MRR 1.9 (1.2-3.0)). Our sample size did not allow stratified analysis according to the presence of neutropenia.

Inappropriate empiric antibiotic treatment was recorded in 30% of the patients and was also associated with an increased mortality (adjusted 30-day MRR 1.4 (95% CI: 0.9-2.1)).

Risk factor	N	30-days mortality		90-day mortality	
		Crude MRR (95% CI)	Adjusted MRR (95% CI)	Crude MRR (95% CI)	Adjusted MRR* (95% CI)
Haematological malignancy					
Acute myeloid leukaemia	81	reference	reference	reference	reference
Hodgkin's Disease	13	1.2 (0.4-3.5)	1.1 (0.3-3.8)	1.4 (0.6-3.2)	1.5 (0.6-3.7)
Multiple myeloma	52	1.3 (0.7-2.5)	1.2 (0.6-2.3)	1.2 (0.7-2.0)	1.0 (0.6-1.8)
Non-Hodgkin lymphoma or chronic lymphocytic leukaemia	157	0.9 (0.6-1.6)	0.7 (0.4-1.2)	1.1 (0.8-1.7)	0.9 (0.6-1.3)
Other	15	1.6 (0.9-2.9)	1.1 (0.6-2.1)	1.4 (0.8-2.2)	1.0 (0.6-1.7)
Type of bacteraemia					
Gram-positive	125	reference	reference	reference	reference
Gram-negative	178	1.1 (0.7-1.7)	1.0 (0.6-1.5)	1.0 (0.7-1.4)	0.9 (0.7-1.3)
Polymicrobial or fungaemia	55	1.9 (1.1-3.2)	1.9 (1.1-3.3)	1.4 (0.9-2.1)	1.4 (0.9-2.3)

Table VIII. Type of haematological malignancy and type of bacteraemia associated with 30- and 90-day mortality in bacteraemia among patients with haematological malignancies.

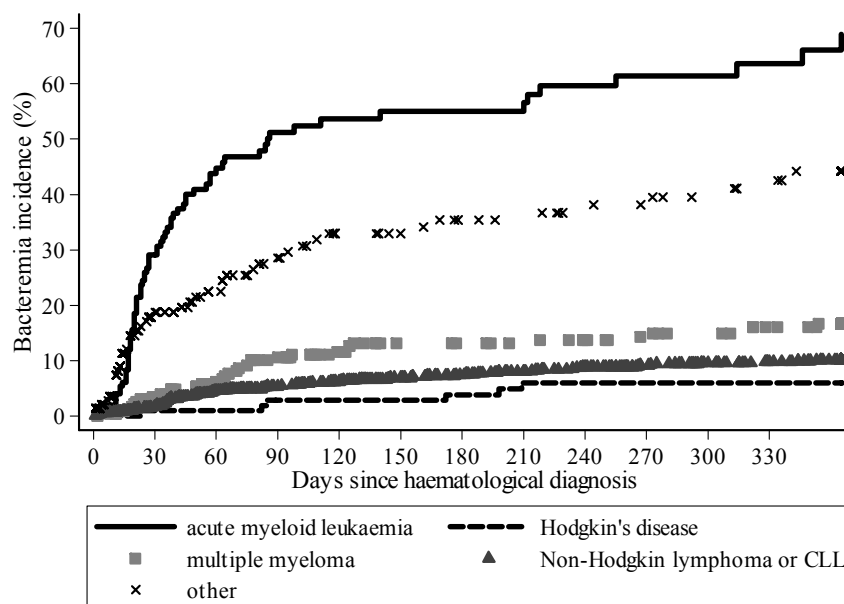


Figure 6. Cumulative incidence of bacteraemia among 1,666 patients with different types of haematological malignancies within one year from the date of the haematological malignancy diagnosis.

Study IV. Short term mortality of bacteraemia in elderly patients with haematological malignancies

Among 1,666 patients registered with a first-time haematological malignancy during the period 1992-2002, 1,102 (66%) were older than 60 years, and 281 (17%) were older than 80 years. Overall 358 (21%) patients had the first episode of bacteraemia during the study period. Of these, 207 (58%) were older than 60 years and 37 (10%) older than 80 years.

The 7-day mortality was 10% among patients younger than 60 years, 21% among patients aged 60-79 years, and 27% for patients aged 80 years or more. After standardization, the 7-day mortality value did not change substantially (Table IX). When compared with patients younger than 60 years the adjusted MRR was 1.9 (95% CI: 0.9-3.8) for patients aged 60-79. For patients 80 years or older the adjusted MRR was 1.6 (95% CI: 0.6-4.2).

After 30 days of follow-up the mortality was 23% among patients younger than 60 years, 35% among patients aged 60-79, and 54% among patients 80 years or older. After standardization to the distribution of comorbidity and malignancy type in the youngest age group, the 30-day mortality was 35% among patients aged 60-79, and 68% among patients 80 years or older. The adjusted MRR was 1.7 (95% CI: 1.1-2.7) for patients aged 60-79 and 2.3 (95% CI: 1.2-4.3) for patients aged 80 years or older, when compared with patients younger than 60 years.

The smoothed age-mortality curve is shown in figure 7 and indicates that 30-day mortality in haematological patients with bacteraemia increases more or less linearly except from a plateau between ages 65 and 80. The age-mortality curve for 7 days of follow-up rises more slowly and becomes horizontal at 65 years of age.

Differences in comorbidity did not have any major impact on the MRR estimates.

Excluding the variable for comorbidity from the analysis caused a slight 30-day MRRs increase from 1.7 (95% CI: 1.1-2.7) to 1.9 (95% CI: 1.2-2.3) for patients aged 60-79, and from 2.3 (95% CI: 1.2-4.3) to 2.5 (95% CI: 1.3-4.6) for patients 80 years or older.

Age group	N	Dead		Standardized	Crude	Adjusted
		at 7 days	7-day mortality (95% CI)	7-day mortality* (95% CI)	7-day MRR (95% CI)	7-day MRR† (95% CI)
15-59 years	151	15	10% (6%-16%)	10% (6%-16%)	1.0 (ref)	1.0 (ref)
60-79 years	170	35	21% (15%-27%)	19% (13%-26%)	2.2 (1.3-3.9)	1.6 (0.8-3.1)
80 or older	37	10	27% (16%-44%)	25% (14%-36%)	2.2 (1.0-5.2)	1.8 (0.7-4.4)

Age group	N	Dead		Standardized	Crude	Adjusted
		at 30 days	30-day mortality (95% CI)	30-day mortality* (95% CI)	30-day MRR (95% CI)	30-day MRR† (95% CI)
15-59 years	151	34	23% (17%-30%)	23% (17%-30%)	1.0 (ref)	1.0 (ref)
60-79 years	170	60	35% (29%-43%)	35% (27%-43%)	1.7 (1.1-2.7)	1.7 (1.1-2.7)
80 or older	37	20	54% (39%-70%)	68% (58%-78%)	2.9 (1.7-5.1)	2.3 (1.2-4.3)

*Standardized to the distribution of comorbidity and malignancy type in the youngest age group

†Adjusted for type of haematological malignancy, type of bacteraemia, comorbidity, gender and whether or not empirical antibiotic treatment was judged appropriate.

Table IX. Crude and adjusted risk of death within 7 or 30 days among patients with haematological malignancies, by age, and risk ratios relative to patients aged 15-59.

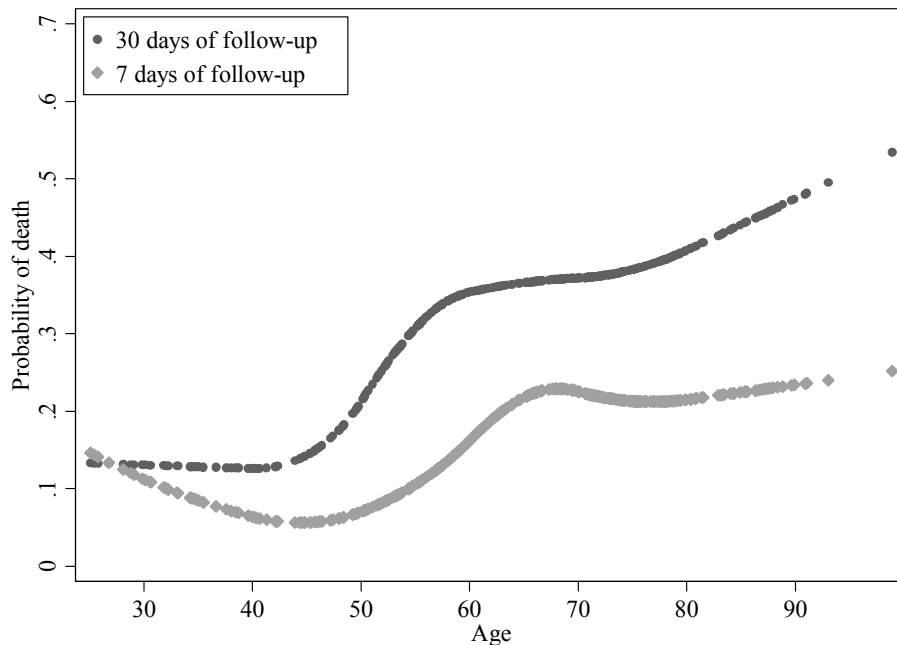


Figure 7. Estimated 7-day and 30-day mortality of bacteraemia for patients with haematological malignancies related to age

Strengths and weaknesses of the studies

Before giving our studies causal interpretation, we first need to critically evaluate potential alternatives to a causal association (55). We have to consider how problems in selection and information, confounding, and statistical imprecision (Figure 8) influence our estimates.

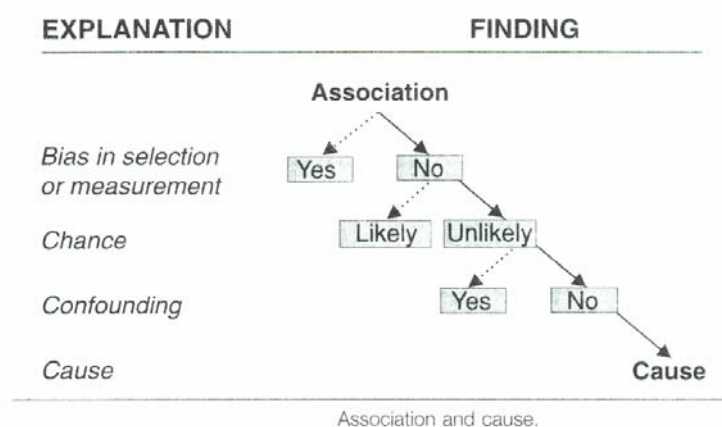


Figure 8. Association and cause from Fletcher “Clinical Epidemiology *The Essentials*” (55).

Study I

The comparison of two registries allowed estimation of the predictive value for haematologic malignancies, but did not provide the opportunity to estimate specificity, since we do not know the true incidence of haematological malignancies in the general population (gold standard). However, it is reasonable to assume a nearly perfect specificity since the general population is large and haematological malignancies are rare (92). Therefore, we do not expect this misclassification type to bias relative estimates.

We estimated the impact of misclassified diagnoses on survival analyses and found that survival curves were similar when looking at the major disease classes. Thus, HDR can be a useful data source in observational studies of haematological malignancies, although data have to be interpreted with caution. Our estimates of the quality of data may be valuable in this interpretation. The results of this study are thus useful when evaluating strengths and weaknesses in studies II-IV.

Studies II-IV

Selection bias

Selection bias arises when the association between exposure and disease differs between participants and non-participants of a study (11). We have to consider selection problems due either to selection into our study populations or to the loss to follow-up. Because of the high quality of the Civil Registration System, we have negligible loss to follow-up (94).

Since we have used different source populations in our studies (see table V) we will discuss selection into the study population for each study separately.

The population of **study II** consisted of all county residents hospitalised for the first time with bacteraemia. Selection into this cohort thus depended on the detection of bacteraemia and thereby on the indications for taking a blood culture. Bacteraemia may be undetected if rapidly fatal, if empirical antibiotic therapy was given before obtaining blood cultures, or if no blood culture was obtained. It is possible that patients with haematological malignancies have a higher proportion of rapidly fatal, and thus undetected, episodes of bacteraemia than other patients. This would cause the mortality rate to be underestimated. Because bacteraemia is a well-known condition among patients with haematological malignancies it is also likely that this increased awareness would lead to blood culture and subsequent treatment of haematological patients at an earlier stage of the infection. Since early antibiotic treatment is associated with decreased mortality (50), such heightened diagnostic efforts could likewise lead to an underestimation of the true mortality.

In **study III**, we calculated the incidence of bacteraemia in the population of all patients with a newly diagnosed haematological malignancy. To achieve a high specificity of the malignancy diagnosis for the study, we included only patients registered in both HDR and DCR. Use of this case definition would result in selection bias if patients registered in only one of the registries had less contact with the health-care system owing to mild or seldom complications, including lower incidence of bacteraemia. In that case, the true incidence of bacteraemia would be overestimated. However, we do not expect the

rate of this bias to differ according to types of haematological malignancies; that combined with the high specificity ensures that relative estimates were unbiased.

In the **prognostic part of study III and in study IV**, the study population was restricted to those with an incident haematological malignancy (i.e. the study population in the incidence part of study III) who also had a first episode of bacteraemia (i.e. were part of the study population in study II). Selection bias could arise if the indications for taking a blood culture differed between the subcategories of haematological malignancies or between different age groups. Detection of bacteraemia at an earlier clinical stage in some of these patients could result in an underestimation of the mortality. However, since PPV among patients registered with both a haematological malignancy and a bacteraemia was high we expect the MRR estimates to be unbiased.

Information bias

Information bias can arise because the information collected about study subjects is erroneous (11). These errors may result in misclassification of the exposure, the outcome, or the confounders. If these errors are differentially distributed among comparison groups, systematic error results.

In **study II**, having haematological or other malignancies was the predictor. The diagnosis of haematological and other types of cancer was based on discharge diagnoses and, as shown in study I, these were not entirely accurate. Patients with an undiagnosed cancer were likewise misclassified. If non-differential, this misclassification of patient malignancy status would tend to cause underestimation of the strength of positive associations.

In **study III**, information bias may have occurred as a result of misclassification of the predictor variables (type of malignancy, type of bacteraemia) or of bacteraemia as the outcome. Since the diagnostic process of haematological malignancies is complex and we used a rather simple categorization, some misclassification of type of haematological malignancies was likely. However, this misclassification was unrelated to risk of bacteraemia and is thus expected to cause under-estimation of positive associations.

In the **incidence part of study III**, bacteraemia was the outcome and information bias (diagnostic bias) may have occurred if frequency of blood cultures varied according to subtypes of haematological malignancies or if bacteraemia detection rates depended on more frequent empiric antibiotic treatment in patients with certain malignancy subtypes.

Confounding

We were able to adjust for the effect of age, gender, type of bacteraemia, comorbidity, calendar time, origin of bacteraemia, focus of bacteraemia, and appropriateness of the empirical antibiotic treatment. However, our relative estimates could still be affected by residual, unmeasured, or unknown confounding. Residual confounding results from improper categorization and misclassification of one or more confounding variables, such as comorbidity. We used the Charlson index (95) to adjust for comorbidity. The Charlson Comorbidity Index is a weighted index of the number and the seriousness of comorbid diseases. The index was developed in a cohort of 559 medical patients and tested for its ability to predict risk of death from comorbid disease in the second cohort of 685 patients during a 10-year follow-up. (95). The index includes 19 major disease categories and has now been widely adapted for use with hospital discharge data in ICD-based databases. This index has been shown to have a high specificity, but a more variable sensitivity when compared with diagnoses abstracted from the medical charts of 14,980 patients (96).

It is possible that comorbid diseases in the hospital discharge registries are coded with different accuracy in patients with and without haematological malignancies. Such situations occur if prodromal symptoms of a haematological malignancy lead to examination and early diagnosis of a comorbid disease, or if patients in contact with the health care system for a comorbid disease are more likely to be diagnosed with a haematological malignancy (Berkson bias). Misclassification of comorbidity could lead to residual confounding. It is likewise possible that comorbidity is recorded more accurately in younger than in elderly patients. Nevertheless, when adjusting for comorbidity we did not observe any major change in the estimates in study IV, suggesting that any residual confounding is likely to be slight.

A limitation of study II is absence of data about leukocyte count. Thus, we could not examine whether different grades of neutropenia influenced the MRR for patients with haematological malignancies. In study IV, we were able to stratify the analyses by neutropenia. Though imprecise, our risk estimates indicated that the association between age and mortality from bacteraemia is more pronounced among neutropenic patients. Information on the duration of neutropenia is difficult to obtain from registry records because its quality depends on the frequency of laboratory tests.

In study IV, we found that patients aged 80 years or older were more likely than younger patients to receive inappropriate empirical antibiotic treatment, and we were able to take this information into account in the analysis. It is also likely that suboptimal treatment of the elderly is not limited to the antibiotic treatment (97). Suboptimal supportive treatment, for example, could worsen the prognosis of bacteraemia.

One of the main weaknesses in this study is lack of clinical details. The patients did not receive antiviral or antifungal prophylaxis, but we did not have data on the use of growth factors. Growth factors may reduce the incidence of infections in patients receiving chemotherapy (98). However, use of growth factors, to our knowledge, has not been shown to improve the outcome of infections (99;100). We also lack information about patients' cytostatic regimens and the stage and severity of the underlying haematological malignancies.

Precision

We have throughout this thesis used 95% confidence interval to report the precision of the estimates. This level of confidence is arbitrary (11;66), and we could have alternatively reported 90% intervals, which are often used. The widths of the confidence intervals express the precision of our estimates and even in our large cohorts; those were wide.

Main conclusions

Based on the results in the four studies and an evaluation of potential sources of bias, the following conclusions were drawn from the studies.

Study I

Misclassification in HDR could bias absolute risk estimates. However, PPV – a measure for the specificity – was high, so that relative estimates are expected to be unbiased. We found that survival estimates were practically unbiased which makes this registry highly suited for quality assessment. Thus, we conclude that hospital discharge is a valuable tool for selected future haematological research.

Study II

We found similar distributions of the microbial agents in patients with and without haematological malignancies. Nevertheless, in patients with haematological malignancies, bacteraemia was less likely to be community-acquired and the focus of infection was more likely to be unknown. Patients with haematological malignancies had higher mortality than with patients without a malignancy diagnosis, but their increased mortality did not differ substantially from the mortality in patients with other types of malignancies. This suggests that poor prognosis in bacteraemic patients is due to factors related to the underlying malignancy.

Study III

Bacteraemia was frequent in patients with haematological malignancies and was associated with high mortality rates. The cumulative incidence of bacteraemia, but not the mortality associated with bacteraemia, varied by type of malignancy.

This study suggests that prophylactic strategies for bacteraemia should be tailored to the type of haematological malignancy, while strategies for treating bacteraemia could be standardized. Special attention needs to be given to polymicrobial bacteraemia and fungaemia because of their association with increased 30-day mortality rates.

Study IV

We found older age to be associated with increased mortality from bacteraemia in patients with haematological malignancies. An increased burden of comorbidity among the elderly patients did not explain this association, suggesting that it was due to other age-related factors. These findings may have implications for the choice of chemotherapeutic regimen, antibiotic therapy, and supportive treatment in elderly haematological patients.

Discussion in relation to the existing literature

In the following our results will be discussed in relation to the aims of this thesis.

Quality of data on haematological malignancy diagnoses in a hospital discharge registry

We estimated the under-notification of cases in DCR to be approximately 7%, which was slightly more than expected based on studies of other types of cancer in Denmark (101;102). The diagnostic process of haematological malignancies is complex and the boundary between precursor conditions and haematological disease can be somewhat arbitrary. This complexity may cause some cases to be classified as benign in one registry and as malignant in the other (103;104). In our study, about one-third of the misclassified patients found in only one of the two registries were classified in the histopathology files with a benign haematological disease. Data quality in our study was similar to that reported by an Irish study of validity of electronically-captured hospital discharge data (105). In contrast, a study from Israel, combining computerised discharge data for hospitalisations and an outpatient oncology database with data from Israel Cancer (106) was less complete and had lower PPV than found in our study. In a Swedish study on acute leukaemia, under-notification rate was found to be 15.4% (107). Importantly, the survival estimates in our study were practically unbiased which makes this registry highly suited for quality assessment.

Bacteraemia-related mortality in patients with and without haematological malignancies

To the best of our knowledge, this is the first study comparing mortality after bacteraemia in patients with haematological malignancies with cancer-free patients. A few studies have, however, compared the outcome of bacteraemia among neutropenic patients with haematological malignancies and those with other types of cancer. Similarly to our study, Elting *et al.* (36) found no significant difference in infection-related death between patients with acute leukaemia and patients with solid tumours. Conversely, Gonzalez-Barca *et al.* found that patients with non-leukaemic malignancies

had a higher 30-day mortality compared with patients with acute leukaemia (OR 2.3 (95% CI 1.5-3.7) (44).

The similarity in distribution of the microbial agents in patients with and without haematological malignancies could be due to the lack of use of prophylactic antibiotic treatment among haematological patients. However, another possible explanation is that we chose only to include the patients' first episode of bacteraemia, while most other studies considered multiple episodes (See tables II and III), and it is unknown whether the patients have had previous episodes. We chose to include only the first episode of bacteraemia since even with the stringent criteria used in our studies, episodes of bacteraemia in the same patient are probably not independent, which could bias results. Thus, we are mainly avoiding survival bias, i.e., the fact that patients who are able to survive one episode of bacteraemia and experience several episodes could be in some way "healthier" or more robust than patients who die after the first episode (similarly to the "healthy –worker effect" (66).

We agree with Friedman *et al.* (41) that infections in haematological patients cared for in outpatient settings should not be categorized as community-acquired. In their cohort, Friedman *et al* find that patients with health care-associated infections resemble those with nosocomial infections in source of infection, frequency of *S. aureus* as a pathogen, and in mortality rates. (41). Our findings suggest that during the first episode of bacteraemia the pathogens do not vary when stratified by origin; this, however, needs more examination in the future.

Risk and mortality of bacteraemia in different types of haematological malignancies

We were only able to identify one other study examining incident rates of bacteraemia among haematological patients. In that hospital-based study by Teira *et al*, written in Spanish, the incidence rate of bacteraemia was 5.8 per 1000 patient-days among patients with acute myeloid leukaemia , and 0.40 per 1000 patient-days for patients with lymphomas (54). Our finding of an overall incidence rate of 96 cases per 1000 person-

years corresponds to the rate of 0.26 per 1000 person days . Although our incidence rate in this population-based cohort was lower than that in the hospital-based Spanish cohort, the incidence rates showed similar variations.

Our findings of an overall 30-day mortality rate on approximately 30% for bacteraemia in patients with haematological malignancies appears high but the findings are in accordance with other referral centre studies (44;70;71). Yet, Cherif *et al* reported 30-day mortality on 16% in a study of 1,402 episodes of bacteraemia in 927 patients with haematological disorders (69). This Swedish study did not account for patient age or other potential confounding factors; in addition, the analysis was not restricted to the first episode of bacteraemia.

We believe that our study is the first one to document 90-day mortality rates in patients with haematological malignancies and bacteraemia. We did no attempt to determine cause-specific mortality. However, as mentioned above, we find that all-cause mortality is a reasonable measure to use, because it is difficult to distinguish between the contribution of the septic process and that of the underlying disorders when examining 30- and 90-day mortality.

We found that polymicrobial bacteraemia and fungaemia had a strong impact on 30-day mortality rates, which is in line with findings of earlier studies (57;70). Our failure to find any substantial difference in mortality rates between patients with Gram-positive and Gram-negative bacteraemia contradicts results from the experimental (RCT) EORTC studies (23) that included 1,074 granulocytopenic patients from 24 different institutions. These trial participants are likely to be a highly selected patient group, compared with the patients in our population-based study.

Age and outcome of bacteraemia in patients with haematological malignancies

Our findings of increased bacteraemia-related mortality associated with increased age in patients with haematological malignancies agree with and extend findings from EORTC studies (23). Similarly, Rossini found that among patients with haematological diseases and neutropenia, the prognosis for infections became poorer in the elderly (age 65 years

or older) (74). In contrast, Garcia-Suarez *et al*, who evaluated 131 episodes of fever and neutropenia in 85 adults with cancer, concluded that patients aged 60 years or older had outcomes similar to those of younger patients (61). However, in that study less than 40% of the patients had documented bacteraemia, whereas we included only patients with the first episode of documented bacteraemia.

Adjusting our analysis for comorbidity did not produce a major change in the effect estimates indicating that comorbidity cannot entirely explain the increased mortality in older patients and that other factors therefore must play a role. We found that patients older than 80 years were more likely than younger patients to receive inappropriate empirical antibiotic treatment. Under-treatment because of age, independent of comorbidities, is apparent in studies of several malignancies including lymphoma (97). Though imprecise, our data indicated that the association between age and mortality from bacteraemia was more pronounced among neutropenic patients. Use of growth factors for prevention of neutropenia may therefore be of importance. In 2003, EORTC found that there was sufficient evidence to affirm that prophylactic granulocyte colony-stimulating factor (G-CSF) reduces the incidence of chemotherapy-induced neutropenia, febrile neutropenia, and infections in elderly patients receiving myelotoxic chemotherapy for non-Hodgkin's lymphoma (NHL) (98). EORTC concluded, however, that there was a need for further well-designed studies in order to identify elderly patients who will benefit most from the prophylactic G-CSF.

Perspectives

Our studies have shown that bacteraemia is a frequent and serious complication in patients with haematological malignancies. Several aspects of preventable or modifiable risk and prognostic factors for bacteraemia in patients with haematological malignancies are still poorly understood and need further examination in the future. We found that population-based registries are valuable as data sources for such studies. The major strength of these registries is their longitudinal perspective. Our studies have, however, exposed some weaknesses in these data-sources, such as limited number of observations and lack of clinical details. In order to assemble samples large enough for meaningful studies, collaboration between several counties would be required. In a few years, we expect to establish collaboration between the new larger Danish regions, and eventually to have access to a nation-wide database. Several types of data, such as hospital pharmacy data, including chemotherapeutic regimens and use of growth factors, are now being registered in patient administrative databases. Thus, in a few years we will be able to incorporate these data in our studies, which will allow better measurement of exposure and confounding.

Based on the findings in this thesis, we conclude that bacteraemia in patients with haematological malignancies confers a poor prognosis because of factors related to the underlying malignancy. Thus, in future studies we would like to focus on identifying possible prognostic factors. The importance of disease stage, and the impact of the type of chemotherapeutic regimen merit further examination. We would like to examine the data quality of precursor condition diagnoses, such as myelodysplastic syndromes in the hospital discharge registries, in order to study risk and prognosis of bacteraemia in these patients. Another hypothesis worth examining is that of bacteraemia being associated with precursor condition's transformation into malignancy.

Bacteraemia may be preventable, and the role of prophylactic antibacterial agents remains controversial (59;108). Our finding that risk of bacteraemia depended on the type of haematological malignancy could have implications for future prophylactic strategies. Conversely, the observation of similar mortality rates among in bacteraemic

patients with different haematological malignancies supports the use of regular guidelines for treatment of such patients. Polymicrobial bacteraemia and fungaemia are probably exceptions most likely occurring secondary to serious breaches in immunocompetence, and should be dealt with differently.

We found that elderly haematological patients have more often received inappropriate empirical antibiotic treatment; future interventions among the elderly could thus focus on optimisation of chemotherapeutic and supportive treatment. Our results suggested that neutropenia increased the MRR among elderly patients, which underscores the importance of carefully following changes in blood counts. RCTs are needed to study whether elderly haematologic patients could benefit from the use of growth factors to prevent neutropenia.

Summary

The incidence of haematological malignancies is increasing in several countries and is strongly associated with age. The prevalence of patients with haematological malignancies will therefore increase in the coming decades. Infectious complications are still among the most serious problems among patients with haematological malignancies, most likely due to the immune system compromised by the underlying malignancy and the antineoplastic treatment.

This thesis includes four observational studies conducted in North Jutland County, Denmark, and is based on data from the Danish Cancer Registry, the County Hospital Discharge Registry, North Jutland County Bacteraemia Registry, and the Civil Registration System.

The aims of the thesis were 1) to evaluate the quality of data on haematological malignancy diagnoses in a hospital discharge registry and to quantify the impact of misclassified diagnoses on survival estimates, 2) to compare the type and the origin of the first episode of bacteraemia in patients with and without a haematological malignancy and to examine 30- and 90-day mortality rates, 3) to estimate the incidence rate of bacteraemia and the bacteraemia-related mortality rate in patients with different haematological malignancies and to examine whether the type of bacteraemia was associated with mortality, and 4) to compare the outcome of bacteraemia among elderly and younger patients with haematological malignancies and to evaluate the impact of comorbidity on the association between age and outcome of bacteraemia.

In study I, we estimated the data quality of a haematological malignancy discharge diagnosis in the County Hospital Discharge Registry, using the Danish Cancer Registry as reference standard, and compared survival analyses based on the County Hospital Discharge Registry and the Danish Cancer Registry, respectively. We found completeness in the Hospital Discharge Registry for all haematological malignancies to be 91.5% (95% confidence interval [CI]: 89.6–93.1) and positive predictive value to be 84.5% (95% CI: 82.2–86.5). This misclassification had, however, no major impact on survival estimates. Mortality rate ratio (MRR) for all haematological malignancies, when registered in the Hospital Discharge Registry compared with being registered in the Danish Cancer Registry, was 0.98 (95% CI: 0.88–1.09).

In study II, we found that despite having similar distributions of the microbial agents causing bacteraemia, patients with haematological malignancies had higher mortality than patients without any malignancy (MRR 1.6 (95% CI 1.3-2.0)). However, patients with non-haematological malignancies had similarly increased mortality. This suggests that bacteraemia patients with malignancies have a poor prognosis because of factors related to their underlying illness.

In study III, we found the risk of bacteraemia within the first year after the diagnosis to vary substantially across different types of haematological malignancies. The mortality, however, did not vary according to the underlying type of malignancy. Polymicrobial bacteraemia or fungaemia was associated with an increased mortality (MRR 2.0 (95% CI; 1.1-3.6)), whereas the mortality was similar for patients with Gram-negative and Gram-positive bacteraemia.

In study IV, we found increasing age to be associated with increased mortality from bacteraemia in patients with haematological malignancies. An increased burden of comorbidity among elderly did not explain this association.

In conclusion, we found that the risk of bacteraemia in patients with haematological malignancies varies according to the underlying type of malignancy. The prognosis, however, varied neither according to the underlying type of haematological malignancy nor according to other types of cancer.

Our studies have shown that the Danish population-based registries are suitable data sources for studying the association between bacteraemia and haematological malignancies. Several data types, such as hospital pharmacy data, are now being registered in patient administrative databases and we expect in few years to have collaboration between the new larger Danish regions. Thus, in few years we hope to be able to conduct our studies in a nation-wide database with more detailed exposure and confounder data.

Dansk resume

Malign hæmatologisk sygdom er en heterogen gruppe af kræftsygdomme, hvor forekomsten stiger med alderen. Mere end 50% af alle nydiagnosticerede patienter med malign hæmatologisk sygdom er ældre end 65 år. Det kan således forventes at antallet af patienter med malign hæmatologisk sygdom vil være kraftigt stigende de kommende årtier.

Svære infektioner er blandt de alvorligste komplikationer til malign hæmatologisk sygdom. Dette skyldes at patienterne ofte har et svækket immunsystem på grund af dels den underliggende maligne sygdom dels den antineoplastiske behandling.

Denne afhandling er baseret på fire observationelle studier bygget på data fra Cancerregisteret, det patient administrative system i Nordjyllands Amt, den Nordjyske bakteriemidatabase og CPR registeret. Fra PAS sker indberetning til Landspatientregistret af diagnose- og behandlingskoder.

Formålene med PhD studiet var 1) at undersøge datakvaliteten af en malign hæmatologisk udskrivningsdiagnose i PAS samt at vurdere hvilken betydning en eventuel misklassifikation har på overlevelses estimater, 2) at sammenligne de mikrobiologiske fund ved første tilfælde af bakteriemæmi hos patienter med og uden malign hæmatologisk sygdom samt sammenligne overlevelsen inden for 90 dage efter første positive bloddyrkning, 3) at belyse risiko og prognose for bakteriemæmi ved forskellige typer af malign hæmatologisk sygdom, samt prognosen ved forskellige typer af bakteriemæmi og 4) at belyse sammenhængen mellem alder og overlevelse af bakteriemæmi blandt patienter med malign hæmatologisk sygdom og vurdere hvilken betydning komorbiditet har på sammenhængen mellem alder og overlevelse.

I studie I fandt vi at PAS havde en kompletthedsgrad på 91.5% (95% konfidensinterval [CI]: 98.6–93.1%) og en positiv prædiktiv værdi [PPV] på 84.5% (95% CI: 82.2–86.5), hvis vi brugte Cancerregisteret som guld standard. Denne misklassifikation havde imidlertid kun beskedne effekt på mortalitetsraten. Mortalitet rate ratioen (MRR) for malign hæmatologisk sygdom i PAS sammenlignet med Cancerregisteret var 0.98 (95% CI: 0.88–1.09).

I Studie II fandt vi, at på trods af at de fundne mikrobiologiske agens var ensartet fordelt i de to grupper, havde patienter med malign hæmatologisk sygdom højere dødelighed af

bakteriæmi end patienter uden malign sygdom (MRR 1.6 (95% CI 1.3-2.0)).

Dødeligheden var imidlertid tilsvarende forhøjet blandt patienter med andre typer cancer. Dette kunne tyde på, at den dårligere overlevelse primært skyldtes faktorer relateret til selve den maligne sygdom.

I studie III fandt vi, at forekomsten af bakteriæmi i modsætning til mortaliteten varierede betydeligt mellem de forskellige typer af malign hæmatologisk sygdom.

Gram-positiv og Gram negativ bakteriæmi havde samme prognose, mens polymikrobiel bakteriæmi eller fungæmi havde dårligere prognose sammenlignet med Gram-positiv bakteriæmi (MRR 2.0 (95% CI; 1.1-3.6)). Patienter med neutropeni havde ligeledes en dårligere prognose end patienter med et neutrofiltal over $0,5 \times 10^9/l$ (MRR = 1.9 (95% CI, 1.2-3.0)).

I Studie IV fandt vi en næsten lineær sammenhæng mellem alder og mortalitet. Vi fandt ikke, at en øget forekomst af komorbiditet kunne forklare den øgede mortalitet blandt de ældre. Sammenhængen mellem mortalitet og alder var mere udtalt ved 30 dages mortalitet end ved 7 dages mortalitet, hvilket tyder på, at den ikke skyldes faktorer relateret umiddelbart til den akutte infektion.

Sammenfattende viste vores undersøgelser, at patienter med malign hæmatologisk sygdom har varierende risiko for bakteriæmi afhængig af den underliggende type af malignitet. Prognosen ved bakteriæmi viser derimod begrænset variation mellem de forskellige typer af hæmatologisk cancer og afviger ikke fra prognosen ved anden cancersygdom. De danske populations-baserede registre er med deres longitudinelle perspektiv velegnede til at studere sammenhængen mellem bakteriæmi og malign hæmatologisk sygdom. Vi håber inden for få år at kunne etablere en landsdækkende database samt inkludere oplysninger om kemoterapeutisk og anden behandling, hvilket vil give bedre eksponerings og konfounder oplysninger.

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Appendices (Study I-IV)

Study I

Nørgaard M, Skriver MV, Gregersen H, Pedersen G, Schönheyder HC, Sørensen HT.
The data quality of haematological malignancy ICD-10 diagnoses in a population-based
Hospital Discharge Registry. *Eur J Cancer Prev.* 2005;14:201-206.

Study II

Nørgaard M, Larsson H, Pedersen G, Schönheyder HC, Sørensen HT.
Haematological malignancies - a predictor of a poor outcome in patients with
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Study III

Nørgaard M, Larsson H, Pedersen G, Schönheyder HC, Sørensen HT.

Risk and mortality of bacteraemia in different haematological malignancies. *Clin Microbiol Infect.* In press

Study IV

Nørgaard M, Larsson H, Pedersen G, Schönheyder HC, Rothman KJ, Sørensen HT.
Short-term mortality of bacteraemia in elderly patients with haematological malignancies. *Br J Haematol.* 2006; 132: 25-31.