Diabetes Mellitus and Community-acquired Bacteremia:

Risk and Prognosis

PhD thesis

Reimar Wernich Thomsen

Department of Clinical Epidemiology, Aarhus University Hospital

Department of Clinical Microbiology, Aalborg Hospital, Aarhus University Hospital

Faculty of Health Sciences

University of Aarhus

2004

Preface

This PhD thesis is based on studies carried out during my employment at the Department of Clinical Epidemiology, Aalborg Hospital, Aarhus University Hospital, during the period 2001-2004.

I am deeply indepted to a number of persons who have made this work possible. First of all, I wish to thank my supervisors. Henrik C. Schønheyder for so enthusiastically introducing me to bacteremia research, for generously sharing his ideas with me, and for being my role model both within scientific research and integrity. Henrik Toft Sørensen for teaching me what clinical epidemiology really is about, for patiently teaching me the art of scientific writing, and for his continuous support and believe in me at all times.

I am grateful to my principal statistician Heidi H. Hundborg for good teamwork; it has been a pleasure to work with her from the beginning. I want to thank my colleague and friend Søren P. Johnsen for a lot of guidance and thoughtful feed-back, and for many good soccer discussions. Thank you to Hans-Henrik Lervang for clinical inspiration and diabetological guidance.

I want to express my sincere gratitude to all my colleagues and friends at the Department of Clinical Epidemiology in both Aalborg and Aarhus for creating a pleasant working atmosphere. Special thanks to Gunnar L. Nielsen for invaluable critique, countless methodological discussions, and for being a great mentor at the department in Aalborg.

I have had the pleasure of working on data from the North Jutland Bacteremia Database, and I am indebted to the staff at the Department of Clinical Microbiology, Aalborg Hospital, who has made investments in order to create this great database. I also wish to thank the staff of the Hospital Discharge Registries in North Jutland County (Amtsgaarden), and the staff at all the larger and smaller hospitals in North Jutland for their help with data collection. Thank you to Lars Pedersen, who together with Henrik Toft Sørensen established the North Jutland County record linkage cohort based on data from the central Civil Registration System, and who never hesitated to help me with my countless questions and demands.

This PhD thesis is based on the following papers:

I   Thomsen RW, Hundborg HH, Lervang H-H, Johnsen SP, Sørensen HT, Schønheyder HC.
Diabetes mellitus and outcome of community-acquired pneumococcal bacteremia:
A 10-year population-based cohort study.
Diabetes Care 2004; 27: 70-76.

II Thomsen RW, Hundborg HH, Lervang H-H, Johnsen SP, Schønheyder HC, Sørensen HT.
Risk of community-acquired pneumococcal bacteremia in patients with diabetes mellitus: A
population-based case-control study.
Diabetes Care 2004, 27: 1143-47.

III Thomsen RW, Hundborg HH, Lervang H-H, Johnsen SP, Schønheyder HC, Sørensen HT.
Diabetes mellitus as a risk factor and prognostic factor for community-acquired bacteremia
with enterobacteria: A 10-year population-based study.
Clinical Infectious Diseases, revised manuscript in press.

List of abbreviations

ASB	Asymptomatic bacteriuria
ARDS	Acute respiratory distress syndrome
ATC	Anatomical, therapeutical, chemical classification
CF	Case-fatality
CI	Confidence interval
CNS	Central nervous system
CRP	C-reactive protein
DM	Diabetes mellitus
ICD	International Classification of Diseases
ICU	Intensive care unit
MRR	Mortality rate ratio
OR	Odds ratio
RR	Relative risk
SMR	Standardized mortality ratio
T1 DM	Type 1 diabetes mellitus
T2 DM	Type 2 diabetes mellitus
UTI	Urinary tract infection

Contents

1. Introduction

"After a careful history had been taken, the patient was given a complete physical examination. Special attention was directed to the finding of foci of possible infection. The teeth, accessory sinuses, chest and digestive system were examined clinically, as well as by x-ray. Special consideration was given to a biliary tract infection, constipation and chronic appendicitis. If any source of septic absorption was located, it was appropriately treated, since such conditions may lower carbohydrate tolerance."

Frederick G. Banting. Nobel Lecture delivered in Stockholm on September 15th, 1925. About clinical routine examinations at the first three diabetes clinics in Toronto.

Diabetes mellitus is a substantial and increasing public health and clinical problem (1). In addition to well-known diabetes complications affecting multiple organ systems, it is a common clinical belief that a close association between diabetes mellitus and infection exists (2). For most infections, this belief appears to be supported by relatively sparse epidemiological evidence (3;4). Bacteremia constitutes the most severe end of the spectrum of frequent infections such as pneumonia (5) and urinary tract infection (6), and the prevalence and thus disease burden of bacteremia has increased during the last decades analogous with diabetes (7). In the present thesis, we aimed to examine the association of diabetes with the two dominant groups of community-acquired bacteremia: pneumococcal bacteremia and enterobacterial bacteremia. As an introduction, we will give an overview of the epidemiology of bacteremia. We will also address the burden of diabetes and what is already known on the association of diabetes with infection. Lastly, prior studies of diabetes and bacteremia will be reviewed, with a discussion of these studies' methodological shortcomings.

1.1. Introduction to bacteremia – definitions, disease burden, risk and prognostic factors

What is bacteremia?

Bacteremia is usually defined as the presence of viable bacteria in the blood stream, as evidenced by blood cultures (8;9). Bacteria may be transiently introduced into the blood which may or may not lead to symptoms, e.g. after manipulation of mucous membranes, and some hematogenous infections are preceeded by clinically silent bacteremia. Nevertheless, more extensive dissemination

of bacteria into the blood stream becomes clinical manifest with only rare exceptions. Such dissemination indicates a breakdown of normal defence mechanisms that serve to restrict an infection to its primary site. In a clinical context, bacteremia can thus be defined as an infectious disease associated with growth in blood cultures of one or more microorganisms that are considered of etiological significance after clinical and microbiological evaluation (10).

Bacteremia is usually classified according to the microbial agent and an eventual coexisting focus of infection, assessed on the basis of microbiological and clinical findings. It is important to distinguish between momomicrobial and polymicrobial bacteremia (one or more than one microbial agent), because polymicrobial bacteremia normally occurs in a quite different clinical setting (11), and for epidemiological research it may be impossible to determine which microbial agent is the "culprit". It is further important to distinguish bacteremias acquired outside a hospital setting (*community-acquired*) from those that arise in hospital (*nosocomial*), because the place of acquisiton is closely associated with the focus of infection, microbial agent, antibiotic resistance, and prognosis (12). In this thesis we focused on community-acquired bacteremia, as our aim was to investigate diabetes as a risk factor for bacteremia in the general population, not among patients already hospitalized.

The distribution of bacterial isolates and foci of infection in community-acquired bacteremias in North Jutland County, Denmark between 1992 and 2002 is shown in Figures 1 and 2. It is seen that the urinary tract and respiratory tract accounted for almost two thirds of episodes, with the predominant bacteria being Enterobacteriaceae (the members of which are referred to as enterobacteria in this thesis) and *Streptococcus pneumoniae* (13;14).

Fig. 1: Microbial isolates in 3,829 episodes of community-acquired bacteremia. North Jutland County, Denmark 1992-2002.
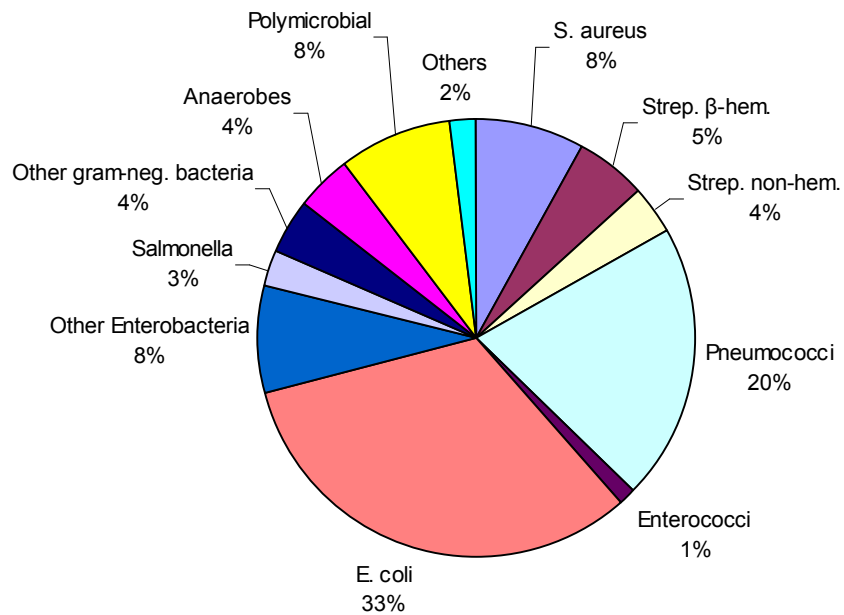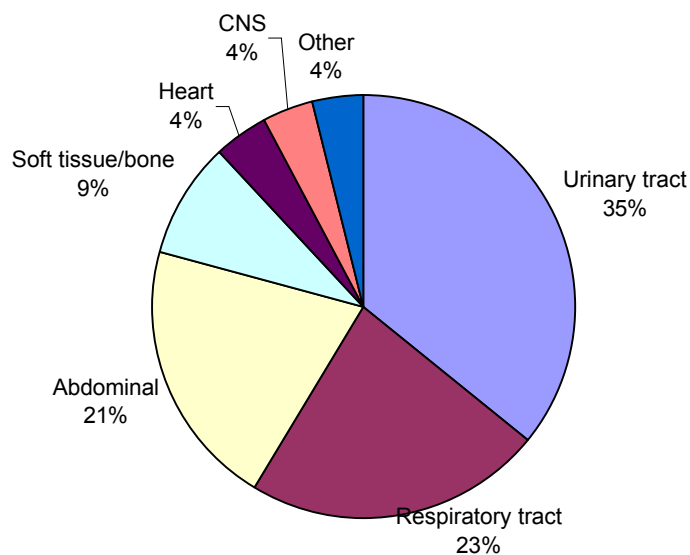

Fig. 2: Focus of infection in 3,141 episodes of community-acquired bacteremia with a determined focus. North Jutland County, Denmark 1992-2002.

Terminology in bacteremia epidemiology

Understanding bacteremia epidemiology has been complicated by the fact that many studies have included the closely related clinical syndromes sepsis and septicemia (15). Sepsis is a systemic response in the patient often elicited during bacteremia or other severe infections due to systemic spread of microbial signal molecules or toxins. It is a clearly defined syndrome characterized by presence of fever or hypothermia, tachycardia, tachypnea, and leukocytosis or leukopenia, associated with confirmed infection (8). Sepsis may intensify over time to severe sepsis or sepsis syndrome, i.e. sepsis with organ dysfunction or hypoperfusion, and eventually to septic shock. Bacteremia has been documented in no more than 50% of patients with sepsis (16-18). Rangel-Frausto et al suggested a dynamic multi-state sepsis model, in which the probability of positive blood cultures and risk of death increases with progression from sepsis to severe sepsis and septic shock (19). Conversely, close to all patients with bacteremia in our definition fulfil criteria of at least uncomplicated sepsis (20) and between 7% and 24% of bacteremia patients reportedly have septic shock (21-24). Septicemia means the presence of bacteria in the blood with clinical signs and symptoms of infection (25), e.g. bacteremia of a "certain clinical severity" (9).

The burden of bacteremia

In a study using discharge data from a representative sample of U.S. hospitals, Martin et al found that the annual prevalence of discharge diagnoses of septicemia, bacteremia or disseminated fungal infections had increased from 0.8 discharges/1,000 inhabitants in 1979 to 2.4 discharges /1,000 inhabitants in 2000 (26). In 2000, septicemia was ranked the 10th leading cause of death in the United States, constituting the largest group of severe infections with known microbial etiology (27). Comparably, the prevalence of severe sepsis in 1995 was estimated as 3.0/1,000 inhabitants in a cross sectional study from seven U.S. states, where a combination of diagnoses of organ failure and infection was used to identify such cases (28). Case series including thousands of bacteremia patients from hospitals in North America and Europe have reported an annual increase in bacteremia episodes per number of discharges over decades (21;29). In England and Wales, microbiological surveillance data showed a 70% increase in the prevalence of clinically significant blood isolates from 1990 to 1998, corresponding to a bacteremia prevalence in 1998 of 1.0/1,000 inhabitants in 1998 (7). In North Jutland County, Denmark, a population-based study showed an increase in the incidence rate of microbiologically detected bacteremias from 0.8/1,000 person-years in 1981 to 1.5/1,000 person-years in 1994 (30).

Figure 3 shows the total number of episodes of community-acquired and nosocomial bacteremia registered in North Jutland County from 1992 through 2002. In accordance with other observations (12;21;24;31), close to half of all episodes are categorized as community-acquired. The 1:1.5 ratio of community-acquired bacteremia to nosocomial bacteremia has been relatively constant in Denmark over the last decades, with an increasing occurrence of both groups (21).

Fig. 3: Prevalence of bacteremia in North Jutland County, Denmark 1981-2002
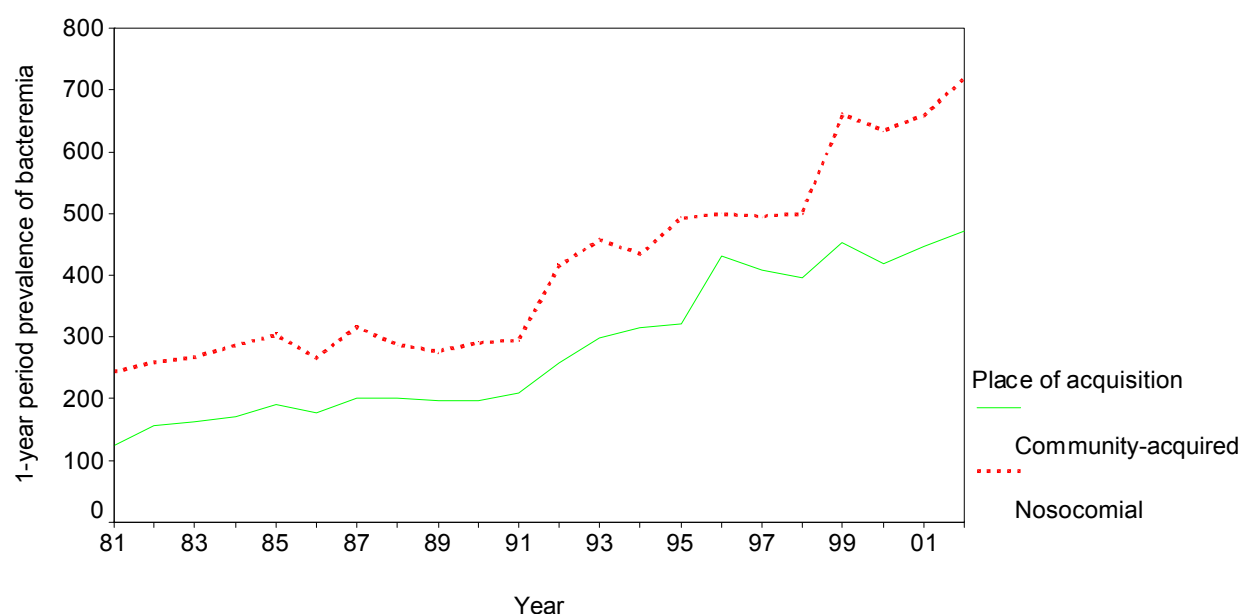
The increasing incidence of bacteremia may be associated with demographic changes, e.g. population ageing and the increasing longevity of patients with chronic diseases. A potential increase in the ascertainment of bacteremia must also be taken into account, as incidence (and prognosis) of bacteremia depends on how many of the milder cases that escape diagnosis (32) Indications for taking blood cultures may have changed over time, and blood culture technology has definitely improved, by recognition of a sufficient blood volume as critical factor for detection of microorganisms (33), and through better growth detection systems and automation (34). Nonetheless, the proportion of bacteremia patients who die either during hospitalization or shortly after still approaches 20%, and this figure has decreased only slightly during the last decades (26;35). Furthermore, several cohort studies have indicated that the long-time survival after bacteremia and sepsis also may be curtailed (23;24). Bacteremia may have important health outcomes other than death (36;37). These include chronic disability due to sequelae, pain and

discomfort, emotional distress, and long-term financial costs for both the individual patient and society. Annual costs of care for patients with sepsis have been estimated at $16.7 billion in the United States alone (28). In another American study, the long-term health-related quality of life of survivors of sepsis assessed by the Short-Form-36 scale was considerably lower than that of the general population (38).

Risk factors for bacteremia

A risk factor for bacteremia may be defined as an exposure or an inborn characteristic of a patient that is causally associated with bacteremia (39). A number of factors have consistently been associated with an increased risk for various bacteremias (Figure 4, left side) (40;41). Most data on suggested risk factors for bacteremia, however, stem from case series, and only few risk factors have been investigated within a proper epidemiological design. It is questionable whether the association with bacteremia is causal for several of the suggested factors.

Fig. 4: Risk factors for bacteremia.

age

chronic diseases

substance abuse

immunosuppressive therapy

genetic or acquired immunodeficiencies

surgical intervention/implants

decreased natural immunity (e.g. via trophic changes, organ disease, manipulation of skin or membranes)

decreased specific immunity

increased exposure to virulent microbial agents (e.g. via hospitals, nursing homes, antibiotic treatment)

localized infection

bacteremia

Most risk factors for bacteremia probably overlap with risk factors for localized infections that may subsequently lead to bacteremia. Important steps on the causal pathway linking cause and effect include the patient's natural and specific immunity and his or her exposure to a microbial agent of a certain virulence (Figure 4). Bacteremia is a multicausal disease, i.e. joint action of a number of risk factors or component causes is required to form one sufficient causal mechanism for the occurrence

of bacteremia (42). From an epidemiological point of view, the microbial agent (often called the "etiological" agent in the field of clinical microbiology) is just one of a multitude of component causes, albeit a necessary one in all the different causal mechanisms for bacteremia. Most other single putative risk factors are not necessary components, illustrated by the fact that a certain proportion of patients hospitalized with bacteremia are not exposed to any of these factors. Moreover, yet unknown factors may be of importance in relation to bacteremia and explain the role of putative risk factors; for example, mutations of genes involved in the innate immune system have only recently been established as risk factors for bacteremia and sepsis (43;44), and these mutations may be associated with various coexisting diseases (45).
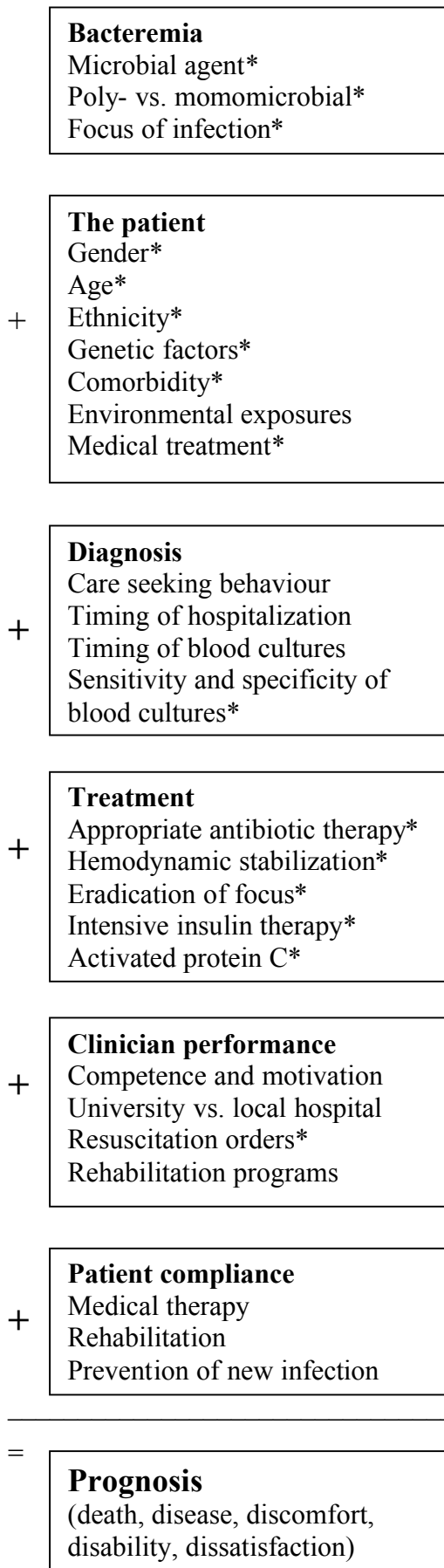
Prognostic factors for bacteremia

Analogous with risk factors, prognostic factors for bacteremia may be defined as exposures or inborn characteristics of a patient that are causally associated with an adverse outcome of bacteremia. Some prognostic factors overlap with risk factors for bacteremia, foremost old age and chronic diseases (14;46). Further, a number of bacteremia-related factors have been associated with a poor prognosis. These include a pulmonary, abdominal or undetermined focus of infection, certain microbial agents such as *Pseudomonas aeruginosa* or polymicrobial bacteremia, and, though debated, bacterial antibiotic resistance (14;15;21;47;48). A number of physiological derangements have been associated with bacteremia or sepsis prognosis (17;49), some of which are included in intensive care scoring systems such as APACHE II (50) and SAPS (51). For pneumococcal bacteremia for instance, mental confusion, hypoxemia, hypotension, acidosis, and an elevated serum creatinine have been associated with a poor prognosis (49;52-55). Further, the level of acute-phase proteins reflecting the magnitude of the inflammatory process, including the C-reactive protein (CRP) (56), have been associated with prognosis of severe infection (57;58).

It is important to distinguish between explanatory studies of disease outcomes, i.e. studies of prognostic factors that are causally related to an event, and studies of variables *predictive* of an event. For instance, living in a nursing home, or being intubated at the ICU, may be clinically useful predictors of bacteremia prognosis, but are not likely to be *causes* of a poor prognosis. Rather, they are intermediary steps on the causal pathway from a prognostic factor to the outcome of bacteremia. In explanatory studies examining the association of a single causal factor with prognosis, it is often relevant to adjust for other prognostic factors. However, intermediary steps or consequences of the putative prognostic factor should not be adjusted for. When studying the association of a pre-

existent chronic disease on bacteremia prognosis in a patient, it seems clearly wrong to adjust for factors reflecting bacteremia severity.

Many other factors than those related to the disease itself or the patient may determine prognosis (59). Figure 5 displays factors that are likely to play a role for the prognosis of bacteremia. Factors that have been substantiated from the literature are marked with an asterix.

Fig. 5: Factors determining the prognosis of bacteremia (36;59).

> **Bacteremia**
> Microbial agent*
> Poly- vs. momomicrobial*
> Focus of infection*

+
> **The patient**
> Gender*
> Age*
> Ethnicity*
> Genetic factors*
> Comorbidity*
> Environmental exposures
> Medical treatment*

+
> **Diagnosis**
> Care seeking behaviour
> Timing of hospitalization
> Timing of blood cultures
> Sensitivity and specificity of
> blood cultures*

+
> **Treatment**
> Appropriate antibiotic therapy*
> Hemodynamic stabilization*
> Eradication of focus*
> Intensive insulin therapy*
> Activated protein C*

+
> **Clinician performance**
> Competence and motivation
> University vs. local hospital
> Resuscitation orders*
> Rehabilitation programs

+
> **Patient compliance**
> Medical therapy
> Rehabilitation
> Prevention of new infection

=
> **Prognosis**
> (death, disease, discomfort,
> disability, dissatisfaction)

Bacteremia research during the last decade has to a large extend been focused on nosocomial episodes, on bacterial antibiotic resistance, and on new modalities of treatment at the ICU setting (48;60;61). Considerably less attention has been given to community-acquired bacteremia (14;62). Patients included in sepsis outcome trials tend to be carefully selected subgroups of previously relatively healthy not-too-old people within a defined severity stage of sepsis, and are therefore by no means representative of community-acquired bacteremia. In summary, we still know relatively little about risk and prognostic factors for these severe infections, and therefore which patients may be potential targets for preventive measures in the community setting, including closer surveillance for infections, lifestyle changes, eradication of bacterial colonization, or vaccination.

1.2. Diabetes mellitus: disease burden and association with infection

The prevalence of type 2 diabetes mellitus (T2 DM) is rising rapidly in many countries including Denmark (63;64). The metabolic dysregulation associated with diabetes affects the function of multiple organ systems that impose a tremendous burden on the individual with diabetes and on health care systems worldwide. It is thus well established that individuals with diabetes have a two- to fourfold increased risk of cardiovascular and cerebrovascular disease (65), and diabetes is the leading cause of end-stage renal disease, nontraumatic lower extremity amputations, and adult blindness in large parts of the Western world (66). The impact of diabetes on other important health outcomes including infectious diseases is not supported by strong evidence (4).

What is diabetes mellitus?

Diabetes mellitus is a syndrome characterized by hyperglycemia resulting from an absolute or relative impairment in insulin secretion and/or insulin action (66). Type 1 diabetes mellitus (T1 DM) most commonly develops before the age of 30-40 years and results from pancreatic beta cell destruction leading to insulin deficiency. T2 DM is usually the type of diabetes diagnosed in patients >40 years, but also occurs in adolescents and children; it is a heterogenous group of disorders characterized by variable degrees of insulin resistance, impaired insulin secretion, and increased hepatic glucose production.

Frequency of diabetes

It has been estimated that the woldwide number of individuals with T2 DM will double from the present 150 million to ca. 300 million in 2025 (63). In Denmark, approximately 3% of the

population have a diagnosis of diabetes, of which T2 DM accounts for 90% (67). Prevalence figures of diabetes in the U.S. are estimated to be twice as high (68). A similar number of individuals probably have undiagnosed diabetes (69), and the prevalence of diabetes in Denmark is estimated to increase by 2% annually (67). The mechanisms behind the increase in T2 DM are vigorously debated. Causes probably include population ageing and the increasing prevalence of obesity (70), but may also include increasing diagnostic activity and a longer survival of diabetic patients due to earlier diagnosis and/or more effective treatment (64). The incidence of T1 DM seems to rise independently, at least in parts of the Western hemisphere (71), the causes for which are highly speculative and beyond the scope of this thesis.

Population-based figures regarding the incidence and prevalence of medically treated diabetes in Denmark can be obtained through prescription databases, as antidiabetic drugs are received exclusively by diabetic patients, completely reimbursed by the National Health Service and not sold over-the-counter in Denmark. A study from the county of Funen, Denmark, which was based on antidiabetic drug prescriptions and mortality data, found an increasing prevalence of diabetes potentially caused by improved survival rather than increasing incidence (64). We have investigated if similar trends in the prevalence and incidence of medically treated diabetes prevail in our county, by examining the number of patients receiving antidiabetic drugs over a ten-year period 1991-2000. Figures 6, 7 and 8 show the prevalent and incident number of persons in North Jutland County who redeemed prescriptions for insulin only (Figure 6), oral antidiabetics ("tablets") only (Figure 7), and insulin after previously redeeming tablets ("shift to insulin") (Figure 8). The stable incident number of patients receiving insulin only (Figure 6) may illustrate a stable T1 DM population in conjunction with a constant policy regarding insulin treatment of T2 DM at debut. The gradual increase in number of patients treated with oral antidiabetics (Figure 7), especially in the last part of the period, probably reflects a true increase in T2 DM incidence, but may also in part be due to an increase in case finding, shifting diagnostic criteria, or an increased survival of treated patients. The steady increase in the number of patients shifting from tablets to insulin (Figure 8) probably reflects a change towards a more intensive attitude to metabolic control of T2 DM.

Fig. 6

Prescription for insulin only

| | Incidence (Number per 100.000 person years) | Period prevalence (Number per 100.000 inhabitants) |

Fig. 7

Prescriptions for oral antidiabetics

| | Incidence (Number per 100.000 person years) | Period prevalence (Number per 100.000 inhabitants) |

Fig. 8

Shift from tablets to insulin

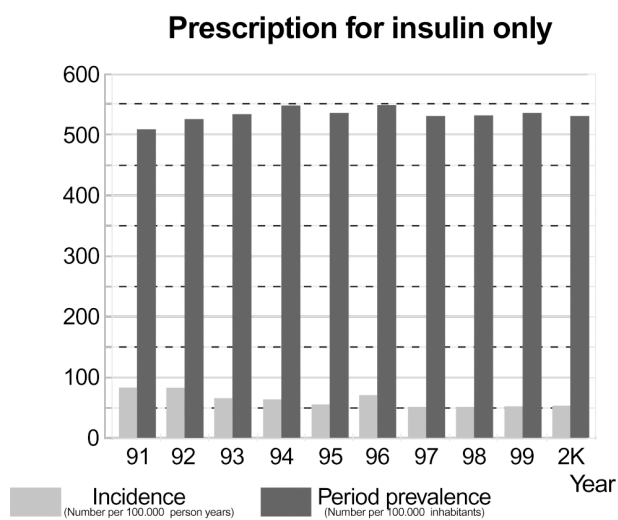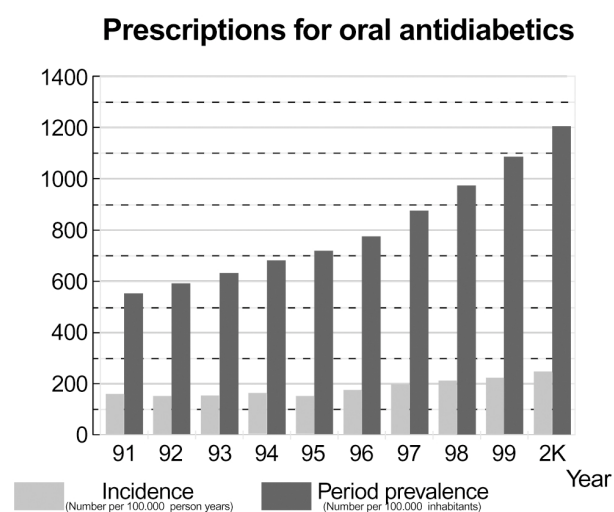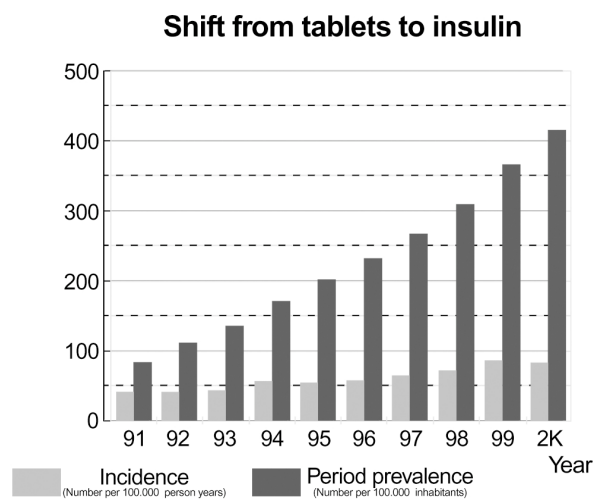| | Incidence (Number per 100.000 person years) | Period prevalence (Number per 100.000 inhabitants) |

In summary, our and others' analyses indicate that the prevalence and thus disease burden of diabetes increases considerably in the current years. It therefore seems important to elucidate the impact of diabetes on yet another substantial health problem in aging populations, namely severe infections including bacteremia.

Diabetes and infections

The belief of a close association between diabetes and infection probably dates back to the pre-insulin era, when sepsis and tuberculosis used to be frequent causes of death in diabetic patients (72;73). In 1928, ATB Jacobsen reviewed the clinical course of the first 251 diabetic patients ever treated with insulin in Denmark (74). Of 34 early deaths within four weeks after treatment start, 14 diabetic patients died of infection (among these five of tuberculosis, and three of pneumonia). Among the 189 patients discharged with continuous insulin treatment and followed for one to five years, 26 died, but only five of these deaths were due to infection.

As reviewed by Boyko and Lipsky in 1995 (3) and Joshi et al in 1999 (4) there is relatively sparse epidemiological evidence to support that diabetes per se is a risk factor or prognostic factor for most infections. It seems well established from case-series that certain rare infections occur almost exclusively in diabetic patients. These include malignant otitis externa due to *P. aeruginosa*, the fungal infection zygomycosis, necrotizing fasciitis (4), certain infections with gas-forming microorganisms e.g. emphysematous pyelonephritis and cholecystitis (75), and the tropical diabetic hand syndrome (76). Of greater importance for public health, diabetes has been observed to occur frequently in more common infections, and to be associated with increased severity of some of them. These include urinary tract infections (UTIs), skin and wound infections, osteomyelitis, candidiasis, pneumonia, tuberculosis, hepatitis B, and bacteremia (77). Most reports are based on case-series, and relatively few case-control or cohort studies exist. To supplement the recent reviews (3;4;78) we searched the literature in MEDLINE for epidemiological and other relevant studies using the Medical Subject Headings: "diabetes AND infection". We also searched the references of these publications. Table 1 tabulates important studies that have reported on diabetes as a risk and/or prognostic factor for infection, with particular focus on studies of respiratory tract infections and UTIs. The association of diabetes with bacteremia, pneumonia and UTI will be discussed in more detail in section 1.3.

Table 1: Studies on diabetes and the risk / prognosis of infections in general, as well as respiratory and urinary tract infections

Study category	Type of infection*	Author, year, country	Study type	Setting†	Sample size (% DM or DM=N) ‡	Measure of interest§	Results for DM [95% Confidence interval]‖
Various infections							
	Any infection	Shah, 2003, Canada (79)	Cohort study	Population-based	Ontario population sample=1,027,498 (DM=513,749)	Risk ratio for an infectious disease hospitalization or physician claim	Overall risk ratio=1.21 [1.20-1.22], risk ratio for inpatient infection=2.01 [1.96-2.06]
	Any infection	Gu, 1998, USA (80)	Cohort study	Sample of U.S. population	13,830 (5%)	MRR for any infectious disease on death certificate	MRR=2.3 males; 1.8 females
	Any infection	Bertoni, 2001, USA (81)	Cohort study	Sample of U.S. population	9,208 (6%)	MRR for any infectious disease on death certificate	MRR=2.0 [1.2-3.2]
	Any infection	Weiderpass, 2001, Sweden (82)	Cohort study	Pop.based, nationwide	Swedish population (DM=144,427)	SMR for infectious and parasitic cause of death	adj. SMR=2.6 [2.3-3.0] males; 2.7 [2.4-3.0] females
Respiratory tract							
	Invasive pneumococc. infection (most with pneumonia)	Smith, 2000, USA (83)	Review of case series	Hospital-based cohorts	Total of 2,386 patients (1-19%)	Case-fatality	Ca. 1.5 times increased in DM when reported (no data for DM in most series)
	Pneumonia and influenza	Moss, 1991, USA (84)	Cohort study	Pop.based, Wisconsin	(DM=1,772)	SMR for pneumonia or influenza on death certificates	SMR=1.7
	Pneumonia	Swerdlow, 1996, UK (85)	Cohort study	Members DM association	(DM=5,783)	SMR for pneumonia on death certificates	SMR=1.3 [1.1-1.7] males; 2.2 [1.8-2.6] females
	Pneumonia	Weiderpass, 2001, Sweden (82)	Cohort study	Pop.based, nationwide	Swedish population (DM=144,427)	SMR for pneumonia as cause of death	adj. SMR=2.6 [2.5-2.8] males; 2.3 [2.2-2.5] females
	Pneumonia and influenza	Gu, 1998, USA (80)	Cohort study	Sample of U.S. population	13,830 (5%)	MRR for pneumonia or influenza on death certificate	MRR=2.4 males; 1.8 females
	Pneumonia	Shah, 2003, Canada (79)	Cohort study	Population-based	Ontario population sample=1,027,498 (DM=513,749)	Risk ratio for pneumonia	Risk ratio=1.5 [1.4-1.5]
	Community-acquired pneumonia	Fine, 1996, USA (86)	Meta-analysis of studies of prognosis	Mostly hospital-based cohorts	Total of 33,148 ptts, 14,655 with data on DM	Summary OR for Case-fatality	OR=1.3 [1.1-1.5]

ASB	Boyko, 1995, USA (3)	Review of case-control/ cross-sectional studies	Outpatient clinics	Total of ca. 2,750 ptts with DM, ca. 2,500 (usually healthy) controls	ORs for ASB in DM vs. controls	OR between 2 – 4
ASB	Geerlings, 2000, The Netherlands (87)	Case-control	Outpatient clinics + GPs	(DM=636), controls=153, females	Prevalence of ASB in DM vs. controls	DM=26%, controls 6%
ASB	Makuyana, 2002, Zimbabwe (88)	Case-control	Outpatient clinics	Total of 176 ptts	Prevalence of ASB in DM vs. controls	DM=32%, controls=11%
ASB	Bonadio, 2004, Italy (89)	Case-control	University hospital	(DM=228), controls=146, females	Prevalence of ASB in DM vs. controls	T1 DM=13.5%, T2 DM =18.8%, controls=18.5%
Cystitis	Boyko, 2002, USA (90)	Case-control	Members of group health cooperative	901 UTI cases, 913 healthy controls	adj. OR for DM	adj. OR=2.2 [1.5-3.1]
Cystitis	Shah, 2003, Canada (79)	Cohort study	Population-based	Ontario population sample=1,027,498 (DM=513,749)	Risk ratio for cystitis	Risk ratio=1.39 [1.36-1.42]
Pyelo-nephritis	Robbins, 1944, USA (91)	Cross-sectional	University hospital	Autopsied ptts: (DM=307), non-DM =2,800	Prevalence of acute pyelonephritis as cause of death	DM=7.3%, non-DM=1.6%
Pyelo-nephritis	Nicolle, 1996, Canada (92)	Cohort study	Population-based	All residents of the Province of Manitoba	Risk ratio for hospitalization with pyelonephritis	Risk ratio between 3.4 [2.0-5.8] in men ≥65y and 24.1 [16.5-35.3] in women 45-64y
Pyelo-nephritis	Shah, 2003, Canada (79)	Cohort study	Population-based	Ontario population sample=1,027,498 (DM=513,749)	Risk ratio for pyelonephritis	Risk ratio=1.95 [1.78-2.13]

*pneumococ.=pneumococcal; ASB=asymptomatic bacteriuria. †Pop.based=population based; DM=diabetes mellitus; GPs =general practices.

‡ptts=patients; UTI=urinary tract infection. §MRR=mortality rate ratio; SMR=standardized mortality ratio; adj.=adjusted; OR=odds ratio. ‖Study by Shah et al = 99% confidence interval.

A few cohort studies have reported on the risk of infection-related death in diabetic patients, either by comparing diabetic cohort and general population estimates (82;84;85), or by comparison within cohorts of diabetic and non-diabetic patients (80;81). One large population-based cohort study from Canada has investigated the risk of hospitalization or a physician claim for treatment of an infectious disease in individuals with and without diabetes (79). Among Ontario residents with diabetes and matched controls (N=513,749 in each group) the risk ratio was 1.21 (99% CI: 1.20-1.22) for any infection, and 2.01 (99% CI: 1.96-2.06) for infections requiring hospitalization. A cohort study from the U.S. followed 9,200 adults included in a health survey (NHANES II) for 12-16 years, among them 533 persons with self-reported diabetes at baseline (81). Infection-related mortality was determined through national death or social security indexes. The relative risk for infection-related death in DM was 2.0 (95% CI: 1.2-3.2).

Biological mechanisms

In the following, we will give an overview of the diverse biological mechanisms that may contribute to an increased risk and a worse prognosis of infection in diabetes.

Immunology

Numerous *in vitro* studies have demonstrated that hyperglycemia can impair a range of functions in neutrophils and macrophages, including chemotaxis, adherence, phagocytosis, and intracellular killing of microorganisms, all of which may be important in limiting invasion by bacteria *in vivo* (93). Kjersem et al found that in polymorphonuclear leukocytes from T1 DM patients, the ingestion of particles coated with lipopolysaccharide from *Escherichia coli* became reduced during change from normo- to hyperglycemia (94). Others demonstrated that hyperglycemia impairs the generation in leukocytes of oxygen free radicals and hydrogen peroxide required for intracellular killing of microorganisms (95). The clinical significance of these findings remains uncertain. Long-term hyperglycemic control in diabetes as assessed by repetitive blood glucose measurements or glycosylated hemoglobin has not been convincingly associated with the risk and outcome of infections (96). Rayfield et al followed 241 diabetic patients at outpatient clinics in New York and noted a weak correlation between mean fasting plasma glucose levels and prevalence of subsequent infections (97). Randomized trials have shown that surgical patients fed parenterally experience more infections as compared to patients on enteral nutrition, potentially associated with development of severe hyperglycemia (98;99). Recent randomized trials in patients undergoing surgery have shown that intensive insulin treatment with corresponding tight hyperglycemic control may reduce the risk of subsequent wound infections and sepsis, at least in certain groups of diabetic and non-diabetic patients

(100;101). It is currently debated whether this observed effect may be due to reduced harm of hyperglycemia, or beneficial anti-inflammatory effects of insulin (102).

Metabolic derangement

It is well-known that infection and ketoacidosis frequently co-occur (103;104). However, it may be difficult to determine if hyperglycemia caused the infection in the patient or vice versa. During periods of influenza epidemics, an increased prevalence of hospitalizations with ketoacidosis has been observed (105). The combination of ketoacidosis and infection may be dangerous for the diabetic patient. Azoulay et al studied 123 episodes of ketoacidosis in intensive care unit patients, and found that 41% had clinically or microbiologically documented infection. Lack of clearance of ketonuria within 12 hours was 3.7 times more frequent among patients with infection (106). Gogos et al studied 49 patients with ketoacidosis or hyperosmolar coma and signs of systemic inflammation, and found 45% of them to have infection; mortality in this group was 23% vs. 7% in cases without infection (107).

The metabolic responses to severe infection are similar to changes associated with trauma and include initial stimulation of gluconeogenesis by secretion of glucagon, cortisol, growth hormone and catecholamines and inhibition of insulin secretion. A subsequent increase in insulin secretion (in T2 DM) is associated with marked insulin resistance, particularly in skeletal muscle and therefore with persistent hyperglycemia. Insulin resistance may be mediated by effects of interleukins and tumor necrosis factor on the insulin receptor (108). Diabetic patients may thus be at risk of metabolic derangement caused by severe infection per se and risk a poorer prognosis of infection compared to non-diabetic patients.

Diabetes complications

Diabetes is associated with pathophysiologic changes in multiple organ systems, each of which may increase the risk and worsen the outcome of infection. Stroke and myocardial infarction, and related sequelae such as dementia and congestive heart failure are frequently coexistent in patients with bacteremia and pneumonia (5;109-111). Sepsis has been shown to be a frequent complication and cause of death in patients with end-stage renal disease (112). Among hemodialysis patients, however, diabetes was not associated with an increased risk of bacteremia (113). Decreased renal function as assessed by serum creatinine level is a well-established negative predictor for bacteremia prognosis (24;55). The distinction between acutely and chronically impaired renal function may be troublesome in bacteremia patients, but presence of asymptomatic nephropathy could well have a negative prognostic impact in diabetic patients. Further, an

elevated serum creatinine level was one of the best predictors for later hospitalization with an infectious disease within 57,722 diabetic adult members of Kaiser Permanente, Northern California (114). The universal micro- and macroangiopathy in diabetes may worsen the outcome of systemic infections due to decreased tissue oxygenation and impaired leukocyte migration. Lastly, frequent diabetes complications may weaken local barriers to infection and constitute portals of entry for pathogens. These include diabetic cystopathia with retention of urine and an increased likelihood of instrumentation of the urinary tract (115), and chronic skin ulcers (116).

Colonization with pathogenic microorganisms

Some studies have suggested an increased prevalence of colonization with microorganisms such as *S. aureus* (117), *Candida* spp. (118), and *E. coli* (87;119) in diabetic patients. Colonization in itself has been suggested to be a risk factor for infection (116,120;121). Insulin injections and blood glucose self monitoring may theoretically increase bacterial colonization, yet manifest infections after such penetrating traumas ("finger sepsis") are rarely reported (122). Growth of certain microorganisms may be augmented in a hyperglycemic environment. Virulence factors in *C. albicans* seem to respond in a dose-dependent fashion to environmental glucose concentrations *in vitro* (123), and addition of glucose enhances the growth rate of *E. coli* in urine in the laboratory (124). Geerlings et al found Type 1-fimbriated *E. coli* to adhere more to diabetic than to control uroepithelial cells (125). Finally, colonization with pathogenic microorganisms may be increased in diabetic patients due to frequent hospitalizations and disruptions of the normal microbial flora by repeated antibiotic therapy. In patients with UTI, diabetes was associated with a 2.4 fold increased risk for multi-drug resistant uropathogens at an emergency department (126), and in another series, the proportion of quinolone-resistant bacteria was 17% in diabetic vs. 3.7% in non-diabetic UTI patients (127). In a study of 311 patients with community-acquired UTI, diabetes was an independent risk factor (adjusted OR=2.6, 95% CI: 1.2-5.5) for infection with extended-spectrum beta-lactamase producing bacteria according to logistic regression analysis (128).

1.3. Diabetes and community-acquired bacteremia

Diabetes and bacteremia or sepsis due to various pathogens

There are at least seven cohort studies of bacteremia specifically comparing prognosis among diabetic and non-diabetic patients (129-135). These studies comprise up to 3,000 episodes of bacteremia irrespective of microbial agent and place of acquisition and are summarized in Table 2.

Table 2: Studies on diabetes and the risk / prognosis of bacteremia

Study category	Bacteremia type studied	Author, year, country	Study type	Setting*	Sample size (% DM or DM=N)	Measure of interest†	Results (diabetes)‡
Bacteremia - various pathogens							
	Bacteremia	Aubertin, 1982, France (129)	Case series	1 Medical department	168 (30)	Case-fatality	16% (23%)
	Bacteremia	Bryan, 1985, USA (130)	Cross-sectional	4 regional hospitals	2,978 (10)	1) Bacteremias/1000 admissions 2) Case-fatality	1) 9.4 (19.4) 2) 30% (33%)
	Bacteremia	MacFarlane 1986, UK (131)	Case-control	General hospital	168 (29)	1) DM prevalence in admitted ptts 2) Case-fatality	1) Cases 29%, all ptts 10% 2) 35% (20%)
	Bacteremia	Leibovici, 1991, Israel (132)	Case series	University hospital	632 (20)	Case-fatality	29% (28%)
	Bacteremia	Guérin, 1992, France (133)	Case series	Intensive care unit	295 (21)	Case-fatality	61% (63%)
	Bacteremia	Carton, 1992, Spain (134)	Cross-sectional	University hospital	1640 (9)	1) Bacteremias/1000 admissions 2) Case-fatality	1) 15.5 (26.8) 2) 31% (29%)
	Bacteremia	Akbar, 1999, Saudi Arabia (135)	Case series	University hospital	171 (42)	Case-fatality	44% (24%)
	Bacteremia	Weinstein, 1983, USA (12)	Case series	2 university hospitals	500 (not given)	Case-fatality	Total 42%, healthy ptts 21% (30%)
	Bacteremia	Arpi, 1995, Denmark (21)	Case series	University hospital	3,491 (7)	Case-fatality	Total 14% (13%)
	Septicemia	Jaar, 2000, USA (113)	Cohort	Hemo-dialysis ptts +/- DM	4,005 (DM=1,600)	1) Incidence proportion septicemia 2) OR for death vs. ptts without septicemia, Cox regression	1) 11.1% (12.5%) 2) adj. OR=2.7 (2.3-3.1) in non-DM vs. adj. OR=2.3 (2.0-2.8) in DM
	Septicemia	Abbott, 2001, USA (136)	Case-control	Renal transplant ptts +/- DM	Study base 33,479 (DM=8,454)	OR for DM in septicemia cases (N=1447) vs. non-cases, logistic regression	adj. OR=2.1 (1.7-2.4)
	Septicemia	Weiderpass, 2001, Sweden (82)	Cohort study	Pop.based, nationwide	Swedish population (DM=144,427)	SMR for septicemia as cause of death	adj. SMR=3.9 (3.3-4.6)
	Sepsis	Shah, 2003, Canada (79)	Cohort study	Population-based	Ontario population sample=1,027,498 (DM=513,749)	Risk ratio for hospitalization with sepsis	Risk ratio=2.5 (2.2-2.7)

					*ptts (DM)		
Gram-negative bacteremia							
	Gram-negative	Du Pont, 1969, USA (137)	Case series	University hospital	860 (5)	Case-fatality	Other comorbidity than DM 52%, healthy 23% (39%)
	Gram-negative	Kreger, 1980, USA (110)	Case series	University hospital	612 (not given)	Case-fatality	"DM associated with case-fatality", X^2=4.0, p<0.05
	Gram-negative	Uzun, 1992, Turkey (138)	Case series	University hospital	448 (1)	Case-fatality	Total 45% (67%)
	E. coli	Olesen, 1995, Denmark (139)	Case series	University hospital	433 (12)	Case-fatality	not given for DM
	Klebsiella and *E. coli*	Hansen, 1998, Denmark (140)	Case-control	University hospital	100 *Klebsiella* (21), 100 *E. coli* (9)	OR for DM in *Klebsiella* vs. *E. coli*, log. regression	adj. OR=2.5 (1.0-6.1)
	Gram-negative	Graff, 2002, USA (141)	Case series	2 university hospitals	326 (24)	MRR, Cox regression	adj. MRR=2.7 (1.5-4.8) in DM
Pneumo-coccal bacteremia							
	Pneumococ. bacteremia	Austrian, 1964, USA (142)	Case series	University hospital	455 (5)	Case-fatality	All with comorbidity 30%, healthy 7% (29%)
	Pneumococ. bacteremia	Mufson, 1974, USA (143)	Case series	County Hospital	325 (4)	Case-fatality	Total 28% (42%)
	Pneumococ. bacteremia	Gransden, 1985, UK (144)	Case series	University hospital	325 (3)	Case-fatality	Not given for DM
	Invasive pneumococ.	Burman, 1985, Sweden (145)	Case series	All hospitals in Göteborg	508 (4)	Case-fatality	All with comorbidity 24%, healthy 9% (27%)
	Pneumococ. bacteremia	Kuikka, 1992, Finland (54)	Case series	University hospital	157 (15)	Case-fatality	Not given for DM
	Pneumococ. bacteremia	Watanakunakorn, 1992, USA (55)	Case series	University hospital	385 (12)	Case-fatality, log. regression	Total 25% (37%), adj. OR=1.0, SE 0.4
	Pneumococ. bacteremia	Afessa, 1995, USA (52)	Case series	University hospital	304 (6)	Case-fatality	Not given for DM
	Pneumococ. bacteremia	Kalin, 2000, Canada-USA-UK-Spain-Sweden (49)	Case series	Multicenter-study, 5 countries	460 (7) (UK 3 – USA 14)	Case-fatality, log. regression	DM not associated with case fatality in univariate analysis
	Invasive pneumococ.	Dahl, 2001, Swe (146)	Case series	All hospitals in Göteborg	876 (12)	Case-fatality	All with comorbidity 19%, healthy 8% (20%)
	Invasive pneumococ.	Nuorti, 2000, USA-Canada (147)	Case-control	Pop.-based, 3 regions	228 (10) cases, 301 (4) controls	Odds ratio for DM, log. regression	"No significant association" between DM and case status

*ptts=patients; DM=diabetes mellitus; pop.based=population based. †OR=odds ratio; SMR=standardized mortality ratio; MRR=mortality rate ratio. ‡adj.=adjusted; X^2=chi-square test; SE=standard error.

The prevalence of coincident diabetes in the series was between 5% and 40%. The two largest studies from North Carolina and Spain compared the prevalence of bacteremia among all hospitalized patients with and without diabetes over several years in a cross-sectional design (130;134). Both studies found a twofold increased number of bacteremia episodes per 1000 hospital admissions in the diabetic group. No adjustment for differences in gender, age and coexisting diseases were made. The crude in-hospital case-fatality in diabetic and non-diabetic patients with bacteremia was similar in most series. In the population-based Canadian cohort studies of diabetic and non-diabetic persons previously mentioned, the risk ratio for hospitalization with sepsis among diabetic patients was 2.5 (95% CI: 2.2-2.7) (79). Another population-based cohort study from Sweden identified 144,000 diabetes patients in a hospital discharge registry and followed them for an average of 6.7 years for cause-specific deaths recorded in a nationwide register (82). Standardized mortality rates for septicemia in diabetic patients, e.g. mortality rates compared with age-, gender- and calendar-year specific mortality rates for the Swedish population, were four times increased, with risk ratios ranging from 2.0 (95% CI: 1.5-2.7) in elderly patients to 8.3 (95% CI: 4.0-17.3) in diabetic patients hospitalized at age under 40.

Special considerations apply to a potential association of diabetes with the two most frequent groups of community-acquired bacteremia: enterobacterial bacteremia and pneumococcal bacteremia.

Diabetes and community-acquired pneumococcal bacteremia
S. pneumoniae accounts for 66% of microbiologically confirmed community-acquired pneumonias (86;148). Pneumococcal bacteremia is probably a common feature of pneumococcal pneumonia, though it may be detected in less than ten percent of hospitalized cases (149-151). Conversely, 80% of patients with pneumococcal bacteremia have a respiratory tract focus of infection (55;144). In cross-sectional and cohort studies based on death certificates, diabetic patients had a 1.5-2.5 times increased risk for death caused by influenza and pneumonia compared with the general population; the highest risk ratios were noted among young patients (82;84;85;152) (Table 1). Case-series of community-acquired pneumonia have reported coexisting diabetes in no more than 5-10% of patients, despite high prevalences of advanced age and cardiac disease (148;153). In a meta-analysis of prognosis studies of community-acquired pneumonia, Fine et al found diabetes to be associated with an odds ratio for death of 1.3 (95% CI: 1.1-1.5) (86). Koziel suggested several mechanisms

behind a possibly increased pneumonia risk and fatality in diabetes, including cardiac disease, reduced lung function, an increased risk of aspiration due to diabetic gastroparesis, and microangiopathic changes of pulmonary blood vessels (154).

In Table 2 we have listed the larger studies of pneumococcal bacteremia that reported on diabetes. As reviewed by Smith and Poland in 2000 (83), data about diabetes as risk factor for pneumococcal bacteremia come primarily from case series. Diabetes prevalence in these studies has varied from 1% to approximately 20%, depending on the patients' age, type of hospital, study period, and country, as well as methods for ascertainment of diabetes. In the cross-sectional study of diabetes and diverse bacteremia from Spain (134), the prevalence of bacteremia with *S. pneumoniae* was two times increased in diabetic patients (13/5,667 hospital admissions compared with 97/95,725 hospital admissions of non-diabetic patients), whereas the similar U.S. study found no increase for this group of bacteremia (130). Marrie observed a three times higher diabetes prevalence (21% vs 7%) in 47 bacteremic compared with 1,071 non-bacteremic cases of pneumococcal pneumonia in a Canadian university hospital (150). In a recent North American case-control study of 228 immunocompetent, 18- to 64-year-old adults with invasive pneumococcal infection and 301 age-matched control subjects, Nuorti et al (147) collected exposure data including diabetes by interview. The self-reported occurrence of diabetes was 10% in cases and 4% in controls (OR=2.5, 95% CI: 1.2-5.1). However, after adjusting for other variables including race, gender, and coexisting morbidity, the authors reported that the association was no longer statistically significant (risk estimates not given). Concerning the outcome of pneumococcal bacteremia, previous cohort studies included relatively few patients with diabetes, making it difficult to assess the impact of diabetes on prognosis (83). In one of very few studies that adjusted for confounders, Watanakunakorn et al found that an association between diabetes and a poor prognosis in 385 patients with pneumococcal bacteremia disappeared after adjustment for higher age and coexisting morbidity in the diabetic group (55).

Diabetes and community-acquired bacteremia due to E. coli and other enterobacteria
The most common focus of infection in enterobacterial bacteremia is the urinary tract, and urinary tract infections seem to be a common clinical problem in diabetic patients (155;156). As reviewed by Boyko and Lipsky (3), a dozen of smaller case-control studies from outpatient clinics have reported that asymptomatic bacteriuria (ASB) is two- to four times more prevalent among women

with diabetes than among non-diabetic women. More recent studies from the Netherlands (ASB 26% in DM vs. 6% in non-DM females) and Zimbabwe (32% in DM vs. 11% in non-DM) have confirmed these findings (87;88), whereas another study from Italy found similar prevalences of ASB (18% in both) in female T2 DM outpatients when compared with female non-diabetic outpatients visiting a cardiology clinic (89). Concerning symptomatic urinary tract infections, an American case-control study from 2002 reported that among 901 women aged 55-75 years with acute symptomatic UTI and 913 controls, the adjusted OR for diabetes was 2.2 (95% CI: 1.6-3.0) (90). A population-based cohort study from Manitoba, Canada found a clearly increased incidence of hospitalizations with pyelonephritis among diabetic patients. Men and women aged over 65 years with diabetes were three to six times more likely than nondiabetic persons to be hospitalized with acute pyelonephritis, whereas diabetic patients under the age of 45 years had a 15-fold increased risk (92).

Studies of the association between diabetes and bacteremia caused by enterobacteria are few (Table 2). However, the prevalence of enterobacterial bacteremia in diabetic patients was two- to threefold increased in most cross-sectional studies of diverse bacteremias (133;134). Recent case-series have reported a diabetes prevalence of 20-30% among patients with enterobacterial bacteremia (141), and up to 40% among patients with community-acquired *Klebsiella pneumoniae* bacteremia (157). Most of the larger studies of gram-negative bacteremia are several decades old, and few have reported mortality estimates specifically for patients with diabetes. One study found a lower mortality among cases with diabetes when compared with non-diabetic cases (137), whereas another large study from the U.S. found diabetes to be associated with increased in-hospital mortality in patients with nonfatal underlying diseases (110). In their study of diverse bacteremias, Bryan et al noted that the prognosis for *E. coli* bacteremia was better among diabetic than non-diabetic patients (16.7% deaths vs. 30.6% deaths) (130). By contrast, in a recent study of 326 adults with gram-negative bacteremia in California diabetes was associated with mortality in a Cox regression model (MRR=2.7, 95% CI: 1.5-4.8) (141).

1.4. Difficulties in studying diabetes and bacteremia: epidemiological considerations

Prior studies of diabetes as risk and prognostic factor for bacteremia have been hampered by a number of methodological problems. We will describe some of these problems in the context of the studies' different epidemiological designs.

Studies of diabetes as a risk factor for community-acquired bacteremia

Case series

The vast majority of studies of diabetes and bacteremia were case series (Table 2), demonstrating diabetes prevalences between one percent and more than 40 percent among bacteremia patients. In the absence of a control group, it is not clear from these studies whether any apparent association between diabetes and bacteremia is causal or related to confounding factors. Diabetes is known to be associated with a high prevalence of characteristics that may be risk factors for bacteremia, including old age and diseases coexistent with diabetes (=comorbidity). Furthermore, most of the cited case series included nosocomial bacteremias in which any apparent association with diabetes might be explained by more frequent hospitalizations and invasive procedures in diabetic patients.

Cross-sectional and case-control studies

At least six studies were cross-sectional studies or case-control studies in which exposure (=diabetes) was measured as the proportion of people with diabetes among bacteremia cases and a control group (Table 2). These studies have been hampered by problems related to selection of cases and control subjects, measurement of diabetes, and risk of confounding.

A major drawback of several studies has been the lumping together of various groups of bacteremia regardless of place of acquisition, focus of infection and microbial agent (131;134). This approach is problematic because risk factors for different agents are widely variable and closely related to the pathogenetic background and corresponding focus of infection. In studies including various bacteremias, any positive association between diabetes and a particular microbial agent might be obscured if diabetes is not or even negatively associated with another one. Therefore, separate analyses according to microbial agent or group and focus of infection are warranted. This approach demands large patient materials that may be difficult to achieve in hospital based studies, but may be obtained from population-based bacteremia registries.

Studies that included a mixture of nosocomial and community-acquired bacteremia cases have used hospitalized patients as control group to estimate the distribution of exposure (in this case diabetes) in the underlying source population (130;131;134). The source population, e.g. the population that gives rise to bacteremia cases, is different, however, for nosocomial and community-acquired bacteremia. For nosocomial episodes it consists of hospitalized patients, whereas for community-acquired episodes it is the general population. Patients admitted for other reasons than bacteremia might constitute a sample of the source population for community-acquired bacteremia, as long as they are representative for the diabetes distribution. This has most probably not been the case in previous studies from referral hospitals, where the hospital also has served as a diabetes referral center (131). Further, diabetes may have increased the chance of being diagnosed as a bacteremia case, leading to an overestimation of the risk of bacteremia in diabetic compared with non-diabetic patients.

In earlier cross-sectional and case-control studies, diabetes was usually recorded after the bacteremia had occurred; for instance, the Spanish study included diagnoses from hospital records at discharge after the bacteremia (134). Further, most reports have determined diabetes status based on interviews or hospital record reviews without strict diagnostic criteria being stated. Bacteremia may lead to false registration of diabetes, if transient hyperglycemia is not excluded (inverse causality). Most studies declared to have done so. Notwithstanding, ascertainment of diabetes in cases and controls by the investigating physicians may be affected by the study hypothesis of an association between bacteremia and diabetes. In studies based on interviews (147), recall bias may have been an issue, as knowledge of outcome status (bacteremia) may improve the accurate recall of diabetes in study subjects. This risk may be decreased in incidence case-control studies based on prospectively collected data (158).

Differences in age and comorbidity related to both diabetes and bacteremia may have introduced major confounding in the previous studies (159), and these differences have rarely been adjusted for.

Cohort studies
Unlike in Denmark, population-based data on disease incidence in individual persons are not readily available in most countries. Therefore, previous cohort studies of diabetic patients have often used

disease-specific mortality based on death-certificates, e.g. the study by Weiderpass et al including septicemia (82). However, disease-specific mortality in a population is a function of the incidence and outcome of the disease in question, and thus mixes the concepts of risk and prognosis. The cohort study from Ontario (79) is probably the only population-based study that has provided estimates on the relative risk for hospitalization with sepsis in diabetic individuals.

Selection bias may have occurred in previous cohort studies by non-complete follow-up of study subjects, if loss of follow-up was related to both diabetes and risk of bacteremia or bacteremia death. For example, the NHANES II cohort study has been criticized for underregistration of mortality records for Afro American subjects (81), and these individuals may have an increased risk of both diabetes and pneumococcal bacteremia (5). In Scandinavian studies, it is possible to censor study subjects at emigration (82), whereas the mentioned U.S. study (81) had to assume complete follow-up for infection-related death until either end of the study or appearance in any death registry.

Information bias in previous cohort studies may have resulted from misclassification of exposure (diabetes) and/or outcome (bacteremia). Contrary to retrospective case-control studies, in a cohort study any misclassification of diabetes will usually be non-differentially associated with later outcomes, thus tending to bias risk estimates for bacteremia toward the null hypothesis. Nevertheless, the diagnoses of septicemia or sepsis recorded on death certificates and in discharge registries, which have been used in previous cohort studies as the outcome of interest, may have a rather low validity. A data quality study of a Danish hospital discharge registry (20) thus revealed that the predictive value of an ICD-coded diagnosis of septicemia was only 22% when compared with data from a microbiological bacteremia registry. In cohort studies, it is further important to avoid information bias caused by differential ascertainment of the outcome related to exposure status. Studies using administrative registries have the advantage of outcome registration independent of the investigators' study hypothesis. Nevertheless, surveillance bias may also affect routinely collected data in everyday clinical practice, e.g. if patients with diabetes are more readily diagnosed with bacteremia.

Sufficient adjustment for confounding by other risk factors for bacteremia associated with diabetes has rarely been possible (79). Several cohort studies have attempted to adjust for crudely

categorized confounders in study subjects at the time of inclusion, such as presence or absence of comorbidity (81;82). Occurrence of comorbidity during follow-up time has not been accounted for.

Studies of diabetes as a prognostic factor for community-acquired bacteremia

Studies of diabetes and bacteremia prognosis have usually been conducted in a cohort design (36;132). Crude classification of bacteremia as one disease entity in these studies may be equally problematic as in risk factor studies. A potentially negative prognostic factor in bacteremia such as diabetes might be overlooked if this factor simultaneously is a risk factor for a frequent group of bacteremia with a mild prognosis. Thus, a relatively mild prognosis for diabetic patients in studies of mixed bacteremias has been attributed by several authors to an increased proportion of community-acquired bacteremic UTIs in the diabetic group (130;133).

In the optimal study of prognosis, observation of a cohort of patients is started from the same well-defined point along the course of disease. The assembly of such an *inception cohort* has probably been rather impossible in bacteremia research, as the infection may develop rapidly over hours or protracted over days. Selection bias may occur, if presence of diabetes in bacteremic patients leads to admission in an earlier stage of infection. Differences in prognosis in diabetic and non-diabetic patients might then be related to timing of hospitalization and not to diabetes. Similarly, a higher proportion of mild cases might in general be hospitalized and thus detected among diabetic than non-diabetic patients.

In the previously cited cohort studies of bacteremia, outcome has generally been reported as the proportion of patients admitted with bacteremia who die either during hospitalization or within the first 30 days after the diagnosis. This measure is often called in-hospital- or 30-day-"case fatality *rate*", though it is actually a cumulative incidence proportion and should be called case-fatality proportion or simply case-fatality (CF). The CF is a summary measure of prognosis that may hide considerable differences in timing of death or survival, which are important to our understanding of the disease course in bacteremia and the mechanisms leading to the patient's eventual death. Often it is given without a specific time referent; the clinical presumption being that essentially all deaths that occur shortly after onset of the infection are a direct consequence of the infection. However, the "death kinetics" following community-acquired bacteremia is complicated and depends both on the focus of infection and microbial agent, coexistent morbidity, timing of hospitalization, and

therapeutic intervention (confer Figure 5). Within the first few days of admission, septic shock and organ failure seem to be the most important determinants of prognosis, and bacteremia is causally significant in more than 90% of deaths (160). In meningococcal and pneumococcal bacteremia a high proportion of deaths occur early despite appropriate therapy (142;144); i.e. a "physiologic point of no return" corresponding to an advanced stage of sepsis may be reached relatively early (19), whereas e.g. *E. coli* bacteremia tends to develop less fulminantly, with CF's increasing more slowly (6). During the first 30 days after the bacteremia, a high proportion of deaths is expected to be causally related to the infection (12;161), whereas for long-term prognosis after 30 days, an increasing proportion of deaths is likely not to be a direct consequence of infection but determined by coexisting morbidity. A prospective cohort study of 2287 patients with community-acquired pneumonia, of whom 208 died within 90 days, found that 78% of 110 "pneumonia-related" deaths occurred within 30 days, whereas 68% of 98 "pneumonia-unrelated" deaths occured after 30 days (162). The distinction between infection-attributable and non-attributable deaths has been criticised, as it appears somewhat theoretical and subjective and may be biased by the investigators' study objectives (163). Based on the above considerations, we would suggest the use of all-cause 30-day and 90-day case-fatality (alternatively denoted 30-day and 90-day mortality) for epidemiological studies of prognostic factors for bacteremia.

Few long-term prognosis studies of bacteremia exist (23;24), probably due to the difficulties in many countries with individual follow-up of patients during the post-discharge period, and diabetes has not been examined as an independent prognostic factor in these studies. Use of population-based bacteremia registries with the possibility of complete long-term follow-up has proved an efficient way for outcome analysis (164).

Diabetic and non-diabetic bacteremia patients in previous series are likely to have differed with respect to other prognostic variables, but few studies have given mortality estimates adjusted for confounding factors (49). Likewise, to our knowledge no studies have considered the issue of differential subsequent treatment of bacteremia related to diabetes.

In conclusion, findings from most case series and a few cross-sectional, case-control and cohort studies suggest that diabetes is associated with a high and possibly increased risk of bacteremia, including pneumococcal and in particular enterobacterial bacteremia. It is not clear from the

existing studies, however, whether any apparent association between diabetes and bacteremia is causal, related to lack of adjustment for confounding factors such as age and comorbidity, or due to increased surveillance of bacteremia in diabetes or vice versa. Some epidemiological studies have indicated an increased risk for pneumonia and in particular UTI in diabetic patients, infections which frequently are underlying community-acquired bacteremia, and predominantly are caused by pneumococci and enterobacteria. Studies of diabetes and the prognosis of bacteremia have been inconclusive and hampered by mixing of various bacteremias, inclusion of too few diabetic patients, risk of selection bias, missing confounder adjustment, and lack of long-term follow-up. Diabetes has emerged as one of the most common chronic diseases in our time, and its role as risk and prognostic factor for community-acquired bacteremia remains uncertain. Properly designed epidemiological studies are needed, taking account of the weaknesses of the previous studies. In this thesis, population-based Danish registries combined with the unique personal identification number system (165) served as a valuable resource for examining the impact of diabetes mellitus on the two dominant microbial groups of community-acquired bacteremia: pneumococcal and enterobacterial bacteremia.

1.5. Aims of thesis

The aims of this thesis were to study:

1) Diabetes as a prognostic factor for community-acquired pneumococcal bacteremia (study I)

2) Diabetes as a risk factor for community-acquired pneumococcal bacteremia (study II)

3) Diabetes as a risk factor and prognostic factor for community-acquired bacteremia caused by *E. coli* and other enterobacteria (study III)

2. Subjects and Methods

2.1. Data sources

Study population

The studies included in this thesis were conducted in North Jutland County, Denmark, within a population of ca. 500,000 inhabitants, approximately 9% of the total Danish population. It is a homogeneous Caucasian, mixed rural and urban study population, which is entirely provided with tax-supported healthcare by the National Health Service, allowing free access to the county's seven public hospitals. All patients hospitalized with acute conditions are treated in these public hospitals, of which one (Aalborg Hospital) serves as both district and referral hospital.

We collected data from the North Jutland County Bacteremia Registry, the County Prescription Database and Hospital Discharge Registry, and the Central Population Registry. Through the use of the 10-digit civil registry number, which is unique to every Danish citizen and encodes gender and date of birth, a complete hospitalization and prescription history could be established for each individual.

The North Jutland County Bacteremia Registry

A computerized microbiological bacteremia registry has been maintained by the Department of Clinical Microbiology at Aalborg Hospital since 1981 (166). The department provides diagnostic bacteriology for the entire county. For the study period 1992-2001 the registry comprises approximately 9,000 episodes of bacteremia. Data have been obtained prospectively and concurrently with the clinical episode by physicians at the department. The registry includes the number of positive culture bottles, detection time in hours, number of bacterial isolates, name of the bacterial species and species group/s, and their susceptibility to a range of antibiotics. The registry also contains information on the patient's civil registry number, age and gender, hospital and department of admission, date of drawing the first positive blood culture, place of acquisition of the bacteremia, focus of infection, and antibiotic therapy given at the time the attending physicians were notified regarding positive blood cultures.

The North Jutland County Prescription Database

All pharmacies in the county are equipped with a computerized accounting system by which data are sent to the Danish National Health Service as part of the national health care program. This program refunds the majority of the costs associated with the purchase of most drugs prescribed by physicians. The County Prescription Database (167) was initiated in 1989 and retains key information on redeemed prescriptions for refundable drugs dispensed from all pharmacies in the county. The database includes the civil registry number of the patient and type of drug prescribed, coded according to the Anatomical Therapeutical Chemical (ATC) classification system. For the purpose of this thesis we retrieved data on prescriptions of antidiabetic drugs, immunosuppressive drugs, and oral antibiotics, all of which were available by prescription only and refunded during the study period (except tetracyclines and cephalosporins, consumption of which amounts to less than five percent of all antibiotics used in the county) (168).

The North Jutland County Hospital Discharge Registry

The County Hospital Discharge Registry (169) is an administrative public registry that is truly population-based and covers all nonpsychiatric hospitalizations in the county from January 1, 1977. The registry includes civil registry numbers, and up to 20 discharge diagnoses coded exclusively by physicians according to the Danish versions of the *International Classification of Diseases* (ICD) (ICD-8 from 1977-1993 and ICD-10 from 1994; ICD-9 was never implemented in Denmark).

The Danish Central Population Registry

The Central Population Registry is electronically updated daily and keeps record of all changes in vital status and migration for the entire Danish population since 1968, including change in address and date of death (170).

Review of hospital records (study I)

For study I, hospital records and laboratory reports were retrieved from 7 hospitals in the county to confirm diabetes diagnoses in patients with pneumococcal bacteremia. Hospital records of confirmed diabetic patients and a group of gender- and age-matched non-diabetic patients were further reviewed to examine variables reflecting bacteremic disease severity at the time of hospital admission.

2.2. Definition of exposure, outcomes, and confounding factors

Diabetes

Data on diabetes in all studies were obtained from the Prescription Database and Hospital Discharge Registry in the county. Diabetes was in this thesis defined as 1) redemption of at least one prescription for insulin (ATC code A10A) or an oral antidiabetic drug (ATC code A10B); and/or 2) a hospital discharge diagnosis of type 1 or type 2 diabetes with or without complications (ICD-8 codes 249-250 and ICD-10 codes E10-E11). All prescriptions and diagnoses recorded before the date of a patient's hospitalization with bacteremia were included. In study I, we included prescriptions and diagnoses of diabetes made during hospitalization with bacteremia, in order to evaluate the proportion of newly diagnosed cases of diabetes and to conduct survival analyses with newly diagnosed cases both included and excluded. For study I, we were also able to obtain clinical details from hospital records including type and duration of diabetes, glycosylated hemoglobin, presence of ketoacidosis, and diabetic complications. For the purpose of studies II and III, we attempted to classify diabetic patients as having T1 DM if they were aged up to 40 years at diagnosis and were treated with insulin as monotherapy, and having T2 DM if they were treated by diet alone, were ever treated with oral antidiabetics, or if they were aged over 40 years at diagnosis, irrespective of treatment.

Bacteremia

Community-acquired bacteremias caused by pneumococci and enterobacteria were the outcomes in the risk studies. We used the County Bacteremia Registry to identify patients aged more than 15 years with a first hospitalization for bacteremia caused by *S. pneumoniae* (study II) and members of the family Enterobacteriaceae (study III). From the latter group, *Salmonella* infections were excluded because they usually originate from an animal reservoir and not from the patient's endogenous flora. For all studies, only the patient's first episode of monomicrobial bacteremia was included. The infection had to be present or incubating at admission to the hospital (171). We excluded patients with either regular contact with hospitals or a hospitalization within 30 days prior to admission with bacteremia, since we consider these cases to constitute a distinct group more affected by factors associated with nosocomial infections (172).

Three different systems for blood culture were used during the study period: inoculation of blood into multiple tubes of bacteriological media in the laboratory (1992); the Colorbact® system (Statens

Serum Institut, Copenhagen, Denmark) (34) (1992-95); and the BacT/Alert® system (bioMérieux Inc., Durham, NC, USA) (1996-2001). The nominal volume per blood culture for the three systems was 16-18 ml, 20-22 ml, and 28-32 ml for adult patients, respectively. Pneumococcal isolates were identified directly by Quellung reaction (Omniserum, Statens Serum Institut) or latex agglutination for pneumococcal antigen (Slidex pneumo-Kit, bioMèrieux Inc.) (173). Optochin susceptibility was confirmed by subculture on 5% horse blood agar. All isolates including occasional ones with ambiguous results were referred to the national reference laboratory at Statens Serum Institut for definitive identification and serotyping. Enterobacteria were identified in accordance with Farmer et al (174) either by conventional methods or by a commercial identification system (175).

Bacteremia episodes in which only one culture-bottle was positive, or with more than 24 hours until first indication of growth, were classified as bacteremia with low bacterial density. All other episodes were classified as high bacterial density.

Antimicrobial susceptibility tests were carried out by disk diffusion (Neo-Sensitabs®; Rosco, Taastrup, Denmark) on Danish horse blood agar (SSI Diagnostika, Copenhagen, Denmark); zone-size interpretive guidelines were as stated by the manufacturer. For pneumococcal isolates, a 1 μg oxacillin disc was employed to screen for the presence of penicillin resistance, and this was confirmed by penicillin Etest (AB Biodisk, Solna, Sweden). Pneumococcal isolates with MIC of penicillin $\geq$ 2 μg/mL were classified as resistant. In study I, ongoing antibiotic therapy at 1st notification of a positive blood culture was categorized as: therapy including a beta-lactam / macrolide antibiotic, any other antibiotic therapy, or no antibiotic therapy. For enterobacteria, empirical antibiotic therapy at 1st notification was regarded as appropriate if given intravenously (except for fluoroquinolones) and if the blood isolate was susceptible in vitro to one or more of the antibiotics given.

Some researchers have attempted to distinguish between a primary focus (sometimes denoted "portal of entry"), e.g. a surgical wound or an intravascular catheter, and a secondary focus, e.g. endocarditis or meningitis (176). For the purpose of this thesis, the focus of infection was defined as the organ or tissues infected at the time when bacteremia becomes clinically apparent (177). The focus was determined based on clinical symptoms and signs of local infection, biochemical markers, imaging techniques, and microbiological confirmation through relevant samples.

Death

The main outcome in the cohort studies included in this thesis was the proportion of patients with bacteremia dying within the first 30 and 90 days after the first positive blood culture was drawn. We have referred to this proportion as 30-day and 90-day mortality of patients with bacteremia (p. 32). No attempt was made to determine the cause of death, i.e. as the fraction directly attributable to the infection. In accordance with some but not all authorities in the field (163) we believe that this distinction in the outcome of severe infections is extremely difficult, especially when using historical data.

For the study of diabetes as a prognostic factor for pneumococcal bacteremia (study I), we examined several variables reflecting bacteremic disease severity at the time of hospital admission in a subsample of the study population. This was done to assess the possibility of surveillance bias (p. 31), i.e. a situation where the proportion of patients with mild or less advanced bacteremic disease is higher among diabetic compared with non-diabetic patients due to closer medical surveillance. Hospital records were reviewed for all diabetic patients and a comparison group of non-diabetic patients matched within gender and age group. Sepsis on admission was defined in accordance with Bone et al's criteria (8), and severe sepsis was defined as sepsis with ≥ 1 of: acute alteration of mental state, sepsis-induced hypotension, or a S-creatinine of more than 140 µmol/L. We also assessed the serum concentration of CRP on admission, because we expect this marker to correlate with the inflammatory insult intensity and thus both severity and duration of pneumococcal infection (56).

Confounding factors

To adjust for existing comorbid diseases in analyses of risk and prognosis, we calculated a summary measure of confounding due to comorbidities (178). The Charlson index includes 19 major disease categories, several of which have been suggested as risk factors for bacteremia, *e.g.*, congestive heart failure and chronic obstructive pulmonary disease for pneumococcal bacteremia (49), and malignancies and liver cirrhosis for enterobacterial bacteremia (138;179). The index has been adapted for use with hospital discharge registry data in ICD databases (180) for the prediction of short- and long-term mortality (181;182). A weight is assigned to each comorbid disease category, and the Charlson index score is the sum of these weights. We calculated the score for each patient and control subject based on previous discharge diagnoses coded according to ICD-8 and ICD-10 in

the Hospital Discharge Registry (see Appendix for codes included). Since diabetes was the main variable in this thesis, diabetes was separated from the Charlson index and included as an independent variable in the analyses. To avoid differential ascertainment of comorbidity related to case status, as well as inclusion of comorbid diagnoses that might be complications of bacteremia, we only included diagnoses recorded before the date of hospitalization with bacteremia. Three levels of the comorbidity score were defined and included as design variables in the analyses: 0 ("low") corresponding to persons with no recorded underlying diseases implemented in the Charlson index; 1-2 ("medium"); and > 2 ("high").

Since alcohol abuse and immunosuppressive therapy have been associated with the risk of pneumococcal infection (146), for study II we also collected data on alcohol-related disorders from the Discharge Registry (ICD-8 codes 291, 303, 979, 980, 577.10; ICD-10 codes F10, K86.0, Z72.1, R78.0, T51) in addition to the diagnoses included in the Charlson index. For this study we further collected data from the Prescription Database on the use of antibiotics and immunosuppressive drugs including corticosteroids before hospitalization, defined as redemption of at least one prescription for a systemic antibiotic of any kind (ATC code J01) within half a year of admission (168), and redemption of at least one prescription for any immunosuppressive drug (ATC codes L01, L04, H02 AB) within one year of admission, respectively.

2.3. Study design and statistical analyses

We conducted two separate analyses to investigate the association of diabetes with the risk (study I) and prognosis (study II) of community-acquired pneumococcal bacteremia. The association of diabetes with community-acquired enterobacterial bacteremia was investigated in a third study combining analyses of risk and prognosis in one paper (study III).

Case-control analysis of the risk for bacteremia

The risk studies were conducted in a nested case-control design (p. 24). Using civil registry numbers, we selected 10 population control subjects for each case of bacteremia individually matched by gender, age (same year of birth), and place of residence (North Jutland County). The control subjects were selected with the incidence density sampling technique (183); that is, controls for a given case were sampled among individuals from the source population who were alive and at risk of first community-acquired bacteremia at the time the case was diagnosed (158).

We used conditional logistic regression to estimate ORs with 95% CIs for community-acquired bacteremia among diabetic persons and population controls, since our dataset was matched in both studies. Initially, we analyzed data by obtaining contingency tables for the main study variables: diabetes, level of comorbidity, and case or control status. Since more than 95% of diabetic bacteremia cases and controls had T2 DM according to our definition, we chose to consider diabetes as one entity in further risk analyses. We then estimated ORs for bacteremia according to presence of diabetes, adjusted for comorbidity. In study II, analyses were conducted with and without adjustment for alcohol-related disorders and use of antibiotics and immunosuppressive therapy. In studies II and III, stratified risk analyses were performed according to gender, age groups (15-39 years; 40-64 years; 65-79 years; 80+ years), and level of comorbidity to assess possible variation in the ORs across the strata. In study III, ORs were further estimated separately for patients with a urinary tract focus of infection, and for patients with bacteremia due to *E. coli* and due to *Klebsiella* spp.

To examine the impact of diabetes on the overall risk of community-acquired bacteremia with pneumococci and enterobacteria, respectively, we estimated the population-attributable risk (PAR) for a diagnosis of diabetes, i.e., the proportion of all cases of bacteremia that are attributable to diabetes (184). In case-control studies, the population-attributable risk (PAR) may be calculated by the following equation:

$$PAR = P \times (OR - 1) / \{[p \times (OR - 1)] + 1\}.$$

The proportion of persons with diabetes in our reference population, p, can be estimated by the diabetes prevalence in controls, since the population prevalence of diabetes is relatively low, and our controls are representative for all non-cases in the population (184).

Cohort analysis of 30- and 90-day mortality
The association of diabetes with the prognosis of community-acquired bacteremia was examined in a cohort design. We linked all included patients with bacteremia to the Central Population Registry, to obtain information on vital status, date of death, or migration.

The duration of follow-up time was calculated from the date when the patient's first positive blood culture was drawn, until death, migration, or 90 days after. We first obtained contingency tables for the main prognostic study variables: diabetes, gender, age group, level of comorbidity, focus of

infection, and determined cumulative mortality after 30 and 90 days based on Kaplan-Meier curve estimates. For each prognostic factor, the category with the lowest risk for death was used as the reference category.

Cox proportional-hazards regression analyses were used to compare the mortality rate among diabetic and non-diabetic bacteremia patients, with estimation of mortality rate ratios (MRRs) and 95% CIs adjusted for gender, age, and level of comorbidity. Analyses were conducted both including and excluding focus of infection. The assumption of proportional hazards in the Cox models was assessed graphically, and found appropriate in all the models.

All statistical analyses were performed with use of STATA® software (version 8.0, STATA, College Station, TX). The study was conducted according to guidelines of the regional scientific ethics committee for use of clinical and laboratory data, and approved by the Danish Registry Board (record no. 2002-611-0060).

3. Results

Below follows a summary of the main results obtained from the three studies.

3.1. Study I

Diabetes as a prognostic factor for community-acquired pneumococcal bacteremia

We identified 628 patients older than 15 years hospitalized with a first episode of community-acquired pneumococcal bacteremia.

Validation of the registry-based diagnosis of diabetes

To validate the diagnosis of diabetes established trough the Prescription Database and Discharge Registry, we searched previous laboratory reports of patients with pneumococcal bacteremia and potential diabetes. We accepted the diagnosis when the World Health Organization diagnostic criteria (185) used during most of the study period were met, with certain modifications followed in most epidemiological studies (186). We thus classified patients as having diabetes if they had a single, fasting venous blood-glucose > 6.7 mmol/L or a random venous blood-glucose > 10.0 mmol/L with a concurrent medical history of diabetes. In order to estimate misclassification, the positive predictive value of the registration of patients with diabetes was calculated as follows: the number of patients with confirmed diagnoses of diabetes according to WHO criteria after hospital record review divided by the total number patients recorded with diabetes in the registries. We found 65 (10.4%) of patients to have a diagnosis of diabetes identified through the registries, of which 63 (10.0%) met the WHO diagnostic criteria, corresponding to a predictive value of a diagnosis of diabetes = 97% (95% CI: 89-100%).

Diabetes as a prognostic factor

Diabetic patients were slightly older (median age 71.7 years *cf* 67.0 years) and were found to have more comorbidity (59% *cf* 46%) than non-diabetic patients with bacteremia. The most common focus of infection was the respiratory tract (92% of diabetic and 80% of non-diabetic cases), followed by the meninges (6% *cf* 10%). Pneumococcal serotype distribution, bacterial density in blood cultures, antibiotic resistance, and choice of antibiotic therapy were all similar between groups. In five diabetic patients (8%), ketoacidosis was present; none of these patients died.

In our subsample study of the 63 diabetic and 63 gender- and age-matched non-diabetic patients, we found the initial CRP to be higher in the diabetic group (median 277 mg/L *cf* 204 mg/L), and a higher proportion of diabetic patients fulfilled criteria of severe sepsis (56% *cf* 40%). Only one of the 126 patients, who had been splenectomized, was known to have a prior pneumococcal vaccination.

The mortality in diabetic compared with non-diabetic patients was 11.1% *cf* 16.5% after 30 days, resulting in a crude mortality rate ratio (MRR) of 0.7 (95% CI: 0.3-1.4) (Table 3). After 90 days, 16.0% of diabetic patients had died, as compared with 19.5% of non-diabetic patients (crude MRR=0.8, 95% CI: 0.4-1.5). Kaplan-Meier curves for 90 days of follow-up for diabetic and non-diabetic patients are shown in Figure 9. After adjustment for gender, age group, and comorbidity, the association between diabetes and mortality after 30 and 90 days of follow-up was almost unchanged (adjusted MRR= 0.6, 95% CI: 0.3-1.2). If focus of infection was included in the analysis, the adjusted MRR remained 0.6 (95% CI: 0.3-1.3) after 30 days and was 0.7 (95% CI: 0.4-1.4) after 90 days. Excluding the 10 patients with newly diagnosed diabetes did not significantly change the estimate (adjusted MRR=0.6 [95% CI: 0.3-1.4] after 30 days).

Table 3: Association between diabetes mellitus and 30-day and 90-day mortality in community-acquired pneumococcal bacteremia.

Diabetes mellitus	N	Dead at 30 days, N	30-day mortality (95% CI)	*Crude* 30-day MRR (95% CI)	*Adjusted*[*] 30-day MRR (95% CI)
Not present	565	93	16.5% (13.7%-19.8%)	1.0 (ref.)	1.0 (ref.)
Present	63	7	11.1% (5.5%-22.0%)	0.7 (0.3-1.4)	0.6 (0.3-1.2)

Diabetes mellitus	N	Dead at 90 days, N	90-day mortality (95% CI)	Crude 90-day MRR (95% CI)	Adjusted[*] 90-day MRR (95% CI)
Not present	565	110	19.5% (16.4%-23.0%)	1.0 (ref.)	1.0 (ref.)
Present	63	10	16.0% (9.0%-27.7%)	0.8 (0.4-1.5)	0.6 (0.3-1.2)

[*]Adjusted by Cox proportional-hazards regression analysis for gender, age, and comorbidity.

Fig. 9:

Mortality curves for patients with community-acquired pneumococcal bacteremia. Patients with diabetes (n=63) and non-diabetic patients (n=565).
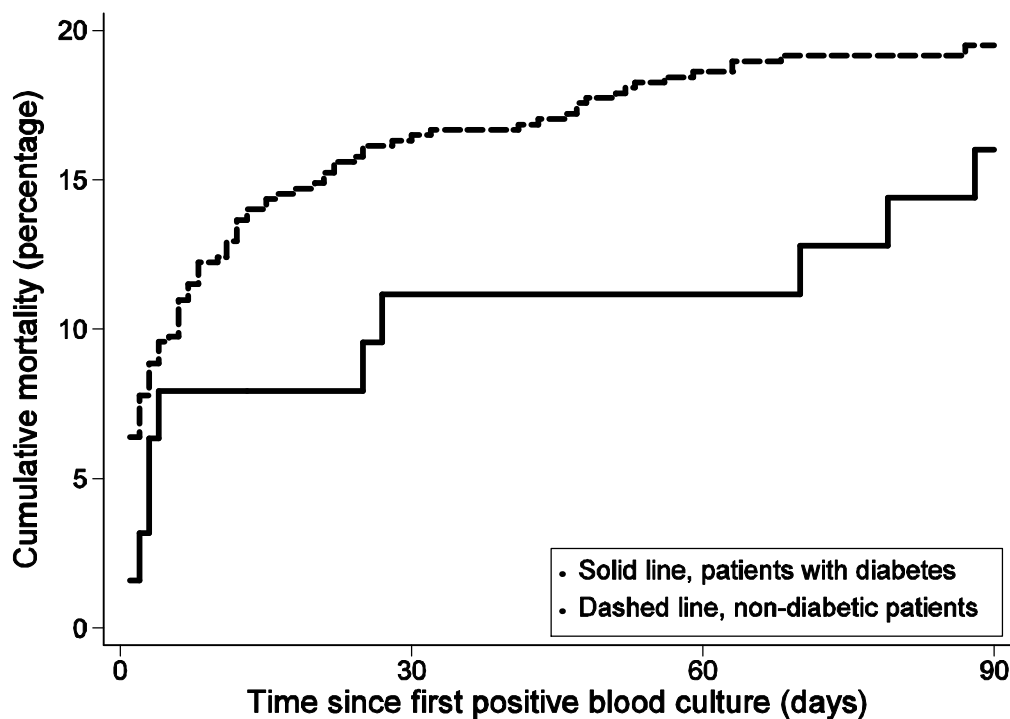
3.2. Study II

Diabetes as a risk factor for community-acquired pneumococcal bacteremia

For study II, we included 598 incident cases with residence in North Jutland County and a first hospitalization with community-acquired pneumococcal bacteremia, and 5,980 population controls. A total of 53 cases (8.9%) had either redeemed a prescription for insulin or oral antidiabetic drugs or had a discharge diagnosis of diabetes recorded before the date of hospitalization with bacteremia, compared with 298 controls (5.0%). A considerably higher proportion of cases than controls (48% *cf*. 27%) had one or more previously recorded discharge diagnoses as evidenced in the Charlson index.

Table 4 gives crude and adjusted ORs for community-acquired pneumococcal bacteremia according to presence or absence of diabetes mellitus. The crude OR for pneumococcal bacteremia in people with diabetes was 1.9 (95% CI: 1.4-2.6). After adjustment for comorbidity, the OR decreased to 1.5 (95% CI: 1.1-2.0), indicating that the association was confounded by a higher level of comorbidity in the diabetic group. Inclusion of antibiotics and immunosuppressive therapy in the analysis left the adjusted OR unchanged 1.5 (95% CI: 1.1-2.0).

Table 4: Crude and adjusted odds ratios (OR) for community-acquired pneumococcal bacteremia according to presence of diabetes mellitus.

Diabetes mellitus	Crude OR* (95% CI)	Adjusted OR† (95% CI)
Not present	1.0 (ref.)	1.0 (ref.)
Present	1.9 (1.4-2.6)	1.5 (1.1-2.0)

* Crude OR for presence of diabetes in cases with pneumococcal bacteremia compared with gender- and age-matched controls.

† OR adjusted for level of comorbidity and alcohol-related disorders.

To evaluate the impact of diabetes on the risk of pneumococcal bacteremia in certain subgroups, we stratified our analyses according to age group, gender, and level of comorbidity. ORs were highest in adults aged 40 and younger (adjusted OR=4.2, 95% CI: 1.1-16.7) and in persons without any other coexisting morbidity (adjusted OR=2.3, 95% CI: 1.3-3.9). Further, ORs appeared to be higher in male than in female diabetic individuals.

Under the assumption that the association was causal, and an overall prevalence of diabetes in the study population of 5.0%, the total population-attributable risk was 2.4%. Thus, of 1,000 admissions with incident pneumococcal bacteremia in our study population, 24 may be attributed to diabetes.

3.3. Study III

We identified 1,317 incident cases with a first hospitalization with bacteremia due to enterobacteria during 1992-2001.

Diabetes as a risk factor for community-acquired enterobacterial bacteremia

A total of 225 of the cases with bacteremia (17.1%) had diabetes recorded before the date of hospitalization with bacteremia, compared with only 779 (5.9%) of 13,170 controls. The adjusted OR for enterobacterial bacteremia in persons with diabetes was 2.9 (95% CI: 2.4-3.4) (Table 5). The OR of bacteremia from diabetes was greatest in adults under 65 years (adjusted OR=5.9, 95% CI: 3.9-9.0) and in persons without any other comorbidity (OR=4.9, 95% CI: 3.7-6.6). The risk appeared to be higher in diabetic females than in males. Further analyses showed a higher risk ratio for bacteremia with a urinary tract origin (adjusted OR=3.4, 95% CI: 2.7-4.2) than for bacteremia with other foci of infection (adjusted OR=2.2, 95% CI: 1.6-2.9). The adjusted OR for *E. coli* bacteremia was 3.0 (95% CI: 2.5-3.6), and for bacteremia due to *Klebsiella* spp. was 2.2 (95% CI: 1.3-3.7). Under the assumption that the association is causal, and a prevalence of diabetes in controls of 5.9%, the population-attributable risk was 10.1%.

Table 5: Crude and adjusted odds ratios (OR) for community-acquired enterobacterial bacteremia according to presence of diabetes mellitus. Overall risk estimates and estimates stratified by age, gender, and level of comorbidity.

	Crude OR* (95% CI)	Adjusted OR† (95% CI)
No diabetes	1.0 (ref.)	1.0 (ref.)
Diabetes present	3.3 (2.8-3.9)	2.9 (2.4-3.4)
Diabetes present, stratified by:		
Age		
15-39 years	10.0 (2.9-34.5)	6.6 (1.6-28.0)
40-64 years	7.3 (4.8-10.9)	5.8 (3.7-9.0)
65-79 years	2.9 (2.2-3.7)	2.5 (1.9-3.3)
80+ years	2.8 (2.2-3.6)	2.5 (1.9-3.3)
Gender		
Males	2.6 (2.1-3.5)	2.3 (1.8-3.1)
Females	3.9 (3.1-4.8)	3.4 (2.7-4.2)
Comorbidity index score		
Low (0)	4.9 (3.7-6.6)	4.9 (3.7-6.6)
Medium (1-2)	2.2 (1.6-3.0)	2.2 (1.6-3.0)
High (>2)	2.0 (1.0-4.3)	2.0 (1.0-4.3)

* Crude OR for presence of diabetes in cases with enterobacterial bacteremia compared with gender- and age-matched controls.

† OR adjusted for level of comorbidity index score (except when stratified by this variable).

Diabetes as a prognostic factor for community-acquired enterobacterial bacteremia

Diabetic patients with enterobacterial bacteremia were more likely than non-diabetic patients to have a urinary tract focus of infection (68% *cf* 59%), compared with an abdominal focus (12% *cf* 19%). There were no major differences in the bacterial density in blood cultures, distribution of different bacterial groups, or appropriateness of empirical antibiotic therapy given (Table 6). Mortality curves for 90 days of follow-up for diabetic and non-diabetic patients with bacteremia are shown in Figure 10. The two curves tended to overlap during the first week but thereafter diverged, corresponding to an increased risk of dying among diabetic patients in the second week after the first positive blood culture.

Table 6: Characteristics of 1,317 patients with community-acquired bacteremia due to enterobacteria in North Jutland County, Denmark, 1992-2001[*].

Characteristic	Community-acquired enterobacterial bacteremia	
	Diabetic patients (N=225)	Non-diabetic patients (N=1,092)
Urinary tract focus of infection	153 (68%)	647 (59%)
Abdominal focus of infection	28 (12%)	210 (19%)
Any other focus	4 (2%)	25 (2%)
Undetermined focus	40 (18%)	210 (19%)
Escherichia coli	186 (83%)	875 (80%)
Citrobacter spp.	0 (0%)	13 (1%)
Enterobacter spp.	6 (3%)	20 (2%)
Klebsiella spp.	20 (9%)	132 (12%)
Proteus mirabilis	9 (4%)	29 (3%)
Proteus vulgaris	2 (1%)	11 (1%)
Other enterobacteria	2 (1%)	12 (1%)
Bacteremia density low	81/194 (42%)	425/989 (43%)
Bacteremia density high	113/194 (58%)	564/989 (57%)
Appropriate empirical antibiotic therapy at 1st notification†	130/196 (66%)	619/989 (63%)
No appropriate antibiotic therapy	66/196 (34%)	370/989 (37%)

[*] Data are given as number (percentage of N) of individuals unless otherwise stated.

† At the time of 1st notification of a positive blood culture. 29 (13%) of diabetic and 103 (9%) of non-diabetic patients were excluded from the denominator due to discharge, death or missing information at time of 1st notification

Fig. 10:

Mortality curves for patients with community-acquired bacteremia due to enterobacteria. Patients with diabetes (N=225) and non-diabetic patients (N=1,092).
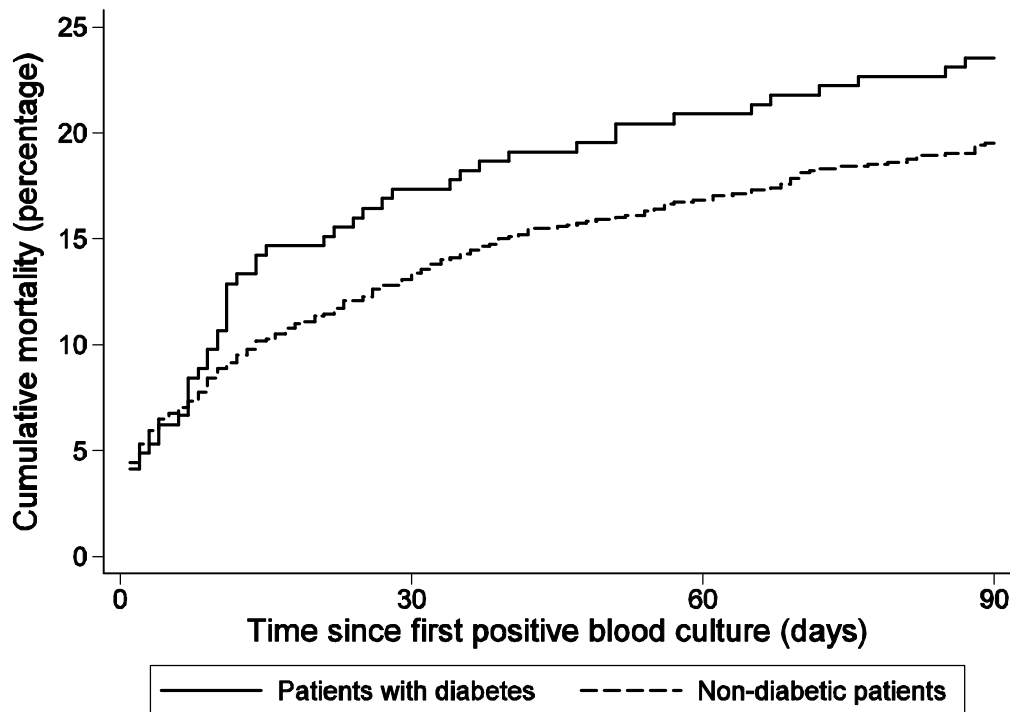
The mortality in diabetic patients compared with non-diabetic patients was 17.3% *cf* 13.4% after 30 days, and 23.6% *cf* 19.5% after 90 days. After adjustment for gender, age group, and comorbidity, the mortality rate ratio for diabetic patients was 1.3 (95% CI: 0.9-1.8) after 30 days, and 1.2 (95% CI: 0.9-1.6) after 90 days. Stratification for focus of infection did not materially affect the association between diabetes and mortality: 30-day MRR=1.3 (95% CI: 0.9-1.9) in bacteremias with a urinary tract focus, and 30-day MRR=1.5 (95% CI: 0.9-2.5) in bacteremias with a focus outside the urinary tract. When focus of infection was included in the final analyses, the adjusted MRR was 1.4 (95% CI: 1.0-2.0) after 30 days, and 1.3 (95% CI: 0.9-1.7) after 90 days.

4. Strengths and weaknesses of the studies

In this section, we will discuss strengths and weaknesses of our research design. To decide if the associations found in the three studies are likely to be causal, we will evaluate the role of potential bias in selection or measurement, confounding factors, and chance (statistical precision) (36).

4.1. Considerations about research design

Cohort vs. nested case-control design in risk factor studies

Prospective cohort studies of diabetic and non-diabetic patients are inefficient as large amounts of risk time are needed to generate a sufficient number of relatively rare events, for instance community-acquired pneumococcal bacteremia which occurs in 1-2 per 10,000 persons per year. A way to remedy this obstacle is to rely on historical cohorts identified from past records e.g. in disease registries and followed to the present time, as in the study by Weiderpass et al. (82). However, there are complex analytic difficulties in modeling a cohort of many hundreds of thousands of study subjects with varying follow-up times for a risk analysis of rare events. Confounders may be variably present, and the study subjects may shift from one confounder category to the next over time, yielding problems with both computer capacity and the researcher's keeping in touch with the data. A cohort design therefore still seems inefficient in relation to the amount of information returned. On the other hand, earlier case-controls studies have been prone to selection and information problems (p. 28 ff).

The nested case-control study used in our studies combines advantages of the cohort and case control design. It enabled us to address the research question with markedly smaller sample sizes, comparing diabetes exposure among bacteremia cases and a limited subset of controls sampled from a well-defined source population in North Jutland County. By sampling control subjects with the incidence density technique, the controls reflected the exposed person-time in the source population, and the estimated ratio of the incidence rates of bacteremia gave us exactly the same result that the underlying cohort study would provide (158).

Analyses of prognosis

The 90-day follow-up analyses in the studies were based on time-to-event data, i.e. the time of occurrence of death as well as the time of censoring for individuals lost during follow-up was taken

into account, and cumulative probabilities of bacteremia survival at any time were calculated with the Kaplan-Meier approach. Most previous cohort studies have reported bacteremia prognosis as in-hospital or 30-day CF, but direct measurement of such cumulative incidence proportions essentially requires that the whole cohort remains at risk and under observation for the entire follow-up period, and most cohort outcome studies have not provided these conditions. The logistic regression model used for confounder adjustment in some of these studies seems equally problematic, because the model estimates cumulative incidence odds and thus assumes complete follow-up (it also assumes that time to outcome/event is not important). For our time-to-event data, we found confounder adjustment by Cox proportional hazards regression analysis to be appropriate, estimating adjusted mortality rate ratios instead of cumulative mortality odds ratios, and taking time to death and censoring into account.

4.2. Considerations about bias, confounding and chance

Study I

Selection bias

Study I was a cohort study of all patients who were hospitalized for the first time with community-acquired pneumococcal bacteremia in North Jutland County 1992-2001. In cohort studies, selection bias due to lack of inclusion in the cohort or loss to follow-up is a potential problem. We used prospective population-based registries with complete follow-up of patients for the outcome = death, including the few patients who moved out of North Jutland County shortly after the bacteremia. Therefore, loss to follow up did not occur in this study.

Conversely, not all episodes of community-acquired pneumococcal bacteremia are likely to be included in our cohort at baseline. The detection of pneumococcal bacteremia during pneumococcal pneumonia may be highly dependent on admission patterns and timing of blood sampling for culture. Selection bias might have occurred if the association between diabetes and pneumococcal bacteremia prognosis differed for patients included in our cohort and those who remained undetected. If diabetes or diabetes-related confounding factors caused bacteremia to be rapidly fatal and thus undetected, diabetes may falsely appear to be associated with a favorable prognosis. On the other hand, diabetic subjects and their physicians may be more alert to early signs of infection, and milder cases of bacteremia may therefore have been admitted and diagnosed at the hospital

among diabetic patients, again leading to an underestimation of mortality in the diabetic group. However, our findings of a comparable measure of bacteremia density and greater severity of inflammation and sepsis in diabetic patients speak against a more meticulous case-ascertainment related to diabetes status in this study. Nevertheless, we can not exclude that some selection bias might be present, which would probably have lead us to underestimate the mortality in bacteremic patients with diabetes.

Information bias

Information problems in this cohort study may have occurred from non-differential or differential misclassification of exposure status, outcome status, or confounder data.

Outcome data on death were recorded completely and independently of diabetes data through administrative registries. This made bias due to differential diagnostic effort by the study hypothesis unlikely.

We evaluated the predictive value of a diagnosis of diabetes established through the registries in this study, and it proved to be high. Concerning completeness, Kristensen et al found that 76% of patients with known diabetes could be identified by a county prescription registry similar to ours, compared with an independent 34% by a regional hospital registry, by collecting data over a one-year period only (187). Thus, we find it likely that our combined data sources are nearly complete regarding known diabetes. On the other hand, pneumococcal bacteremia patients not registered with diabetes may have included some diabetic cases who had never been hospitalized previously or ever treated with antidiabetic drugs. This may have led us to underestimate any differences in prognosis between bacteremic patients with diabetes and those without.

We identified ten additional patients with newly diagnosed diabetes during admission with pneumococcal bacteremia who fulfilled the WHO diagnostic criteria *after* recovering from the infection. This effectively ruled out misclassification of transient hyperglycemia as diabetes. Because diagnosis of diabetes may have required survival of the acute stage of infection in these patients, we conducted outcome analyses both in- and excluding them, which did not significantly change the mortality estimates.

We used discharge diagnoses from hospital registries for comorbidity adjustment, and this approach may be hampered by data quality problems. The data problems may be categorized as: 1) errors in discharge diagnoses due to either incorrect data entry or lack of entry of available information, and 2) correct entry of discharge data that do not reflect the true condition of the patient (170). The validity of discharge diagnoses in the Hospital Discharge Registry is variable but generally high for major diseases (169). Most important for our studies was the possibility that coding and diagnosis of comorbidity might have been more complete for diabetic patients due to more frequent hospitalizations. This would lead to differential confounder control between diabetic and non-diabetic patients thus leading to an underestimation of the MRR for diabetic patients in this study. However, crude and adjusted estimates were almost similar, as adjustment for comorbidity decreased the MRR for the diabetic group slightly from 0.8 in the unadjusted analysis to 0.6. Selective adjustment for comorbidity might have contributed to this decrease, but it could not explain the observed mortality differences in the unadjusted analyses.

It is debatable if comorbidity should be included as confounding variable if diagnosed after the day of admission with bacteremia. It is clinically well-known that an episode of bacteremia may demask the presence of hitherto unknown severe morbidity. However, this approach bears the risks of asymmetric data collection dependent on survival time after hospitalization and thus differential confounder ascertainment. Therefore, we chose to include only comorbidity recorded before the day of admission with bacteremia.

Confounding

We were able to adjust for several potential confounders related to both diabetes and bacteremia mortality, including age, gender and comorbidity. Nevertheless, our mortality rate estimates may still be affected by residual confounding. Residual confounding after adjustment may be due to misclassification (see above) or use of crude categories for included confounders, or due to unmeasured or unknown confounders not included in the analyses.

The Charlson index used in our study is the most extensively studied and validated comorbidity index for predicting mortality (181). The weights applied to individual diseases in the Charlson index were based on the relative risk of dying in one cohort of American patients (178). Other weights would probably apply for different cohorts and other outcomes than death. A modified

score based on empirically derived weights of individual diagnoses might have improved adjustment for comorbidity in our study population (188). Furthermore, there is a possibility of residual confounding in our study by diseases not included in the Charlson index. Nevertheless, the overall credibility of our methodology was supported by the fact that the MRRs for pneumococcal bacteremia were stepwise increasing for rising levels of the Charlson index score (adjusted 30-day MRR=1.0 (ref.) for Charlson score = 0, MRR=1.4 for Charlson score 1-2, and MRR=2.0 for Charlson score >2). Similar stepwise increases in MRRs were found in the prognosis analyses for enterobacterial bacteremia in study III (data not shown).

A number of unmeasured factors may have had an impact on the prognosis for pneumococcal bacteremia in this study (Figure 5). For instance, different medical therapy given before the bacteremia associated with diabetes may have played a role for bacteremia prognosis. Many medications (including insulin) are likely to be part of the exposure's (diabetes) effect that we wish to study and thus should not be considered as a potential confounding factor. Other medications are closely associated with coexisting diseases (e.g. asthma drugs in chronic lung disease), therefore yielding a risk of over-adjustment if we included both previous discharge diagnoses and drug prescriptions as confounders in the analyses. Statins have recently been associated with a reduced case-fatality of bacteremia (189). However, as stated in paper I the prevalence of patients in lipid-lowering drug therapy was generally very low in our county during the study period. The issue of pneumococcal vaccination will be discussed in the context of our case-control analysis in study II; it is uncertain if prior pneumococcal vaccination can influence the prognosis of bacteremic pneumococcal disease. Lastly, we may speculate whether potential differences in the treatment after hospitalization, such as more intensive intravenous fluid therapy associated with diabetes, might have played a role for the outcome of bacteremia. Appropriateness of empirical antibiotic therapy, however, was similar and very high for both diabetic and non-diabetic patients in our cohort study.

Chance (statistical precision)
Although our cohort constitutes one of the largest study bases of community-acquired pneumococcal bacteremia to date, the statistical precision of the mortality rate estimates is only modest. Thus, the observed tendency towards a better prognosis in diabetic patients may be due to chance alone.

Study II

Selection bias

The main strength of this case-control study was the uniformly organized medical healthcare system allowing the use of a truly population-based design for the identification of cases and controls. The population-based sampling of controls minimized the risk of selection bias compared with previous studies.

Selection bias in our case-control study comes about if the selection of cases and controls into the study did dependent on diabetes. As previously discussed (p. 54), there might be a risk that diabetes could have increased the likelihood of being diagnosed as a case of pneumococcal bacteremia. This would have lead to an overestimation of the risk of bacteremia in diabetic patients. However, our observations on disease severity in pneumococcal bacteremia from study I argued against this situation. Previous findings (20) have demonstrated that adults included in the Bacteremia Registry are almost entirely severe cases of systemic bacterial infection, which are unlikely to not being hospitalized given a health care system with free and equal access to hospitals. Further, it is common practice in the Danish region where these studies are set, upon hospital admission, to obtain blood cultures from all patients suspected of systemic bacterial infection. Such cultures are obtained by trained technicians and are not an obligation for housemen or residents (30). Still, surveillance bias might have contributed to the only modestly increased risk estimates of pneumococcal bacteremia in this study.

Information bias

Misclassification of exposure and confounder data may have influenced our findings. Data on diabetes (exposure) was ascertained in the same way in cases and controls, namely by searching prospectively recorded databases for earlier hospitalizations with diabetes or earlier prescriptions for insulin or oral antidiabetic drugs before the time of the bacteremia events. This should make the classification of diabetes independent of the index hospitalization of the cases. We thereby avoided recall bias and non-response bias, which may have hampered previous case-control studies (147).

Both bacteremia cases and controls may have included a limited number of diet-treated diabetic persons who have never previously been drug treated or hospitalized, but we expect such misclassification to be non-differential, leading to a conservative risk estimate.

We choose to include comorbidity as confounding variable only if diagnosed before the day of admission with bacteremia. Therefore, registration of comorbidity was not influenced by case status. The registration period for both exposure (diabetes) and confounder data (comorbidity and use of certain drugs) was the cumulative time during which study subjects were residents in North Jutland County (observation time) within the period of existence of the registries used. The mean observation time was equal (57.3 years) for cases and controls, yet the individual "risk sets" of one case and 10 controls were sampled on identical age, not identical observation times. We may have missed some discharge diagnoses or prescriptions redeemed outside North Jutland County, possibly leading to underregistration of diabetes and confounders. We have, however, no reason to believe that this misclassification was associated with the later risk of developing bacteremia.

The completeness of the prescription data used for confounder adjustment in this study is probably high due to the Danish reimbursement system that encourages the pharmacists to register the data correctly (167;187). Data quality problems in the Hospital Discharge Registry have already been discussed in relation to study I. Any non-differential misclassification of comorbidity or drug use would lead to residual confounding and could have resulted in both attenuation and inflation of the relative risk estimate in this study. By contrast, a systematically more complete diagnosing and coding of comorbidity for diabetic patients would have lead to differential confounder control between cases with and without diabetes, and thus an underestimation of pneumococcal bacteremia risk in the diabetic group. Residual confounding by differential misclassification of comorbidity would therefore not change our main conclusions of diabetes being a risk factor for bacteremia.

Confounding
Comorbidity showed to be a relatively strong confounder of the association between diabetes per se and the risk of bacteremia, i.e. adjustment for a higher level of comorbidity in diabetes decreased the relative risk from 1.9 to 1.5. Apart from residual confounding due to misclassification of comorbidity (see above), the risk estimate may be affected by use of crude categories for the included confounders, or by confounders not included in the analyses. The Charlson index has not been validated as a method to measure confounding by comorbidity in explanatory studies of risk factors for an index disease. However, if many comorbid diseases are to be adjusted for, a comprehensive measure of comorbidity is needed for reasons of statistical efficiency, even in a

relatively large study. The Charlson index includes most diseases that have been suggested as risk factors for pneumococcal bacteremia, and similar to our prognosis analyses the risk estimates for bacteremia were stepwise increasing for rising levels of the Charlson index score (0, 1-2, and >2) in both this study and in study III. Among diseases not included in the Charlson index, alcoholism seems to be the most important risk factor for pneumococcal bacteremia (). Inclusion of alcohol-related disorders did not materially affect our risk estimate.

We chose to include a few medications as potential confounders in addition to comorbidity, i.e. prior antibiotics and immunosuppressive drugs. Use of these drugs was clearly associated with bacteremia risk (data not shown), but adjustment for the drugs left the relative risk estimates for diabetes virtually unchanged. We had no data on pneumococcal vaccination, which has been shown to reduce the incidence of invasive pneumococcal disease among adults and the immunocompetent elderly in observational studies (190). However, the general vaccine coverage in proposed "at risk" persons in our county is low, as the uptake of pneumococcal vaccine has been as low as 2 of 1,000 people per year since 1997 (191), when national vaccine recommendations were revised (Statens Serum Institut, Copenhagen, Dec. 1996), and probably extremely low before that time. Thus, we expect that pneumococcal vaccination did not have a major impact on our estimates. Nevertheless, diabetic individuals in our study population may have been vaccinated at higher rates than non-diabetic persons. The resulting bias, however, would lead to an underestimation of the true risk for pneumococcal bacteremia in diabetic patients.

Other unmeasured potential confounders included tobacco smoking, socioeconomic status, and living with young children attending daycare (147). We were able to adjust for major smoking-related diseases which we consider proxy measures of smoking in our aged study population. Living with children attending daycare is probably an uncommon risk factor in persons aged 50 years or more, who constituted 73% of our study population. Obesity is prevalent in diabetes and has been associated with increased risk of pneumonia among healthy women (192), but has to our knowledge not previously been established as risk factor for pneumococcal bacteremia.

Chance (statistical precision)
This study is to our knowledge the largest of its kind to date, but considerable statistical imprecision was still seen for the risk estimates, particularly in stratified analyses. The overall finding of an

increased risk estimate in diabetic patients was supported by consistent subgroup analyses according to age and gender.

Study III

This study combined the nested case-control analysis of risk and cohort analysis of prognosis developed in studies I and II. The findings may have been influenced by similar types of bias and confounding as in the first two studies.

Selection bias

Similar to bacteremia during pneumococcal pneumonia, the detection of bacteremia with enterobacteria during severe UTI such as pyelonephritis may depend on admission patterns and timing of blood cultures, though this has not been well studied. Selection bias may have occurred if diabetes did influence the chance of being diagnosed with bacteremia and consequently included as a case. Patients with diabetes may be closer surveyed for UTI; on the other hand, focal UTI symptoms may be more vague in diabetic patients (127). We found a higher mortality of enterobacterial bacteremia in diabetic patients, and a similar bacterial density in blood cultures from diabetic and non-diabetic patients; both findings argue against a more meticulous case-ascertainment among diabetic persons. Any residual selection bias would lead us to overestimate the risk of enterobacterial bacteremia in diabetic patients, and probably to underestimate the differences in mortality between bacteremic patients with and without diabetes. It seems unlikely however, that selection bias might have caused risk estimates of a magnitude observed in this study.

Information bias

Misclassification of exposure, outcome, and confounder data may have influenced our findings. The mean total observation time for diabetes and comorbidity was similar (65.9 vs. 66.6 years) for cases and controls included in the study. Both bacteremia cases and controls may have included a limited number of diet-treated diabetic persons who have never previously been drug treated or hospitalized. Further, diagnosis and coding of comorbidity may have been more complete in diabetic patients due to more frequent previous hospitalizations. This possibility might in this study have been exaggerated by non-inclusion of diagnoses during hospitalization with bacteremia, as gram-negative bacteremia probably quite often demasks severe underlying comorbidity. However, a more complete confounder control among diabetic patients would lead to a conservative risk

estimate. In the mortality analyses, adjustment for comorbidity and other factors including the focus of infection had only minor influence on the estimated MRRs.

Confounding

Unmeasured factors may have had an impact on the risk and prognosis of bacteremia in this observational study. The majority of episodes of enterobacterial bacteremia had a urinary tract origin. High sexual activity and use of spermicides (193), and pregnancy (92) are well-established risk factors for UTIs in younger women. However, these are probably not common risk factors in the vast majority of our study population, and the association of the factors with diabetes is uncertain. Urinary tract catheterization may be a risk factor for enterobacterial bacteremia and associated with diabetes, but should be regarded as a direct diabetes complication not to be included as confounder in our analyses.

We may again speculate whether potential differences in treatment after hospitalization, such as ICU admission, resuscitation orders etc. related to diabetes might have played a role for the mortality rate estimates. As expected, the appropriateness of empirical antibiotic therapy was much lower than for pneumococcal bacteremia in study I, but appeared to be unrelated to diabetes. As previously discussed (p. 12), treatment factors are likely to reflect bacteremia severity and should therefore not be adjusted for.

Chance (statistical precision)

This cohort of community-acquired enterobacterial bacteremia is one of the largest reported in the literature. Still, the statistical precision of the mortality rate estimates for diabetes was only modest. Notwithstanding, the adjusted risk estimates for bacteremia from diabetes were remarkably high and reached statistical significance across all strata of age, gender, and comorbidity.

The PAR, i.e. the proportion of all enterobacterial bacteremia episodes in the population that might be attributable to diabetes, was 10.1% in this study compared with only 2.4% for pneumocccal bacteremia in study II. It is important to notice that interpretation of the PAR assumes a causal association without any biases. Furthermore, the measure is dependent on the observed pattern of exposure in a given population, which calls for caution when comparing between different populations. Lastly, it may be problematic to interpret the PAR as the proportion of bacteremias that

could have been prevented had diabetes not been present, because absence of diabetes would probably expand the person-years at risk for bacteremia by removing other competing risks for death (158).

5. Main conclusions

Based on the results obtained and an examination of potential bias, confounding and chance in the three studies, the following main conclusions were drawn:

Study I:

The study provides strong evidence against the belief that patients with diabetes mellitus carry a higher case-fatality of community-acquired pneumococcal bacteremia, as compared with non-diabetic patients. Whether the slightly better prognosis observed in patients with diabetes is due to closer surveillance, undiagnosed comorbidity in non-diabetic patients, biological mechanisms of diabetes or its treatment, or chance, still remains to be elucidated.

Study II:

We found a 1.5-fold increased risk of community-acquired pneumococcal bacteremia in individuals with diabetes mellitus, when compared with non-diabetic individuals. The impact of diabetes on the relative risk was most pronounced in younger adults and in persons without any coexisting morbidity.

Study III:

Diabetes was associated with a highly increased risk of community-acquired bacteremia due to enterobacteria, approaching a six-fold increased risk in adults below 65 years. Even in our region with a relatively low prevalence of diabetes, more than 10 percent of cases of enterobacterial bacteremia may be attributable to diabetes. In addition, diabetes seems to be associated with a slightly poorer prognosis of enterobacterial bacteremia.

6. Overall discussion and perspectives

6.1. Discussion

In the following the results of our studies will be discussed in relation to the aims they have addressed, together with some considerations about the patophysiology underlying our findings.

Community-acquired pneumococcal bacteremia

Diabetes as a risk factor

To our knowledge, our study is the first population-based case-control study to examine the relative risk of pneumococcal bacteremia specifically in diabetic patients. Our results are consistent with the case-control study by Nuorti et al, in which diabetes prevalences among 25 year younger American patients with invasive pneumococcal infection and age-matched controls were remarkably close to ours (147). However, their study focused on smoking and probably did not have sufficient statistical power to detect any independent association between diabetes and pneumococcal bacteremia. In the Spanish cross-sectional study (134) the prevalence of bacteremia due to *S. pneumoniae* was two times increased in diabetic patients, whereas a similar study from North Carolina found similar prevalences in diabetic and non-diabetic patients (130). However, differences in age and other risk factors were not accounted for in these studies. Our relative risk estimate for pneumococcal bacteremia was somewhat lower than the risk estimates for pneumonia death in previous diabetic cohort studies (RRs between 1.5 and 2.5) (80;82;84;85), but similar to the risk estimate for pneumonia (RR= 1.5) in the population-based study by Shah et al (79). We observed a similar age-dependency as in previous studies with the highest risk estimates among young diabetic adults. In conclusion, diabetes may be a modest risk factor for community-acquired pneumococcal bacteremia, although increased surveillance may have contributed to the findings.

Diabetes as a prognostic factor

Our findings agree with the limited data available on the prognosis of pneumococcal bacteremia specifically in patients with diabetes (49;55). In one of the few studies adjusting for confounding by age and comorbidity, Watanakunakorn et al found no association (OR=1.0) between diabetes and a poor outcome of pneumococcal bacteremia (55). In Fine et al's meta-analysis of pneumonia outcome (which included 11 case series of bacteremic patients) (86), the 1.3 times increased OR for

death in diabetic patients appears rather low, given the many old studies that probably included selected diabetic patients without comorbidity adjustment. Our data combined with previous results gives strong evidence that diabetes is not associated with a worse prognosis in pneumococcal bacteremia.

Pathophysiology

Systemic pneumococcal disease will not occur without preceding colonization of the nasopharynx with the homologous strain (Bogaert 2004), whereas conversion of colonization to invasive disease is rare and in most cases requires microaspiration and multiplication of bacteria in the alveolar spaces (Dallaire 2001). In patients with diabetes, a compromised inflammatory response and macrophage function in alveoli might result in more episodes of invasive disease, but this has to our knowledge not been studied. Also, patients with diabetes may have a lower threshold of bacterial translocation into the bloodstream during less severe pneumococcal infection, due to leukocyte dysfunction and vascular changes (Marrie 1992). The antibody response directed against pneumococcal capsular polysaccharides, however, appears to be normal in presence of diabetes (83). In a recent case-control study from the UK focusing on genotypes, Roy et al reported an increased risk of invasive pneumococcal disease in patients with mannose-binding lectin deficiency (44). This common immunodeficiency has been associated with several autoimmune diseases including systemic lupus erythematosus and rheumatoid arthritis, but to our knowledge hitherto not with diabetes mellitus. It has been speculated that a less active inflammatory cascade may protect diabetic patients with sepsis against the development of acute respiratory distress syndrome (ARDS). Moss et al found that in patients with septic shock, diabetes was associated with a lower risk of developing ARDS, as compared with non-diabetic patients (194). The fact that we found a lower mortality during the first week of infection in the diabetic group could support this hypothesis, as a high proportion of fatalities in pneumococcal bacteremia is known to occur during the first few days due to organ dysfunction (142). However, CRP on admission tended to be higher in diabetic patients thus not supporting the hypothesis of a general hypoinflammation.

Community-acquired enterobacterial bacteremia

Diabetes as a risk factor

Our finding of a substantially increased risk for this group of bacteremia is consistent with suggestions from previous cross-sectional studies (130;134). In contrast to case-series especially from the Far East (157), and a previous Danish case-control study (140), diabetes tends to be a stronger risk factor for bacteremia caused by *E. coli* than by *Klebsiella* spp. in our region. Our findings support the hypothesis that urinary tract infections link diabetes with an increased risk of enterobacterial bacteremia. We further observed a similar effect modification by age as in a previous population-based study of the association between acute pyelonephritis and diabetes (92), with the highest relative impact of diabetes on the risk for enterobacterial bacteremia in adults less than 40 years of age.

Diabetes as a prognostic factor

Conflicting results on diabetes and in-hospital CF in older case-series of gram-negative bacteremia (110;137) may be due to comparison with differentially selected patients in referral hospitals, such as patients with malignancies or severe gastrointestinal diseases and related invasive procedures, since these studies dealt with both community-acquired and nosocomial gram-negative bacteremia. It is well substantiated that community-acquired bacteremic urinary tract infection is a clinically more benign disorder than gram-negative bacteremia with other foci of infection (6). We found evidence that diabetes tends to be associated with a poorer prognosis of community-acquired enterobacterial bacteremia, regardless of whether the focus of infection is within or outside the urinary tract, corroborating findings from a recent study (141).

Pathophysiology

Enterobacterial bacteremia strains originate primarily from the patient's own gastrointestinal tract (195). The composition of the gut microflora is important in preventing colonization by pathogens and may be altered by probiotics and nondigestible carbohydrates from fruit and vegetables (196). It is uncertain if these food components that may be part of recommended diabetes diets can influence the risk of enterobacterial infections in humans. Similarly to pneumococci, the key steps of colonization and invasion of the urinary tract and other foci by enterobacteria depend on a complex balance of bacterial virulence and host immunity factors, the latter being impaired in diabetes as

formerly discussed. Asymptomatic bacteriuria (ASB) seems to occur with increased prevalence in diabetic women (87), and ASB has further been shown to be a risk factor for symptomatic UTI in both diabetic and non-diabetic women (121). It is noteworthy that the impact of diabetes on the risk for enterobacterial bacteremia was – as for pyelonephritis in a prior study – highest at an age where diabetic cystopathia and indwelling catheters are unlikely to be frequent causes for urinary tract infections. The role of glucose in urine for the growth of *E. coli* and other enterobacteria *in vivo* remains undetermined (124). Concerning the prognosis of enterobacterial bacteremia, our data suggest that the poorer prognosis among diabetic patients is caused by an increased mortality during the second week of infection. As compared to pneumococcal bacteremia, the mortality of gram-negative bacteremia has been reported to increase more tardily over several weeks, in particular when originating from the urinary tract (6). We may only speculate that in pneumococcal bacteremia, a less active inflammatory cascade may protect diabetic patients against early severe manifestations of sepsis and death, while in bacteremia caused by enterobacteria, protracted multi-organ failure promoted by diabetic organ disease may play a role in the diabetic patients' higher mortality.

6.2. Perspectives

The burden and costs of community-acquired bacteremia and associated sepsis are high and estimated to increase with further population ageing (28). The same holds true for diabetes. This thesis demonstrates that diabetes may have a considerable public health impact on the risk of bacteremia with enterobacteria acquired in the community setting, potentially contributing to one tenth of episodes in our region. Conversely, diabetes is probably not a major contributor to the risk of community-acquired pneumococcal bacteremia. The observed decreasing risk estimates with increasing age in our studies must be viewed against the low absolute risk for bacteremia among young persons, and may reflect less frailty of diabetic persons reaching later age groups, or different risk patterns for patients with T1 DM compared with T2 DM. From a population perspective, a modest increase in bacteremia risk among elderly people caused by diabetes may be much more important than a many times increased risk among young diabetic subjects. For the young individual with diabetes, however, the impact on his or her risk for bacteremia may be substantial in the absence of other important risk factors.

Bacteremia may be preventable. An important issue for further studies will be the influence of long-term hyperglycemic control on both risk and prognosis of bacteremia. Observational studies based on population-based laboratory registries may yield valuable information, as randomized controlled trials of glycemic control in diabetes have largely failed to provide data on infectious diseases. The 23-valent pneumococcal vaccine is associated with a reduction of approximately 50% in the incidence of invasive pneumococcal disease among adults and the immunocompetent elderly in observational studies, whereas the vaccine's efficacy against pneumonia or death is unproven (197). It has been debated for decades if persons with diabetes should be included as a special risk group in pneumococcal immunization recommendations (198;199). The results of the present thesis might qualify these discussions. Other preventive measures for the adult diabetic patient would be to avoid risk factors for pneumococcal colonization and/or infection, e.g. crowding, active and passive smoking, influenza, and probably unnecessary antibiotic use. A recent randomized trial showed that treatment of ASB in women with diabetes unfortunately did not reduce the risk of urinary tract infection (200). Preventive measures for diabetic females might be to avoid well-known risk factors for UTI, including certain sexual "risk" behavior and use of spermicides in younger women with diabetes and unnecessary catheterizations, and to increase the surveillance for UTI even more during pregnancy.

The present studies have shown notable differences in risk and prognosis related to the microbial agent of community-acquired bacteremia in diabetic and non-diabetic subjects. Other important microbial agents including beta-hemolytic streptococci and *S. aureus* also merit study. However, these bacteria are more rare causes of community-acquired bacteremia and therefore collaborative efforts in several counties would be needed. Still, the current designs for risk and prognosis studies and the methods for data acquisition would probably be very useful.

During the last 10-15 years, the epidemiology of community-acquired bacteremia has been treated rather stepmotherly (62). Unfortunately, our knowledge about preventable or modifiable risk factors and prognostic factors for bacteremia in a population-based setting remains limited. These factors include chronic diseases other than diabetes, various medications, and lifestyle factors, information on which is contained in several Danish registries. Moreover, we are only beginning to understand the impact of genetic factors within the host's innate immune system on the risk and outcome of severe infections, at both a patient level and a population level. It is hoped that in the future, joined

efforts from disciplines including clinical-, molecular- and pharmaco-epidemiology, clinical microbiology, infectious diseases, and clinical medicine will provide new insights into the etiology, course and prevention of community-acquired bacteremia. The unique possibilities in Scandinavia and in particular Denmark for combining data from population-based registries of discharge diagnoses, prescriptions, clinical and laboratory databases will contribute to this work.

7. Summary

Epidemiological studies have shown that the prevalence of both diabetes mellitus and bacteremia/sepsis is increasing worldwide. Patients with diabetes may have an increased risk and a poorer outcome of bacteremia, due to hyperglycemia, decreased immunity, angiopathy, and diabetic complications. The aims of this thesis were; 1) to examine the association of diabetes with prognosis (study I) and risk (study II) of community-acquired pneumococcal bacteremia, and 2) to examine the association of diabetes with risk and prognosis of community-acquired bacteremia caused by *E. coli* and other enterobacteria (study III).

Our studies were based on data from the North Jutland County Bacteremia Registry, Prescription Database and Hospital Discharge Registry. Linkage between these population-based registries could be performed by use of civil registry numbers.

We conducted a prognostic cohort study among 628 patients hospitalized with community-acquired pneumococcal bacteremia in North Jutland County from January 1992 to December 2001. Ten percent had verified diabetes based on data from the Prescription Database and Hospital Discharge Registry. The predictive value of a diagnosis of diabetes identified by these registries was 97%, using WHO diagnostic criteria as gold standard in a hospital record review. After adjustment for potential confounders, the mortality rate ratio (MRR) for diabetic patients with bacteremia was 0.6 (95% confidence interval: 0.3-1.2) after both 30 and 90 days of follow-up, compared with the non-diabetic bacteremia patients. Our findings combined with previous results give strong evidence that, against common clinical belief, diabetes is not associated with a worse prognosis in pneumococcal bacteremia (study I).

The association between diabetes and the risk of community-acquired pneumococcal bacteremia was investigated in a population-based case-control design, including 10 gender- and age-matched population controls per case. We found a 50% increased risk of pneumococcal bacteremia in diabetic individuals. The odds ratio of bacteremia from diabetes was greatest among young persons and persons without other morbidity, consistent with previous studies of the effect of diabetes on pneumonia and other infections (study II).

Infections originating from the urinary tract seem to be a particular common clinical problem in diabetic patients. In a third study we included 1,317 patients with community-acquired bacteremia due to *E. coli* and other enterobacteria, combining our case-control and cohort study design. We found that diabetes was associated with a highly increased risk of enterobacterial bacteremia, with a six-fold increased risk in diabetic adults below 65 years. Even in our region with a relatively low

prevalence of diabetes, one out of every ten cases of enterobacterial bacteremia may be attributable to diabetes. In addition, diabetes was associated with a 30-40% increased mortality rate for enterobacterial bacteremia, regardless of the underlying focus of infection (study III).

In conclusion, we found evidence that diabetes mellitus may have a substantial impact on the risk for community-acquired bacteremia, at both an individual level and a population level. The association of diabetes with risk and prognosis of community-acquired bacteremia shows notable differences related to the microbial agent, underscoring the complexity of bacteremia as a disease entity. The combination of primary and secondary data sources and the epidemiological analytic strategies used proved an efficient approach to examine the association of diabetes with infection, which should be further explored in the future.

8. Danish Summary

Epidemiologiske studier har vist en stigende prævalens af både diabetes mellitus og bakteriæmi/sepsis verden over. Diabetikere har muligvis en øget risiko og forværret prognose for bakteriæmi på grund af hyperglykæmi, nedsat immunforsvar, angiopati og sendiabetiske komplikationer. Formålet med afhandlingen var at undersøge 1) associationen mellem diabetes og prognose [studie I] og risiko [studie II] for community-erhvervet pneumokokbakteriæmi, samt 2) associationen mellem diabetes og risiko og prognose for community-erhvervet bakteriæmi med *E. coli* og andre enterobakterier [studie III].

Studierne var baseret på udtræk fra den Nordjyske Bakteriæmidatabase, Lægemiddeldatabasen i Nordjyllands Amt og det Nordjyske Landspatientregister.

I det første kohortestudie indgik 628 patienter førstegangs-indlagt med community-erhvervet pneumokokbakteriæmi mellem 1992 og 2001. Ti procent havde verificeret diabetes defineret som tidligere recept på diabetesmedicin og/eller tidligere udskrivningsdiagnose med diabetes i registrene. WHO-kriterierne for diabetes var opfyldte for 97% af disse patienter ved journalgennemgang. Efter justering for mulige confoundere var diabetikeres risiko for at dø inden for 30 og 90 dage efter bakteriæmien 60% af ikke-diabetikeres (Mortalitets rate ratio = 0,6; 95% konfidensinterval: 0,3-1,2). Vores fund kombineret med tidligere resultater giver god evidens for, at diabetes - i modsætning til en udbredt klinisk opfattelse - ikke er associeret med dårligere prognose for pneumokokbakteriæmi [studie I].

Sammenhængen mellem diabetes og risikoen for community-erhvervet pneumokokbakteriæmi blev undersøgt i et populationsbaseret case-control design. Ti køns- og aldersmatchede kontroller per case blev udtrukket via CPR-registeret. Vi fandt en 50% forøget risiko for pneumokokbakteriæmi hos diabetikere. Den relative risikoøgning var størst hos yngre diabetikere og i gruppen uden anden komorbiditet, konsistent med tidligere resultater for pneumoni og andre infektioner hos diabetikere [studie II].

Urinvejsinfektioner synes at være et hyppigt problem hos diabetikere. Det tredje studie inkluderede 1.317 patienter indlagt med community-erhvervet bakteriæmi forårsaget af *E. coli* og andre enterobakterier. I denne undersøgelse kombinerede vi vores case-kontrol risikoanalyse og kohorte prognoseanalyse design. Vi fandt, at diabetes er associeret med en kraftigt forøget risiko for bakteriæmi med enterobakterier, blandt diabetikere under 65 år var risikoen således seks gange forøget i forhold til ikke-diabetikere. Vore resultater tyder på, at hvert tiende tilfælde af bakteriæmi med enterobakterier i vores region kan tilskrives diabetes. Samtidig var diabetes associeret med en

30-40% højere mortalitetsrate for denne gruppe af bakteriæmier, uafhængigt af det underliggende infektionsfokus [studie III].

Konkluderende viser vores resultater, at diabetes kan have en betydelig effekt på risikoen for community-erhvervet bakteriæmi, både på individniveau og populationsniveau. Sammenhængen mellem diabetes og bakteriæmi-risiko og -prognose varierer afhængig af det mikrobiologiske agens, hvilket understreger kompleksiteten af bakteriæmi som sygdomsenhed. Kombinationen af primære og sekundære datakilder og de epidemiologiske analysemetoder anvendt i vore studier udgør tilsammen et effektivt redskab til videre udforskning af sammenhængen mellem diabetes og infektioner.

9. References

(1) Zimmet P, Alberti KG, Shaw J. Global and societal implications of the diabetes epidemic. Nature 2001; 414(6865):782-787.

(2) Larkin JG, Frier BM, Ireland JT. Diabetes mellitus and infection. Postgrad Med J 1985; 61(713):233-237.

(3) Boyko EJ, Lipsky BA. Infection and diabetes. In: Harris MI et al, editors. Diabetes in America, 2 ed. National Institutes of Health Publication 1995, No. 95-1468: 485-499.

(4) Joshi N, Caputo GM, Weitekamp MR, Karchmer AW. Infections in patients with diabetes mellitus. N Engl J Med 1999; 341(25):1906-1912.

(5) Marrie TJ. Pneumococcal pneumonia: epidemiology and clinical features. Semin Respir Infect 1999; 14(3):227-236.

(6) Bryan CS, Reynolds KL. Community-acquired bacteremic urinary tract infection: epidemiology and outcome. J Urol 1984; 132(3):490-493.

(7) Reacher MH, Shah A, Livermore DM, Wale MC, Graham C, Johnson AP et al. Bacteraemia and antibiotic resistance of its pathogens reported in England and Wales between 1990 and 1998: trend analysis. BMJ 2000; 320(7229):213-216.

(8) Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest 1992; 101(6):1644-1655.

(9) Young LS. Sepsis syndrome. In: Mandell GL, Bennett JE, Dolin R, editors. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. 5 ed. Philadelphia: Churchill Livingstone, 2000: 806-819.

(10) Schønheyder HC. [Two thousands seven hundred and thirty nine episodes of bacteremia in the county of Northern Jutland 1996-1998. Presentation of a regional clinical database]. Ugeskr Laeger 2000; 162(20):2886-2891.

(11) Pittet D, Li N, Wenzel RP. Association of secondary and polymicrobial nosocomial bloodstream infections with higher mortality. Eur J Clin Microbiol Infect Dis 1993; 12(11):813-819.

(12) Weinstein MP, Murphy JR, Reller LB, Lichtenstein KA. The clinical significance of positive blood cultures: a comprehensive analysis of 500 episodes of bacteremia and fungemia in adults. II. Clinical observations, with special reference to factors influencing prognosis. Rev Infect Dis 1983; 5(1):54-70.

(13) Mylotte JM, Kahler L, McCann C. Community-acquired bacteremia at a teaching versus a nonteaching hospital: impact of acute severity of illness on 30-day mortality. Am J Infect Control 2001; 29(1):13-19.

(14) Pedersen G, Schønheyder HC, Sørensen HT. Source of infection and other factors associated with case fatality in community-acquired bacteremia--a Danish population-based cohort study from 1992 to 1997. Clin Microbiol Infect 2003; 9(8):793-802.

(15) Geerdes HF, Ziegler D, Lode H, Hund M, Loehr A, Fangmann W et al. Septicemia in 980 patients at a university hospital in Berlin: prospective studies during 4 selected years between 1979 and 1989. Clin Infect Dis 1992; 15(6):991-1002.

(16) Bates DW, Sands K, Miller E, Lanken PN, Hibberd PL, Graman PS et al. Predicting bacteremia in patients with sepsis syndrome. Academic Medical Center Consortium Sepsis Project Working Group. J Infect Dis 1997; 176(6):1538-1551.

(17) Brun-Buisson C, Doyon F, Carlet J, Dellamonica P, Gouin F, Lepoutre A et al. Incidence, risk factors, and outcome of severe sepsis and septic shock in adults. A multicenter prospective study in intensive care units. French ICU Group for Severe Sepsis. JAMA 1995; 274(12):968-974.

(18) Peduzzi P, Shatney C, Sheagren J, Sprung C. Predictors of bacteremia and gram-negative bacteremia in patients with sepsis. The Veterans Affairs Systemic Sepsis Cooperative Study Group. Arch Intern Med 1992; 152(3):529-535.

(19) Rangel-Frausto MS, Pittet D, Costigan M, Hwang T, Davis CS, Wenzel RP. The natural history of the systemic inflammatory response syndrome (SIRS). A prospective study. JAMA 1995; 273(2):117-123.

(20) Madsen KM, Schønheyder HC, Kristensen B, Nielsen GL, Sørensen HT. Can hospital discharge diagnosis be used for surveillance of bacteremia? A data quality study of a Danish hospital discharge registry. Infect Control Hosp Epidemiol 1998; 19(3):175-180.

(21) Arpi M, Renneberg J, Andersen HK, Nielsen B, Larsen SO. Bacteremia at a Danish university hospital during a twenty-five-year period (1968-1992). Scand J Infect Dis 1995; 27(3):245-251.

(22) Aube H, Milan C, Blettery B. Risk factors for septic shock in the early management of bacteremia. Am J Med 1992; 93(3):283-288.

(23) Bates DW, Pruess KE, Lee TH. How bad are bacteremia and sepsis? Outcomes in a cohort with suspected bacteremia. Arch Intern Med 1995; 155(6):593-598.

(24) Leibovici L, Samra Z, Konigsberger H, Drucker M, Ashkenazi S, Pitlik SD. Long-term survival following bacteremia or fungemia. JAMA 1995; 274(10):807-812.

(25) Eykyn SJ. Bacteraemia, septicaemia and endocarditis. In: Collier L, Balows A, Sussman M, editors. Topley and Wilson's microbiology and microbial infections. London: Arnold, 1998: 277-298.

(26) Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. N Engl J Med 2003; 348(16):1546-1554.

(27) Minino AM, Arias E, Kochanek KD, Murphy SL, Smith BL. Deaths: final data for 2000. Natl Vital Stat Rep 2002; 50(15):1-119.

(28) Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med 2001; 29(7):1303-1310.

(29) McGowan JE, Jr., Barnes MW, Finland M. Bacteremia at Boston City Hospital: Occurrence and mortality during 12 selected years (1935-1972), with special reference to hospital-acquired cases. J Infect Dis 1975; 132(3):316-335.

(30) Madsen KM, Schønheyder HC, Kristensen B, Sørensen HT. Secular trends in incidence and mortality of bacteraemia in a Danish county 1981-1994. APMIS 1999; 107(3):346-352.

(31) Bryan CS, Reynolds KL, Brenner ER. Analysis of 1,186 episodes of gram-negative bacteremia in non-university hospitals: the effects of antimicrobial therapy. Rev Infect Dis 1983; 5(4):629-638.

(32) Schønheyder HC, Sørensen HT, Kristensen B, Korsager B. Reasons for increase in pneumococcal bacteraemia. Lancet 1997; 349(9064):1554.

(33) Washington JA, Ilstrup DM. Blood cultures: issues and controversies. Rev Infect Dis 1986; 8(5):792-802.

(34) Prag J, Jensen J, Lebech K. Colorbact, a visually read blood culture system using darkening of haemoglobin in aerobic blood cultures as an early growth indicator, compared with Bactec 6A and 7A. APMIS 1991; 99(12):1089-1095.

(35) Haug JB, Harthug S, Kalager T, Digranes A, Solberg CO. Bloodstream infections at a Norwegian university hospital, 1974-1979 and 1988-1989: changing etiology, clinical features, and outcome. Clin Infect Dis 1994; 19(2):246-256.

(36) Fletcher RH, Fletcher SW, Wagner EH. Clinical epidemiology: the essentials. 3 ed. Baltimore: Lippincott Williams & Wilkins, 1996.

(37) Perl TM, Dvorak L, Hwang T, Wenzel RP. Long-term survival and function after suspected gram-negative sepsis. JAMA 1995; 274(4):338-345.

(38) Heyland DK, Hopman W, Coo H, Tranmer J, McColl MA. Long-term health-related quality of life in survivors of sepsis. Short Form 36: a valid and reliable measure of health-related quality of life. Crit Care Med 2000; 28(11):3599-3605.

(39) Last JM. A dictionary of epidemiology. 4 ed. New York: Oxford, 2001.

(40) Rangel-Frausto MS. The epidemiology of bacterial sepsis. Infect Dis Clin North Am 1999; 13(2):299-312, vii.

(41) Weinstein MP, Towns ML, Quartey SM, Mirrett S, Reimer LG, Parmigiani G et al. The clinical significance of positive blood cultures in the 1990s: a prospective comprehensive evaluation of the microbiology, epidemiology, and outcome of bacteremia and fungemia in adults. Clin Infect Dis 1997; 24(4):584-602.

(42) Rothman KJ. Epidemiology: an introduction. 1 ed. New York: Oxford University Press, 2002.

(43) Holmes CL, Russell JA, Walley KR. Genetic polymorphisms in sepsis and septic shock: role in prognosis and potential for therapy. Chest 2003; 124(3):1103-1115.

(44) Roy S, Knox K, Segal S, Griffiths D, Moore CE, Welsh KI et al. MBL genotype and risk of invasive pneumococcal disease: a case-control study. Lancet 2002; 359(9317):1569-1573.

(45) Kronborg G, Garred P. Mannose-binding lectin genotype as a risk factor for invasive pneumococcal infection. Lancet 2002; 360(9340):1176.

(46) Pittet D, Thievent B, Wenzel RP, Li N, Gurman G, Suter PM. Importance of pre-existing co-morbidities for prognosis of septicemia in critically ill patients. Intensive Care Med 1993; 19(5):265-272.

(47) Gatell JM, Trilla A, Latorre X, Almela M, Mensa J, Moreno A et al. Nosocomial bacteremia in a large Spanish teaching hospital: analysis of factors influencing prognosis. Rev Infect Dis 1988; 10(1):203-210.

(48) Turnidge J. Impact of antibiotic resistance on the treatment of sepsis. Scand J Infect Dis 2003; 35(9):677-682.

(49) Kalin M, Ôrtqvist Å, Almela M, Aufwerber E, Dwyer R, Henriques B et al. Prospective study of prognostic factors in community-acquired bacteremic pneumococcal disease in 5 countries. J Infect Dis 2000; 182(3):840-847.

(50) Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med 1985; 13(10):818-829.

(51) Le Gall JR, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. JAMA 1993; 270(24):2957-2963.

(52) Afessa B, Greaves WL, Frederick WR. Pneumococcal bacteremia in adults: a 14-year experience in an inner-city university hospital. Clin Infect Dis 1995; 21(2):345-351.

(53) Balakrishnan I, Crook P, Morris R, Gillespie SH. Early predictors of mortality in pneumococcal bacteraemia. J Infect 2000; 40(3):256-261.

(54) Kuikka A, Syrjanen J, Renkonen OV, Valtonen VV. Pneumococcal bacteraemia during a recent decade. J Infect 1992; 24(2):157-168.

(55) Watanakunakorn C, Greifenstein A, Stroh K, Jarjoura DG, Blend D, Cugino A et al. Pneumococcal bacteremia in three community teaching hospitals from 1980 to 1989. Chest 1993; 103(4):1152-1156.

(56) Povoa P. C-reactive protein: a valuable marker of sepsis. Intensive Care Med 2002; 28(3):235-243.

(57) Almirall J, Bolibar I, Toran P, Pera G, Boquet X, Balanzo X et al. Contribution of C-reactive protein to the diagnosis and assessment of severity of community-acquired pneumonia. Chest 2004; 125(4):1335-1342.

(58) Oberhoffer M, Vogelsang H, Russwurm S, Hartung T, Reinhart K. Outcome prediction by traditional and new markers of inflammation in patients with sepsis. Clin Chem Lab Med 1999; 37(3):363-368.

(59) Sackett DL, Haynes RB, Guyatt GH, Tugwell P. Clinical epidemiology: a basic science for clinical medicine. 2 ed. Philadelphia: Lippincott-Raven, 1991.

(60) Hotchkiss RS, Karl IE. The pathophysiology and treatment of sepsis. N Engl J Med 2003; 348(2):138-150.

(61) Sasse KC, Nauenberg E, Long A, Anton B, Tucker HJ, Hu TW. Long-term survival after intensive care unit admission with sepsis. Crit Care Med 1995; 23(6):1040-1047.

(62) Mylotte JM, Kahler L, McCann C. Community-acquired bacteremia at a teaching versus a nonteaching hospital: impact of acute severity of illness on 30-day mortality. Am J Infect Control 2001; 29(1):13-19.

(63) King H, Aubert RE, Herman WH. Global burden of diabetes, 1995-2025: prevalence, numerical estimates, and projections. Diabetes Care 1998; 21(9):1414-1431.

(64) Støvring H, Andersen M, Beck-Nielsen H, Green A, Vach W. Rising prevalence of diabetes: evidence from a Danish pharmaco-epidemiological database. Lancet 2003; 362(9383):537-538.

(65) Almdal T, Scharling H, Jensen JS, Vestergaard H. The independent effect of type 2 diabetes mellitus on ischemic heart disease, stroke, and death: a population-based study of 13,000 men and women with 20 years of follow-up. Arch Intern Med 2004; 164(13):1422-1426.

(66) Powers AC. Diabetes mellitus. In: Braunwald E et al, editors. Harrison's principles of internal medicine. Online edition. McGraw-Hill, 2004: chapter 333.

(67) Pedersen OB, Beck-Nielsen H, Mandrup-Poulsen T, Flyvbjerg A. Diabetes mellitus. In: Hansen NE, Haunsø S, Schaffalitzky de Muckadell OB, editors. Medicinsk kompendium. 16 ed. Copenhagen: Nyt Nordisk Forlag Arnold Busck, 2004: 2396-2446.

(68) Prevalence of diabetes and impaired fasting glucose in adults--United States, 1999-2000. MMWR Morb Mortal Wkly Rep 2003; 52(35):833-837.

(69) Green A, Christian HN, Pramming SK. The changing world demography of type 2 diabetes. Diabetes Metab Res Rev 2003; 19(1):3-7.

(70) Flegal KM, Carroll MD, Ogden CL, Johnson CL. Prevalence and trends in obesity among US adults, 1999-2000. JAMA 2002; 288(14):1723-1727.

(71)   Onkamo P, Vaananen S, Karvonen M, Tuomilehto J. Worldwide increase in incidence of Type I diabetes--the analysis of the data on published incidence trends. Diabetologia 1999; 42(12):1395-1403.

(72)   Flynn JM. The changing cause of death in diabetes mellitus. American Journal of the Medical Sciences 1935; 189:157.

(73)   Joslin EP. The treatment of diabetes mellitus with observations based upon thirteen hundred cases. 2 ed. Philadelphia: Lea and Febiger, 1917.

(74)   Jacobsen ATB. Varige resultater af insulinbehandlingen. Hospitalstidende 1928; 33:20-28.

(75)   Pontin AR, Barnes RD, Joffe J, Kahn D. Emphysematous pyelonephritis in diabetic patients. Br J Urol 1995; 75(1):71-74.

(76)   Gill GV, Famuyiwa OO, Rolfe M, Archibald LK. Tropical diabetic hand syndrome. Lancet 1998; 351(9096):113-114.

(77)   Joshi N, Mahajan M. Infection and diabetes. In: Pickup JC, Williams G, editors. Textbook of diabetes. Oxford: Blackwell Science, 2003: 1-16.

(78)   Tan JS. Infectious complications in patients with diabetes mellitus. International Diabetes Monitor 2000; 12(2):1-7.

(79)   Shah BR, Hux JE. Quantifying the risk of infectious diseases for people with diabetes. Diabetes Care 2003; 26(2):510-513.

(80)   Gu K, Cowie CC, Harris MI. Mortality in adults with and without diabetes in a national cohort of the U.S. population, 1971-1993. Diabetes Care 1998; 21(7):1138-1145.

(81)   Bertoni AG, Saydah S, Brancati FL. Diabetes and the risk of infection-related mortality in the U.S. Diabetes Care 2001; 24(6):1044-1049.

(82)   Weiderpass E, Gridley G, Nyren O, Pennello G, Landstrom AS, Ekbom A. Cause-specific mortality in a cohort of patients with diabetes mellitus: a population-based study in Sweden. J Clin Epidemiol 2001; 54(8):802-809.

(83)   Smith SA, Poland GA. Use of influenza and pneumococcal vaccines in people with diabetes. Diabetes Care 2000; 23(1):95-108.

(84)   Moss SE, Klein R, Klein BE. Cause-specific mortality in a population-based study of diabetes. Am J Public Health 1991; 81(9):1158-1162.

(85)   Swerdlow AJ, Jones ME. Mortality during 25 years of follow-up of a cohort with diabetes. Int J Epidemiol 1996; 25(6):1250-1261.

(86)   Fine MJ, Smith MA, Carson CA, Mutha SS, Sankey SS, Weissfeld LA et al. Prognosis and outcomes of patients with community-acquired pneumonia. A meta-analysis. JAMA 1996; 275(2):134-141.

(87)   Geerlings SE, Stolk RP, Camps MJ, Netten PM, Hoekstra JB, Bouter KP et al. Asymptomatic bacteriuria may be considered a complication in women with diabetes. Diabetes Mellitus Women Asymptomatic Bacteriuria Utrecht Study Group. Diabetes Care 2000; 23(6):744-749.

(88)   Makuyana D, Mhlabi D, Chipfupa M, Munyombwe T, Gwanzura L. Asymptomatic bacteriuria among outpatients with diabetes mellitus in an urban black population. Cent Afr J Med 2002; 48(7-8):78-82.

(89)   Bonadio M, Boldrini E, Forotti G, Matteucci E, Vigna A, Mori S et al. Asymptomatic bacteriuria in women with diabetes: influence of metabolic control. Clin Infect Dis 2004; 38(6):e41-e45.

(90) Boyko EJ, Fihn SD, Scholes D, Chen CL, Normand EH, Yarbro P. Diabetes and the risk of acute urinary tract infection among postmenopausal women. Diabetes Care 2002; 25(10):1778-1783.

(91) Robbins SL, Tucker AW. The cause of death in diabetes. N Engl J Med 1944; 231:865-868.

(92) Nicolle LE, Friesen D, Harding GK, Roos LL. Hospitalization for acute pyelonephritis in Manitoba, Canada, during the period from 1989 to 1992; impact of diabetes, pregnancy, and aboriginal origin. Clin Infect Dis 1996; 22(6):1051-1056.

(93) Delamaire M, Maugendre D, Moreno M, Le Goff MC, Allannic H, Genetet B. Impaired leucocyte functions in diabetic patients. Diabet Med 1997; 14(1):29-34.

(94) Kjersem H, Hilsted J, Madsbad S, Wandall JH, Johansen KS, Borregaard N. Polymorphonuclear leucocyte dysfunction during short term metabolic changes from normo- to hyperglycemia in type 1 (insulin dependent) diabetic patients. Infection 1988; 16(4):215-221.

(95) Marhoffer W, Stein M, Schleinkofer L, Federlin K. Evidence of ex vivo and in vitro impaired neutrophil oxidative burst and phagocytic capacity in type 1 diabetes mellitus. Diabetes Res Clin Pract 1993; 19(3):183-188.

(96) Leibovici L, Yehezkelli Y, Porter A, Regev A, Krauze I, Harell D. Influence of diabetes mellitus and glycaemic control on the characteristics and outcome of common infections. Diabet Med 1996; 13(5):457-463.

(97) Rayfield EJ, Ault MJ, Keusch GT, Brothers MJ, Nechemias C, Smith H. Infection and diabetes: the case for glucose control. Am J Med 1982; 72(3):439-450.

(98) Perioperative total parenteral nutrition in surgical patients. The Veterans Affairs Total Parenteral Nutrition Cooperative Study Group. N Engl J Med 1991; 325(8):525-532.

(99) Moore FA, Feliciano DV, Andrassy RJ, McArdle AH, Booth FV, Morgenstein-Wagner TB et al. Early enteral feeding, compared with parenteral, reduces postoperative septic complications. The results of a meta-analysis. Ann Surg 1992; 216(2):172-183.

(100) Furnary AP, Zerr KJ, Grunkemeier GL, Starr A. Continuous intravenous insulin infusion reduces the incidence of deep sternal wound infection in diabetic patients after cardiac surgical procedures. Ann Thorac Surg 1999; 67(2):352-360.

(101) Van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M et al. Intensive insulin therapy in critically ill patients. N Engl J Med 2001; 345(19):1359-1367.

(102) Das UN. Is insulin an antiinflammatory molecule? Nutrition 2001; 17(5):409-413.

(103) Campbell IW, Munro JF, McCuish AC, Duncan LJ. Infection and severe diabetic metabolic decompensation. Practitioner 1974; 213(1278):813-818.

(104) Soler NG, Bennett MA, Fitzgerald MG, Malins JM. Intensive care in the management of diabetic ketoacidosis. Lancet 1973; 1(7810):951-954.

(105) Watkins PJ, Soler NG, Fitzgerald MG, Malins JM. Diabetic ketoacidosis during the influenza epidemic. BMJ 1970; 4(727):89-91.

(106) Azoulay E, Chevret S, Didier J, Barboteu M, Bornstain C, Darmon M et al. Infection as a trigger of diabetic ketoacidosis in intensive care-unit patients. Clin Infect Dis 2001; 32(1):30-35.

(107) Gogos CA, Giali S, Paliogianni F, Dimitracopoulos G, Bassaris HP, Vagenakis AG. Interleukin-6 and C-reactive protein as early markers of sepsis in patients with diabetic ketoacidosis or hyperosmosis. Diabetologia 2001; 44(8):1011-1014.

(108) Johnston CLW. Infection and diabetes mellitus. In: Pickup J, Williams G, editors. Textbook of diabetes. Oxford: Blackwell Science, 1997: 1-14.

(109) Kieft H, Hoepelman AI, Zhou W, Rozenberg-Arska M, Struyvenberg A, Verhoef J. The sepsis syndrome in a Dutch university hospital. Clinical observations. Arch Intern Med 1993; 153(19):2241-2247.

(110) Kreger BE, Craven DE, McCabe WR. Gram-negative bacteremia. IV. Re-evaluation of clinical features and treatment in 612 patients. Am J Med 1980; 68(3):344-355.

(111) Leibovici L. Bacteraemia in the very old. Features and treatment. Drugs Aging 1995; 6(6):456-464.

(112) Sarnak MJ, Jaber BL. Mortality caused by sepsis in patients with end-stage renal disease compared with the general population. Kidney Int 2000; 58(4):1758-1764.

(113) Jaar BG, Hermann JA, Furth SL, Briggs W, Powe NR. Septicemia in diabetic hemodialysis patients: comparison of incidence, risk factors, and mortality with nondiabetic hemodialysis patients. Am J Kidney Dis 2000; 35(2):282-292.

(114) Selby JV, Karter AJ, Ackerson LM, Ferrara A, Liu J. Developing a prediction rule from automated clinical databases to identify high-risk patients in a large population with diabetes. Diabetes Care 2001; 24(9):1547-1555.

(115) Stapleton A. Urinary tract infections in patients with diabetes. Am J Med 2002; 113 Suppl 1A:80S-84S.

(116) Roghmann MC, Siddiqui A, Plaisance K, Standiford H. MRSA colonization and the risk of MRSA bacteraemia in hospitalized patients with chronic ulcers. J Hosp Infect 2001; 47(2):98-103.

(117) Lipsky BA, Pecoraro RE, Chen MS, Koepsell TD. Factors affecting staphylococcal colonization among NIDDM outpatients. Diabetes Care 1987; 10(4):483-486.

(118) Willis AM, Coulter WA, Fulton CR, Hayes JR, Bell PM, Lamey PJ. Oral candidal carriage and infection in insulin-treated diabetic patients. Diabet Med 1999; 16(8):675-679.

(119) Vejlsgaard R. Studies on urinary infection in diabetics. I. Bacteriuria in patients with diabetes mellitus and in control subjects. Acta Med Scand 1966; 179(2):173-182.

(120) Von Eiff C, Becker K, Machka K, Stammer H, Peters G. Nasal carriage as a source of Staphylococcus aureus bacteremia. N Engl J Med 2001; 344(1):11-16.

(121) Geerlings SE, Stolk RP, Camps MJ, Netten PM, Collet JT, Schneeberger PM et al. Consequences of asymptomatic bacteriuria in women with diabetes mellitus. Arch Intern Med 2001; 161(11):1421-1427.

(122) Monami M, Mannucci E, Masotti G. Finger sepsis in two poorly controlled diabetic patients with reuse of lancets. Diabetes Care 2002; 25(6):1103.

(123) Hostetter MK. Handicaps to host defense. Effects of hyperglycemia on C3 and Candida albicans. Diabetes 1990; 39(3):271-275.

(124) Geerlings SE, Brouwer EC, Gaastra W, Verhoef J, Hoepelman AI. Effect of glucose and pH on uropathogenic and non-uropathogenic Escherichia coli: studies with urine from diabetic and non-diabetic individuals. J Med Microbiol 1999; 48(6):535-539.

(125) Geerlings SE, Meiland R, van Lith EC, Brouwer EC, Gaastra W, Hoepelman AI. Adherence of type 1-fimbriated Escherichia coli to uroepithelial cells: more in diabetic women than in control subjects. Diabetes Care 2002; 25(8):1405-1409.

(126) Wright SW, Wrenn KD, Haynes M, Haas DW. Prevalence and risk factors for multidrug resistant uropathogens in ED patients. Am J Emerg Med 2000; 18(2):143-146.

(127) Horcajada JP, Moreno I, Velasco M, Martinez JA, Moreno-Martinez A, Barranco M et al. Community-acquired febrile urinary tract infection in diabetics could deserve a different management: a case-control study. J Intern Med 2003; 254(3):280-286.

(128) Colodner R, Rock W, Chazan B, Keller N, Guy N, Sakran W et al. Risk factors for the development of extended-spectrum beta-lactamase-producing bacteria in nonhospitalized patients. Eur J Clin Microbiol Infect Dis 2004; 23(3):163-167.

(129) Aubertin J, Gin H, Ragnaud JM, Bonnal F, Lacut JY, Loste P. [Septicemia and diabetes]. Rev Med Interne 1982; 3(2):177-183.

(130) Bryan CS, Reynolds KL, Metzger WT. Bacteremia in diabetic patients: comparison of incidence and mortality with nondiabetic patients. Diabetes Care 1985; 8(3):244-249.

(131) MacFarlane IA, Brown RM, Smyth RW, Burdon DW, Fitzgerald MG. Bacteraemia in diabetics. J Infect 1986; 12(3):213-219.

(132) Leibovici L, Samra Z, Konisberger H, Kalter-Leibovici O, Pitlik SD, Drucker M. Bacteremia in adult diabetic patients. Diabetes Care 1991; 14(2):89-94.

(133) Guérin JM. Septicémies chez le diabétique. Réan Soins Intens Méd Urg 1992; 8(3):142-145.

(134) Carton JA, Maradona JA, Nuno FJ, Fernandez-Alvarez R, Perez-Gonzalez F, Asensi V. Diabetes mellitus and bacteraemia: a comparative study between diabetic and non-diabetic patients. Eur J Med 1992; 1(5):281-287.

(135) Akbar DH. Adult bacteremia - Comparative study between diabetic and non-diabetic patients. Saudi Medical Journal 2000; 21(1):40-44.

(136) Abbott KC, Oliver JD, III, Hypolite I, Lepler LL, Kirk AD, Ko CW et al. Hospitalizations for bacterial septicemia after renal transplantation in the united states. Am J Nephrol 2001; 21(2):120-127.

(137) DuPont HL, Spink WW. Infections due to gram-negative organisms: an analysis of 860 patients with bacteremia at the University of Minnesota Medical Center, 1958- 1966. Medicine (Baltimore) 1969; 48(4):307-332.

(138) Uzun O, Akalin HE, Hayran M, Unal S. Factors influencing prognosis in bacteremia due to gram-negative organisms: evaluation of 448 episodes in a Turkish university hospital. Clin Infect Dis 1992; 15(5):866-873.

(139) Olesen B, Kolmos HJ, Ørskov F, Ørskov I, Gottschau A. Bacteraemia due to Escherichia coli in a Danish university hospital, 1986-1990. Scand J Infect Dis 1995; 27(3):253-257.

(140) Hansen DS, Gottschau A, Kolmos HJ. Epidemiology of Klebsiella bacteraemia: a case control study using Escherichia coli bacteraemia as control. J Hosp Infect 1998; 38(2):119-132.

(141) Graff LR, Franklin KK, Witt L, Cohen N, Jacobs RA, Tompkins L et al. Antimicrobial therapy of gram-negative bacteremia at two university-affiliated medical centers. Am J Med 2002; 112(3):204-211.

(142) Austrian R, Gold J. Pneumococcal bacteremia with especial reference to bacteremic pneumococcal pneumonia. Ann Intern Med 1964; 60:759-76.

(143) Mufson MA, Kruss DM, Wasil RE, Metzger WI. Capsular types and outcome of bacteremic pneumococcal disease in the antibiotic era. Arch Intern Med 1974; 134(3):505-510.

(144) Gransden WR, Eykyn SJ, Phillips I. Pneumococcal bacteraemia: 325 episodes diagnosed at St Thomas's Hospital. BMJ (Clin Res Ed) 1985; 290(6467):505-508.

(145) Burman LA, Norrby R, Trollfors B. Invasive pneumococcal infections: incidence, predisposing factors, and prognosis. Rev Infect Dis 1985; 7(2):133-142.

(146) Dahl MS, Trollfors B, Claesson BA, Brandberg LL, Rosengren A. Invasive pneumococcal infections in Southwestern Sweden: a second follow-up period of 15 years. Scand J Infect Dis 2001; 33(9):667-672.

(147) Nuorti JP, Butler JC, Farley MM, Harrison LH, McGeer A, Kolczak MS et al. Cigarette smoking and invasive pneumococcal disease. Active Bacterial Core Surveillance Team. N Engl J Med 2000; 342(10):681-689.

(148) Community-acquired pneumonia in adults in British hospitals in 1982-1983: a survey of aetiology, mortality, prognostic factors and outcome. The British Thoracic Society and the Public Health Laboratory Service. Q J Med 1987; 62(239):195-220.

(149) Basi SK, Marrie TJ, Huang JQ, Majumdar SR. Patients admitted to hospital with suspected pneumonia and normal chest radiographs: Epidemiology, microbiology, and outcomes. Am J Med 2004; 117(5):305-311.

(150) Marrie TJ. Bacteraemic pneumococcal pneumonia: a continuously evolving disease. J Infect 1992; 24(3):247-255.

(151) Nielsen SV, Henrichsen J. Incidence of invasive pneumococcal disease and distribution of capsular types of pneumococci in Denmark, 1989-94. Epidemiol Infect 1996; 117(3):411-416.

(152) Valdez R, Narayan KM, Geiss LS, Engelgau MM. Impact of diabetes mellitus on mortality associated with pneumonia and influenza among non-Hispanic black and white US adults. Am J Public Health 1999; 89(11):1715-1721.

(153) Fine MJ, Smith DN, Singer DE. Hospitalization decision in patients with community-acquired pneumonia: a prospective cohort study. Am J Med 1990; 89(6):713-721.

(154) Koziel H, Koziel MJ. Pulmonary complications of diabetes mellitus. Pneumonia. Infect Dis Clin North Am 1995; 9(1):65-96.

(155) Patterson JE, Andriole VT. Bacterial urinary tract infections in diabetes. Infect Dis Clin North Am 1997; 11(3):735-750.

(156) Ronald A, Ludwig E. Urinary tract infections in adults with diabetes. Int J Antimicrob Agents 2001; 17(4):287-292.

(157) Ko WC, Paterson DL, Sagnimeni AJ, Hansen DS, Von Gottberg A, Mohapatra S et al. Community-acquired Klebsiella pneumoniae bacteremia: global differences in clinical patterns. Emerg Infect Dis 2002; 8(2):160-166.

(158) Rothman KJ, Greenland S. Modern epidemiology. 2 ed. Philadelphia: Lippincott-Raven, 1998.

(159) Guerin JM. Bacteraemia in diabetic patients: comparison with non-diabetic patients. Eur J Med 1993; 2(1):62-63.

(160) Pedersen G, Schønheyder HC. Patients with bacteremia dying before notification of positive blood cultures: a 3-year clinical study. Scand J Infect Dis 1997; 29(2):169-173.

(161) Roberts FJ, Geere IW, Coldman A. A three-year study of positive blood cultures, with emphasis on prognosis. Rev Infect Dis 1991; 13(1):34-46.

(162)   Mortensen EM, Coley CM, Singer DE, Marrie TJ, Obrosky DS, Kapoor WN et al. Causes of death for patients with community-acquired pneumonia: results from the Pneumonia Patient Outcomes Research Team cohort study. Arch Intern Med 2002; 162(9):1059-1064.

(163)   Mylotte JM, Tayara A. Staphylococcus aureus bacteremia: predictors of 30-day mortality in a large cohort. Clin Infect Dis 2000; 31(5):1170-1174.

(164)   Hanon FX, Monnet DL, Sørensen TL, Mølbak K, Pedersen G, Schønheyder H. Survival of patients with bacteraemia in relation to initial empirical antimicrobial treatment. Scand J Infect Dis 2002; 34(7):520-528.

(165)   Frank L. Epidemiology. When an entire country is a cohort. Science 2000; 287(5462):2398-2399.

(166)   Schønheyder HC, Højbjerg T. The impact of the first notification of positive blood cultures on antibiotic therapy. A one-year survey. APMIS 1995; 103(1):37-44.

(167)   Nielsen GL, Sørensen HT, Zhou W, Steffensen FH, Olsen J. The Pharmacoepidemiologic Prescription Database of North Jutland - a valid tool in pharmacoepidemiological research. Int J Risk Safety Med 1997; 10:203-205.

(168)   Pedersen G, Schønheyder HC, Steffensen FH, Sørensen HT. Risk of resistance related to antibiotic use before admission in patients with community-acquired bacteraemia. J Antimicrob Chemother 1999; 43(1):119-126.

(169)   Andersen TF, Madsen M, Jørgensen J, Mellemkjær L, Olsen JH. The Danish National Hospital Register. A valuable source of data for modern health sciences. Dan Med Bull 1999; 46(3):263-268.

(170)   Sørensen HT. Regional administrative health registries as a resource in clinical epidemiology. Int J Risk Safety Med 1997; 10:1-22.

(171)   Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections, 1988. Am J Infect Control 1988; 16(3):128-140.

(172)   Friedman ND, Kaye KS, Stout JE, McGarry SA, Trivette SL, Briggs JP et al. Health care--associated bloodstream infections in adults: a reason to change the accepted definition of community-acquired infections. Ann Intern Med 2002; 137(10):791-797.

(173)   Kristensen B, Højbjerg T, Schønheyder HC. Rapid immunodiagnosis of streptococci and enterococci in blood cultures. APMIS 2001; 109(4):284-288.

(174)   Farmer JJ, III, Davis BR, Hickman-Brenner FW, McWhorter A, Huntley-Carter GP, Asbury MA et al. Biochemical identification of new species and biogroups of Enterobacteriaceae isolated from clinical specimens. J Clin Microbiol 1985; 21(1):46-76.

(175)   Holmes B, Costas M, Thaker T, Stevens M. Evaluation of two BBL Crystal systems for identification of some clinically important gram-negative bacteria. J Clin Microbiol 1994; 32(9):2221-2224.

(176)   Jensen AG, Wachmann CH, Poulsen KB, Espersen F, Scheibel J, Skinhøj P et al. Risk factors for hospital-acquired Staphylococcus aureus bacteremia. Arch Intern Med 1999; 159(13):1437-1444.

(177)   Hindsholm M, Schønheyder HC. Clinical presentation and outcome of bacteraemia caused by beta-haemolytic streptococci serogroup G. APMIS 2002; 110(7-8):554-558.

(178)   Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987; 40(5):373-383.

(179)   Thulstrup AM, Sørensen HT, Schønheyder HC, Møller JK, Tage-Jensen U. Population-based study of the risk and short-term prognosis for bacteremia in patients with liver cirrhosis. Clin Infect Dis 2000; 31(6):1357-1361.

(180)   Halfon P, Eggli Y, van Melle G, Chevalier J, Wasserfallen JB, Burnand B. Measuring potentially avoidable hospital readmissions. J Clin Epidemiol 2002; 55(6):573-587.

(181)   De Groot V, Beckerman H, Lankhorst GJ, Bouter LM. How to measure comorbidity: a critical review of available methods. J Clin Epidemiol 2003; 56(3):221-229.

(182)   Lesens O, Methlin C, Hansmann Y, Remy V, Martinot M, Bergin C et al. Role of comorbidity in mortality related to Staphylococcus aureus bacteremia: a prospective study using the Charlson weighted index of comorbidity. Infect Control Hosp Epidemiol 2003; 24(12):890-896.

(183)   Wacholder S, McLaughlin JK, Silverman DT, Mandel JS. Selection of controls in case-control studies. I. Principles. Am J Epidemiol 1992; 135(9):1019-1028.

(184)   Szklo M, Nieto FJ. Epidemiology: Beyond the Basics. 1 ed. Gaithersburg, Maryland: Aspen Publishers, 2000.

(185)   World Health Organisation. Diabetes Mellitus: Report of a WHO Study Group. Geneva, World Health Organisation, 1985 (Tech. Rep. Ser., no. 727, 1-104).

(186)   DECODE Study Group on behalf of the European Diabetes Epidemiology Study Group. Will new diagnostic criteria for diabetes mellitus change phenotype of patients with diabetes? Reanalysis of European epidemiological data. BMJ 1998; 317(7155):371-375.

(187)   Kristensen JK, Sandbæk A, Lassen JF, Bro F, Lauritzen T. Use and validation of public data files for identification of the diabetic population in a Danish county. Dan Med Bull 2001; 48(1):33-37.

(188)   Schneeweiss S, Wang PS, Avorn J, Glynn RJ. Improved comorbidity adjustment for predicting mortality in Medicare populations. Health Serv Res 2003; 38(4):1103-1120.

(189)   Liappis AP, Kan VL, Rochester CG, Simon GL. The effect of statins on mortality in patients with bacteremia. Clin Infect Dis 2001; 33(8):1352-1357.

(190)   Dear K, Holden J, Andrews R, Tatham D. Vaccines for preventing pneumococcal infection in adults. Cochrane Database Syst Rev 2003;(4):CD000422.

(191)   Danish Medicines Agency. Lægemiddelstatistik, amtsfordelt: den primære sundhedssektor og sygehussektoren. Available from http://www.laegemiddelstyrelsen.dk/statistik/aarsstatistik.asp. Accessed 11 August 2003.

(192)   Baik I, Curhan GC, Rimm EB, Bendich A, Willett WC, Fawzi WW. A prospective study of age and lifestyle factors in relation to community-acquired pneumonia in US men and women. Arch Intern Med 2000; 160(20):3082-3088.

(193)   Hooton TM, Scholes D, Hughes JP, Winter C, Roberts PL, Stapleton AE et al. A prospective study of risk factors for symptomatic urinary tract infection in young women. N Engl J Med 1996; 335(7):468-474.

(194)   Moss M, Guidot DM, Steinberg KP, Duhon GF, Treece P, Wolken R et al. Diabetic patients have a decreased incidence of acute respiratory distress syndrome. Crit Care Med 2000; 28(7):2187-2192.

(195)   Olesen B, Kolmos HJ, Ørskov F, Ørskov I. A comparative study of nosocomial and community-acquired strains of Escherichia coli causing bacteraemia in a Danish University Hospital. J Hosp Infect 1995; 31(4):295-304.

(196) Gibson GR. Dietary modulation of the human gut microflora using the prebiotics oligofructose and inulin. J Nutr 1999; 129(7 Suppl):1438S-1441S.

(197) Mangtani P, Cutts F, Hall AJ. Efficacy of polysaccharide pneumococcal vaccine in adults in more developed countries: the state of the evidence. Lancet Infect Dis 2003; 3(2):71-78.

(198) Austrian R, Winegrad AI. Diabetes mellitus and the pneumococcus. Another point of view. JAMA 1980; 244(14):1573-1574.

(199) Moss JM. Pneumococcus infection in diabetes mellitus. Is this a justification for immunization? JAMA 1980; 243(22):2301-2303.

(200) Harding GK, Zhanel GG, Nicolle LE, Cheang M. Antimicrobial treatment in diabetic women with asymptomatic bacteriuria. N Engl J Med 2002; 347(20):1576-1583.

10. Appendix

Translation of disease categories in the Charlson index into discharge diagnoses in
ICD-8 and ICD-10.

Disease category	ICD8	ICD10
Myocardial infarction	410	I21;I22;I23
Congestive heart failure	427.09; 427.10; 427.11; 427.19; 428.99; 782.49	I50; I11.0; I13.0; I13.2
Peripheral vascular disease	440; 441; 442; 443; 444; 445	I70; I71; I72; I73; I74; I77
Cerebrovascular disease	430-438	I60-I69; G45; G46
Dementia	290.09-290.19; 293.09	F00-F03; F05.1; G30
Chronic pulmonary disease	490-493; 515-518	J40-J47; J60-J67; J68.4; J70.1; J70.3; J84.1; J92.0; J96.1; J98.2; J98.3
Connective tissue disease	712; 716; 734; 446; 135.99	M05; M06; M08; M09;M30;M31; M32; M33; M34; M35; M36; D86
Ulcer disease	530.91; 530.98; 531-534	K22.1; K25-K28
Mild liver disease	571; 573.01; 573.04	B18; K70.0-K70.3; K70.9; K71; K73; K74; K76.0
Diabetes type1	249.00; 249.06; 249.07; 249.09	E10.0, E10.1; E10.9
Diabetes type2	250.00; 250.06; 250.07; 250.09	E11.0; E11.1; E11.9
Hemiplegia	344	G81; G82
Moderate to severe renal disease	403; 404; 580-583; 584; 590.09; 593.19; 753.10-753.19; 792	I12; I13; N00-N05; N07; N11; N14; N17-N19; Q61
Diabetes with end organ damage type1 type2	249.01-249.05; 249.08 250.01-250.05; 250.08	E10.2-E10.8 E11.2-E11.8
Any tumor	140-194	C00-C75
Leukemia	204-207	C91-C95
Lymphoma	200-203; 275.59	C81-C85; C88; C90; C96
Moderate to severe liver disease	070.00; 070.02; 070.04; 070.06; 070.08; 573.00; 456.00-456.09	B15.0; B16.0; B16.2; B19.0; K70.4; K72; K76.6; I85
Metastatic solid tumor	195-198; 199	C76-C80
AIDS	079.83	B21-B24