Risk of Community-Acquired Pneumococcal Bacteremia in Patients With Diabetes

A population-based case-control study

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OBJECTIVE — We conducted this population-based case-control study to examine whether diabetes is associated with an increased risk of community-acquired pneumococcal bacteremia.

RESEARCH DESIGN AND METHODS — We included 598 cases in the North Jutland County Bacteremia Registry, Denmark, with residence in the county and a first hospitalization for community-acquired pneumococcal bacteremia from 1992 through 2001. Ten sex- and age-matched population control subjects per case were selected, using a unique personal identifier. Diabetes was determined by record linkage with the County Prescription Database (for prescriptions for antidiabetic drugs) and the Hospital Discharge Registry (for previous hospitalizations with diabetes or diabetic complications). We performed conditional logistic regression to estimate odds ratios (ORs) for pneumococcal bacteremia among diabetic and nondiabetic persons, with adjustment for a range of comorbid diseases considered to be risk factors for pneumococcal infection.

RESULTS — The crude OR for pneumococcal bacteremia in persons 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). The impact of diabetes on the risk for pneumococcal bacteremia was most pronounced in adults aged 40 years 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). Under the assumptions that the association was causal and that there is a 5% overall prevalence of diabetes in our study population, 24 of 1,000 admissions with incident pneumococcal bacteremia may be attributed to diabetes.

CONCLUSIONS — Diabetes seems to be a risk factor for community-acquired pneumococcal bacteremia.

Diabetes Care **27:1143–1147, 2004**

It remains uncertain whether diabetes is a risk factor for invasive pneumococcal infection, as presumed in immunization recommendations (1). Several biological mechanisms may contribute to an increased risk of bacterial infection in diabetic patients. Hyperglycemia can impair a range of functions in neutrophils and macrophages in vitro, including chemotaxis, adherence, phagocytosis, and intracellular killing of microorganisms, which may be important in limiting invasion by bacteria in vivo (2). Further, decreased immunity, pulmonary microangiopathy, and reduced lung function have been suggested to predispose diabetic patients to lower respiratory tract infections (3).

Recently, we showed that among patients with pneumococcal bacteremia, diabetes was not associated with a higher case-fatality (mortality rate ratio after 90 days = 0.6 [95% CI 0.3–1.2]) (4). Data about diabetes and the risk of pneumococcal infection come primarily from case series. As reviewed by Smith and Poland (5), the reported prevalence of diabetes in these series has varied from 1 to 20%, depending on the patients' age, type of hospital, study period, and country, as well as methods for ascertainment of diabetes. It is not clear whether any apparent association between diabetes and pneumococcal bacteremia in the studies is causal or related to the existence of confounding factors, since no control groups have been used. Other diseases that have been suggested as risk factors for pneumococcal bacteremia are congestive heart failure, chronic obstructive pulmonary disease, malignancies (pulmonary, hematological, and other), alcohol abuse, cerebrovascular disease, liver cirrhosis, and HIV infection (6–11).

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, the self-reported occurrence of diabetes was 10% in cases and 4% in control subjects (odds ratio [OR] 2.5, 95% CI 1.2–5.1). However, after adjusting diabetes for other variables including race, sex, and comorbidity, the authors reported that the association was no longer significant (risk estimates not given) (12). Thus, few if any other population-based studies within a proper epidemiological design exist about this issue. We therefore conducted a population-based case-control study in Denmark to examine whether patients with diabetes have an increased risk of com-

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Received for publication 28 November 2003 and accepted in revised form 6 February 2004.

Abbreviations: PAR, population-attributable risk.

munity-acquired pneumococcal bacteremia, as compared with persons without diabetes.

RESEARCH DESIGN AND METHODS

— The study was conducted during 1992–2001 in North Jutland County, Denmark, within a population of 496,000 inhabitants, ~9% of the total Danish population. The study population was homogeneous Caucasian (96.7% inhabitants were of Danish origin by 1 January 1997) (13) and mixed rural and urban. The entire population was provided with tax-supported health care by the National Health Service, allowing free access to the county's seven public hospitals. Through the use of the 10-digit civil registry number, which is unique to every Danish citizen and encodes sex and date of birth, a complete hospitalization and prescription history can be established for each individual, and unambiguous linkage between population-based registries can be performed.

Cases of pneumococcal bacteremia

Patients older than 15 years with a first hospitalization for community-acquired pneumococcal bacteremia were identified in the population-based microbiological County Bacteremia Registry, as described in detail earlier (4,14). We excluded 30 cases with bacteremia, compared with our previous cohort study, because they were not residents in North Jutland County; place of residence was a sampling criterion in the present case-control study.

Population control subjects

Using the Central Population Registry, which has electronic records on all changes in vital status, including change of address, date of emigration, and date of death for the entire Danish population since 1968, we selected 10 control subjects for each case individually matched by sex, age (same year of birth), and place of residence (North Jutland County). The control subjects were selected with the risk set sampling technique (15); that is, the control subjects had to be alive and at risk of first community-acquired pneumococcal bacteremia at the time the corresponding case was diagnosed. When using risk set sampling, the estimated exposure OR in a case-control design is an unbiased estimate of the relative risk (16).

Diabetes

We identified diabetic patients among case and control subjects by record-linkage with two population-based registries as described previously (4): the North Jutland County Prescription Database (17) and the County Hospital Discharge Registry (18). We ascertained presence of diabetes in the same way among case and control subjects, namely by searching the databases for earlier hospitalizations with diabetes or earlier prescriptions for insulin or an oral antidiabetic drug. We have recently estimated the predictive value of a diagnosis of diabetes identified by this approach to be 97% (95% CI 89–100%) (4). Information on diabetes in the databases was recorded earlier than and independent of hospitalization with bacteremia. To ensure that the classification of diabetes was independent from the case's hospitalization, we did not include 10 diabetic patients among cases who in our prognostic cohort study were diagnosed during the admission with bacteremia.

We classified diabetic patients as having type 1 diabetes if they were aged up to 40 years at diagnosis and were treated with insulin in monotherapy. Having type 2 diabetes was classified if they were treated by diet alone or ever treated with oral antidiabetics, or if they were older than 40 years at diagnosis, regardless of treatment.

Confounding factors

To adjust for comorbid diseases that may both be risk factors for pneumococcal infection and associated with presence of diabetes, we calculated a summary measure of confounding due to comorbidities developed by Charlson et al. (19). The Charlson index includes 19 major disease categories, including the suggested risk factors for pneumococcal bacteremia mentioned, and has been adapted for use with hospital discharge registry data in ICD databases (20, 21). We therefore considered it a suitable method to adjust for the patients' overall level of comorbidity.

For calculating the Charlson index score, a weight is assigned to each comorbid disease category and the score is the sum of these weights. Diabetes was separated from the Charlson index because it was the exposure variable in this study. All other diseases in the index were considered as potential confounders. We first translated disease categories in the Charlson index into corresponding ICD-8 and ICD-10 codes, similar to previous approaches, such as the translation to ICD-9 codes by Deyo et al. (20). We identified ICD codes for all previous hospitalizations of case and control subjects in the County Hospital Discharge Registry. To ensure an equal chance of being diagnosed with comorbid diseases in bacteremia case and control subjects, we only included diagnoses recorded before the date of hospitalization of cases. The Charlson index was calculated, and three levels of comorbidity were defined: 0 ("low"), corresponding to patients with no recorded underlying diseases implemented in the Charlson index; 1–2 ("medium"); and >2 ("high").

Since alcohol abuse is not included in the Charlson index, we collected data on alcohol-related disorders from the Discharge Registry (ICD-8 codes 291, 303, 979, 980, and 577.10; ICD-10 codes F10, K86.0, Z72.1, R78.0, and T51) in addition to the diagnoses included in the index. We further collected data from the Prescription Database on the use of antibiotics and immunosuppressive therapy, including corticosteroids before hospitalization, defined as redemption of at least one prescription for a systemic antibiotic of any kind (Anatomical Therapeutical Chemical [ATC] classification system code J01) within half a year of admission, and redemption of at least one prescription for any immunosuppressive drug (ATC codes L01, L04, and H02 AB) within 1 year of admission, respectively.

Statistical analysis

We used conditional logistic regression to estimate ORs for community-acquired pneumococcal bacteremia among diabetic and nondiabetic patients, with associated 95% CIs. Initially, we analyzed data by obtaining contingency tables for the main study variables: pneumococcal bacteremia, diabetes, and the possible confounding factors (i.e., all disease categories included in the Charlson index, the overall level of Charlson index, as well as alcohol-related disorders and the use of antibiotics and immunosuppressive therapy before hospitalization). We then estimated the OR adjusted for possible confounding factors. Stratified analyses were performed according to sex, age-groups (>15–40 years, >40–65 years,

Table 1—*Characteristics of case subjects with community-acquired pneumococcal bacteremia and control subjects from North Jutland County, Denmark, 1992–2001*

	Case subjects	Control subjects
n	598	5,980
Diabetes		
Present	53 (8.9)	298 (5.0)
Not present	545 (91.1)	5,682 (95.0)
Age (years)	67 (18–94)	67 (17–94)
Sex		
Male	283 (47.3)	2,830 (47.3)
Female	315 (52.7)	3,150 (52.7)
Comorbidity*		
Comorbidity index low (0)	312 (52.2)	4,386 (73.3)
Comorbidity index medium (1–2)	219 (36.6)	1,316 (22.0)
Comorbidity index high (>2)	67 (11.2)	278 (4.6)
Alcohol-related disorders	26 (4.3)	72 (1.2)

Data are *n* (%) or median (range). *Charlson index (see text).

>65–80 years, and >80 years), and level of comorbidity.

To examine the impact of diabetes on the overall risk of community-acquired pneumococcal bacteremia, we calculated the population-attributable risk (PAR) for a diagnosis of diabetes (i.e., the proportion of all cases of community-acquired pneumococcal bacteremia that are attributable to diabetes [16]). In case-control studies, 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 control subjects, since the population prevalence of diabetes is relatively low and our control subjects are representative for all noncases in the population (16).

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 was approved by the Danish Registry Board (J.nr 2002-611-0060).

RESULTS — A total of 598 incident cases with residence in North Jutland County and a first hospitalization for community-acquired pneumococcal bacteremia were identified during the study period. Patients included 283 (47%) men and 315 (53%) women. Age ranged from 18 to 94 years (median 67 years) (Table 1). The most common focus of infection was the respiratory tract (485 cases [81%]), followed by the meninges (56 cases [9%]). The focus was undetermined in 39 cases (7%).

Table 1 shows further details about the 598 cases and 5,980 control subjects. 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, as compared with 298 control subjects (5.0%). According to our criteria, the vast majority of diabetic subjects (340 of 351) had type 2 diabetes; therefore, we chose to consider diabetes as one entity in further analyses. A considerably higher proportion of case subjects than control subjects (48 vs. 27%) had one or more previously recorded discharge diagnoses as evidenced in the Charlson index.

Table 2 gives crude and adjusted ORs for community-acquired pneumococcal bacteremia according to presence or absence of diabetes. 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. When use of antibiotics and immunosuppressive therapy before hospitalization was included in the analysis, the adjusted OR remained unchanged 1.5 (95% CI 1.1–2.0).

Table 2—*Crude and adjusted OR for community-acquired pneumococcal bacteremia according to presence of diabetes*

Diabetes	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 sex- and age-matched control subjects; †OR adjusted for level of comorbidity and alcohol-related disorders (see text).

To evaluate the impact of diabetes on the risk of pneumococcal bacteremia in certain subgroups of persons, we stratified our analyses according to age-group, sex, and level of comorbidity (Table 3). Adults with diabetes ≤40 years of age were four times more likely to be hospitalized with pneumococcal bacteremia than persons of comparable age, sex, and level of comorbidity without diabetes. At older ages, the adjusted ORs decreased gradually. Compared with nondiabetic persons, diabetic individuals between 65 and 80 years (adjusted OR 1.3, 95% CI 0.8–2.1) and more than 80 years (adjusted OR 1.2, 95% CI 0.6–2.2) had just a slightly increased risk for pneumococcal bacteremia. When we stratified according to the level of comorbidity, the association between diabetes and an increased risk of infection seemed to be largely restricted to persons without any comorbid diseases (adjusted OR 2.3, 95% CI 1.3–3.9), whereas ORs in individuals with one or more other previously recorded diagnoses were close to 1. Further, ORs appeared to be higher in male than in female diabetic individuals (Fig. 3).

Under the assumptions that the association was causal and that there was an overall prevalence of diabetes in the study population of 5.0%, the total PAR (etiological fraction) was 2.4%. Thus, of 1,000 admissions with incident pneumococcal bacteremia in our study population, 24 may be attributed to diabetes.

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

The main strengths of our study are

Table 3—*OR for community-acquired pneumococcal bacteremia according to presence of diabetes, stratified by age, sex, and level of comorbidity*

	Crude OR* (95% CI)	Adjusted OR† (95% CI)
Age (years)		
>15–40	4.3 (1.1–16.6)	4.2 (1.1–16.7)
>40–65	3.2 (1.8–5.7)	2.1 (1.1–3.9)
>65–80	1.5 (0.9–2.5)	1.3 (0.8–2.1)
>80	1.4 (0.8–2.6)	1.2 (0.6–2.2)
Sex		
Male	2.2 (1.4–3.4)	1.8 (1.2–2.8)
Female	1.6 (1.0–2.5)	1.2 (0.8–2.0)
Comorbidity‡		
Comorbidity index low (0)	2.3 (1.3–3.9)	2.3 (1.3–3.9)
Comorbidity index medium (1–2)	0.8 (0.4–1.6)	0.8 (0.4–1.6)
Comorbidity index high (>2)	1.1 (0.3–3.3)	1.1 (0.3–3.3)

*Crude OR for presence of diabetes in cases with pneumococcal bacteremia compared with sex- and age-matched control subjects; †OR adjusted for level of comorbidity (except when stratified by this variable) and alcohol-related disorders (see text); ‡using the Charlson index (see text).

the uniformly organized medical health care system, which allows for a truly population-based design, and the ability to adjust for comorbid diseases.

Pneumococcal bacteremia is probably a very common feature of pneumococcal pneumonia, but its detection is highly dependent on admission patterns and timing of blood sampling for culture. We cannot exclude the possibility that physicians caring for diabetic patients may be more alert to possible infections. Thus, a higher proportion of cases of bacteremia may have been admitted to hospital among patients with diabetes, and blood cultures may have been ordered more frequently. Such surveillance bias would lead to an overestimation of the risk of pneumococcal bacteremia in diabetic patients. Nevertheless, we found in our previous prognosis study of the cases included in this report that bacteremia density on admission was similar in diabetic and nondiabetic patients (44 vs. 45% with low density) and that the median level of C-reactive protein (277 vs. 204 mg/l) and the proportion with severe sepsis (56 vs. 40%) was even higher among diabetic patients, which argues against a more meticulous case-ascertainment among persons with diabetes.

Diabetes data in our study were collected prospectively and independently of the patient's hospitalization with pneumococcal bacteremia. We thereby avoided recall bias, which may hamper case-control studies where diabetes data are based on interviews or questionnaires, such as the study by Nuorti et al. (12). The positive predictive value of a diagnosis of diabetes established through the registries proved to be high. Concerning completeness, Kristensen et al. (22) recently found that 76% of patients with known diabetes could be identified by a county prescription registry similar to ours, as compared with an independent 34% by a regional hospital registry, by collecting data over a 1-year period only. We thus find it likely that our combined data sources are nearly complete regarding known diabetes. Both case and control subjects may have included additional patients with diabetes who have never previously been hospitalized or drug treated, but we expect such misclassification to be nondifferential, leading to a conservative risk estimate.

An increasing level of comorbidity was associated with both presence of diabetes and the risk of pneumococcal bacteremia and, therefore, confounded the association of diabetes per se with the risk in unadjusted analyses. Coding and diagnosis of comorbidity may have been more complete for diabetic patients due to more frequent hospitalizations. This would, however, lead to a conservative risk estimate. The same holds true for any nondifferential coding errors in the discharge registry. A number of unmeasured factors may have had an impact on the risk for pneumococcal bacteremia in this observational study, including tobacco smoking, socioeconomic status, and living with young children attending daycare (12). However, we were able to adjust for all 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.

Observational studies suggest that pneumococcal vaccination reduces the incidence of invasive pneumococcal disease among adults and the immunocompetent elderly (23). Therefore, we would like to emphasize that the general vaccine coverage in proposed "at-risk" individuals in our study population is much lower than that, for example, in many states of the U.S., where two-thirds of individuals over 65 years of age are vaccinated (24). In our county, the uptake of pneumococcal vaccine unfortunately has been as low as 2 of 1,000 people per year since 1997 (25). Before 1997, when national vaccine recommendations were revised (Statens Serum Institut, Copenhagen, 1996), vaccine coverage rates were probably extremely low. 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 nondiabetic persons. The resulting bias, however, would lead to an underestimation of the true risk for pneumococcal bacteremia in diabetic patients.

To our knowledge, our study is the first population-based case-control study to examine the risk of pneumococcal bacteremia specifically in diabetic patients. The North American case-control study (12) focused on cigarette smoking and did not have sufficient power to assess the relation between diabetes and invasive pneumococcal disease. Two earlier cross-sectional studies from institutions in North Carolina and Spain have compared the prevalence of unspecified bacteremia in hospitalized adults with and without diabetes (26,27). Both found a twofold increased prevalence in the diabetic group. In the Spanish report, but not in the American study, the prevalence of bacteremia with *S. pneumoniae* was also increased in diabetic patients (13 of 5,667 hospital admissions compared with 97 of 95,725 hospital admissions of nondiabetic patients); however, the figures were not adjusted for differences in age and other risk factors.

The specific biological mechanisms linking diabetes with an increased risk of pneumococcal bacteremia have not been established. Interestingly, in a recent case-control study from the U.K. that focused on genotypes, Roy et al. (28) reported an increased risk of invasive pneumococcal disease in patients with mannose-binding lectin deficiency. This common immunodeficiency has been associated with several autoimmune diseases, including systemic lupus erythematosus and rheumatoid arthritis, but to our knowledge not with diabetes.

In conclusion, we found a clearly increased risk of community-acquired pneumococcal bacteremia in individuals with diabetes, when compared with nondiabetic individuals.

Acknowledgments— This study has received financial support from the Western Danish Research Forum for Health Sciences ("Vestdansk Forskningsforum") and by grants from the Medical Research Council of North Jutland, the North Jutland County Medical Association, the "Heinrich Kopp's Legat," and the A.P. Møller Foundation for the Advancement of Medical Science. Research at the Department of Clinical Microbiology, Aalborg Hospital, is supported by a grant from "Det Obelske Familiefond."

We thank the staff of the Hospital Discharge Registries in North Jutland County (Amtsgaarden) for preparing the data.

Results of this study have been presented in part at the 20th Annual Meeting of the Scandinavian Society for Antimicrobial Chemotherapy, Odense, Denmark, October 24–26, 2003.

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