Peer reviewed article

The role of diabetes mellitus in patients with bloodstream infections

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Summary

Background: Since diabetes mellitus predisposes to infection, we evaluated whether diabetes increases the risk of bloodstream infection and worsens its outcome.

Methods: During a 4-year period 71 diabetic and 252 non-diabetic patients with bloodstream infection were included. Risk factors for death were assessed by univariate and multivariate analysis.

Results: Bloodstream infection was more frequent in diabetics than in non-diabetics (25.8/1000 admissions vs. 5.8/1000 admissions, p <0.0001). Urinary tract infection was the predominant source, and *Escherichia coli* the most frequent microorganism in both groups. *Klebsiella pneumoniae* was more frequent in diabetics than in non-diabetics (18% vs 5%, p <0.001). Whereas sepsis of unknown origin was more common in diabetics (14% vs. 6%, p <0.05), catheter-related bloodstream infection predominated in non-diabetics (3% vs 10%, p <0.05). Secondary septic foci (p <0.05) and disseminated intravascular coagulation (p <0.05) were more frequent in diabetics. The in-hospital mortality rate was similar in the two groups (18% vs. 14%). Univariate analysis (RR [CI 95%]) in diabetics revealed glycaemia >20 mmol/L (3.9 [1.7–22]), ICU stay (7.1 [2–25]), mechanical ventilation (8.4 [1.2–57]) and chronic renal/hepatic failure (8.2 [1.6–43]) as significant risk factors. Hyperglycaemia (4.3 [3.4–5.2]) and ICU stay (3.3 [1.9–4.9]) remained significant in multivariate analysis.

Conclusions: Diabetics had a 4.4-fold higher risk of bloodstream infection, were more prone to sepsis of unknown origin and had more septic complications than non-diabetics. The mortality rate was similar in the two groups.

Key words: diabetes mellitus; bloodstream infection; sepsis; outcome; Klebsiella pneumoniae

Introduction

It is a dogma that patients with diabetes mellitus are at increased risk of infection or death associated with an infection [1–4]. However, clinical studies do not consistently support diabetes as a risk factor for infectious complications (including death) [5–10]. In a recent study on *S. aureus* bacteraemia, patients with diabetes were overrepresented (25%) but diabetes mellitus was not a prognostic factor for poor outcome [9].

Risk of infection depends on several factors, including host defence mechanisms, functional or anatomical abnormalities of the host, and the type, inoculum and virulence of the infecting microorganism. Outcome of infection is determined not only by host defence, but also by the timing and appropriateness of antimicrobial treatment. According to a recently published large prospective cohort study, diabetic patients are at increased risk of urinary tract infections, lower respiratory tract infections and skin/soft tissue infections, compared to a control group of patients with hypertension [10]. It has been hypothesised that the increased susceptibility of diabetic patients to infection may be due to impaired host defense mechanisms. However, impaired host defense has been shown exclusively in diabetic patients with poor glucose control, especially ketoacidosis. These defects include impaired function of polymorphonuclear leukocytes and decreased serum levels of complement factor C4 and zinc, as well as an impaired cytokine response and lymphocyte transformation after stimulation [1, 11–17].

In addition to impaired host defence mechanisms, other factors may increase diabetic patients' susceptibility to infection [15]. Microangiopathy impairs leukocyte migration by thickening of the capillary basement membrane, and

No financial support from any source.

macroangiopathy favours acral skin and soft tissue infection as well as foot osteomyelitis. Autonomous neuropathy results in an increased residual urine volume of the bladder which favours urinary tract infection. Diabetic patients are also at increased risk of colonisation with *Staphylococcus aureus* [18], resulting in a higher rate of skin and soft tissue infection and of *S. aureus* sepsis [9, 19, 20]. In addition, diabetes is a risk factor for group A and B streptococcal disease [5, 6], bacteraemia due to Enterobacteriaceae [21], pyogenic liver abscess [22] and metastatic infection from pyogenic liver abscesses [23]. However, no recent data is available on the influence of diabetes mellitus on the incidence and outcome of bloodstream infections in general.

In the present study we analysed all bloodstream infections in hospitalised patients with or without diabetes mellitus, to determine whether diabetes mellitus is associated with increased susceptibility to bloodstream infection and influences its outcome, to evaluate differences between the two groups regarding the type of primary focus and microorganism, and to assess whether the quality of the metabolic control influences prognosis.

Methods

Study type and location

This retrospective cross-sectional study was performed at the Basel University Medical Clinic Liestal, Switzerland. This is a 400-bed teaching hospital with 11,000–12,700 adult admissions per year and includes clinics for medicine (including oncology), general surgery (no burn unit, transplantations or cardiac surgery), urology, orthopaedic surgery, ear, nose and throat and gynaecology.

Study population and definitions

Episodes with positive blood cultures collected during a 4-year period (1998–2001) were identified by the Central Laboratory for Microbiology, followed by hospital chart review of all hospitalised patients aged 16 years or over with at least one positive blood culture. Patients with a true bloodstream infection, defined as ≥1 positive blood culture with a clinically plausible microorganism and ≥2 criteria of the systemic inflammatory response syndrome (SIRS) were included. Fulfilment of SIRS criteria was not required in patients with a positive blood culture and concomitant isolation of the same microorganism from an infectious focus. Where there was a positive blood culture with a microorganism of low virulence, such as coagulase-negative staphylococci, *Propionibacterium* spp., *Corynebacterium* spp. or *Bacillus* spp., two separate positive blood cultures with the same microorganism and at least two SIRS criteria were required. A new episode of bloodstream infection was defined as positive blood cultures >3 months apart.

Patients were excluded from the study if the microorganisms isolated in blood cultures were considered contaminants (according to the above definition), if they were not treated in our institution, their charts were not available, no antimicrobial therapy was administered or the result of the first positive blood culture was available only after death.

A patient was classified as diabetic under the following conditions: (a) diagnosis of diabetes previous to the index hospitalisation, or (b) diagnosis established during hospitalisation according to international standards and discharge with the diagnosis of diabetes mellitus. Patients exclusively with high blood glucose values during acute infection were not classified as having diabetes.

Specimen collection and processing

During a febrile episode at least two sets of blood culture pairs were obtained, each pair consisting of an aerobic and an anaerobic bottle. Blood culture bottles were incubated in the BACTEC 9240 blood culture system (Becton Dickinson, Sparks, Md.) for at least five days at 35 °C. Identification of microorganisms and antibiotic susceptibility testing were done according to standard laboratory operating procedures.

Data collection

Patients with bloodstream infection were classified as diabetics or non-diabetics according to standard definitions by the admitting physician. The patient's age, sex, underlying conditions, and predisposing factors for sepsis were recorded. In diabetic patients the type and duration of diabetes, treatment and HbA1c (measured during the index hospitalisation, or the most recent value from the referring physician) were noted. Bloodstream infections were classified into community-acquired and nosocomial infections. The source of sepsis, the causative microorganism(s) isolated from blood and if possible from a suspected primary source, and the antimicrobial therapy (type of drug, daily dose, mode of administration), before and after receiving the microbiology result, were recorded.

The following clinical and laboratory parameters were recorded at the time of the the initial diagnosis of bloodstream infection: systolic blood pressure, heart rate, body temperature, blood leukocyte count (total leukocytes and percentage of band forms), C-reactive protein, and blood glucose level.

The following outcome criteria were recorded: occurrence of complications such as septic shock, acute renal or hepatic failure, disseminated intravascular coagulation and secondary foci. Also documented were admission to the intensive care unit, need for mechanical ventilation, length of sepsis-related hospital stay, transfer to other institutions and death.

Data analysis

We compared demographic data, underlying conditions, predisposing factors for sepsis, source of bloodstream infection, causative microorganisms, and clinical and laboratory parameters in septic patients with and without diabetes. To determine whether diabetes is associated with a complicated course or death due to sepsis, we compared diabetic and non-diabetic patients with respect to rate of complications, rate and duration of ICU stay, length of hospital stay due to the septic episode, survivors' outcome (discharge / transfer to another institution) and sepsis-related mortality rate. To estimate the role of metabolic control we compared complications and

outcome between well controlled and poorly controlled diabetic patients, using HbA1c as the parameter of quality of metabolic control. Since acute infection may lead to increased blood glucose levels, random or fasting blood glucose levels at admission were not used to discriminate between well and poorly controlled diabetic patients.

To evaluate differences between groups, the unpaired Student's t-test for normally distributed continuous variables and the Mantel-Haenszel chi-square test or two-tailed Fisher's exact test for categorical variables was used. Parameters found to be of borderline statistical significance (P <0.1) by univariate analyses or with biological plausibility were further analysed by a step-wise logistic regression model (statistical package SPSS 10.0 for Windows, SPSS, Chicago, IL, USA). A p value <0.05 was considered significant (two-tailed).

Results

Demography and site of infection

During the 4-year study period, 45,850 adult patients were admitted to the hospital. Among them, approximately 6% had, according to the referring physician, a diagnosis of diabetes mellitus prior to admission. During the study period 449 episodes of positive blood cultures were recorded in the bacteriology laboratory. 126 (28.1%) of these episodes were excluded according to the exclusion criteria (79 microorganisms in blood culture were considered as contamination, 30 episodes were not treated at our hospital, 10 charts were not available, 5 preterminal patients received no antibiotics, and in three episodes the blood culture result was received only post mortem).

Table 1 summarises the characteristics of the study population. We observed 71 episodes of bloodstream infection in 2,750 patients with diabetes (25.8 episodes / 1000 admissions), and 252 in 43,100 patients without diabetes (5.8 episodes / 1000 admissions). Thus the relative frequency of bloodstream infection was >4 times higher in diabetic than in non-diabetic patients (<0.0001). The median age was similar (74 vs. 70 years). The fraction of nosocomial bloodstream infections did not differ between the groups. Urinary tract infection was the most frequent origin of bacteraemia, occurring in approximately one third of the patients in both groups, followed by abdominal and lower respiratory tract infection. Regarding the relative frequency of the origin of bacteraemia there were only two significant differences between the two groups. In diabetic patients the focus of infection remained undetermined 2.2 times more often than in non-diabetics, whereas in non-diabetic pa-

Table 1

Demographics and source of bloodstream infection in 71 diabetic and 252 non-diabetic patients.

Characteristic	Diabetics (n = 71)	Non-diabetics (n = 252)	p
No. admissions with characteristic	2750	43,100	
No. episodes of bacteraemia / 1000 admissions	**25.8**	**5.8**	**<0.0001**
Median age (range)	74 (43-92)	70 (18-96)	0.764
Male sex	38 (53.5%)	133 (52.8%)	0.912
Type of diabetes			
Type 1	2 (2.8%)	n.a.	
Type 2, controlled with diet only	18 (25.4%)	n.a.	
Type 2, oral antidiabetic drugs	33 (46.5%)	n.a.	
Type 2, insulin treatment	14 (19.7%)	n.a.	
Secondary diabetes	4 (5.6%)	n.a.	
Mean duration of diabetes in years (range)	5 (0–40)	n.a.	
HbA1c (range)	7.9% (5–14.8)	n.a.	
Nosocomial infection	20 (28.2%)	89 (35.5%)	0.261
Primary site of infection:			
Unknown	**10 (14.3%)**	**16 (6.3%)**	**0.002**
Urinary tract	22 (31.4%)	85 (33.7%)	0.665
Lower respiratory tract	8 (11.4%)	36 (14.3%)	0.513
Abdominal	12 (16.9%)	35 (13.9%)	0.526
Skin	2 (2.9%)	14 (5.6%)	0.348
Bone/joint	4 (5.7%)	6 (2.4%)	0.163
Surgical site	7 (10%)	13 (5.2%)	0.147
Intravenous catheter	**2 (2.9%)**	**26 (10.3%)**	**0.048**
Heart valve	2 (2.9%)	13 (5.2%)	0.408
Other	1 (1.4%)	8 (3.2%)	04.25

NOTE. Data are no. (%) unless otherwise indicated. n. a. = not applicable

tients, iv-catheter associated infection was 3.6 times more frequent than in diabetics.

Underlying conditions and comorbidities

Table 2 summarises the underlying conditions. Significantly fewer diabetic than non-diabetic patients had no underlying conditions (2.8% vs. 23.0%; p = 0.001). Hypertension was the most frequent comorbidity in both groups, but was still 1.8 times more frequent in diabetics (54.9% vs. 30.6%; P = 0.001). The other two significant differences were peripheral arterial occlusive disease, which was 2.8 times more frequent (15.5% vs. 5.6%; p = 0.006), and neuropathy, 5.8 times more frequent in diabetic than non-diabetic patients (25.4% vs. 4.4%; p <0.001). Interestingly, there was no significant difference between the two groups in the prevalence of renal failure.

Microorganisms

Table 3 shows the most common microorganisms isolated from blood cultures in the two groups. *Escherichia coli* (28.2% vs. 37.3%; p = 0.156) and *S. aureus* (23.9% vs. 15.9%; p = 0.117) were the most frequent isolates in both groups. *Klebsiella pneumoniae* was 3.5 times more prevalent

Table 2
Underlying conditions.

Variable	Diabetics (n = 71)	Non-diabetics (n = 252)	p
None	**2 (2.8%)**	**58 (23.0%)**	**0.001**
Hypertension	**39 (54.9%)**	**77 (30.6%)**	**0.001**
Congestive heart failure	3 (4.2%)	16 (6.3%)	0.502
Heart valve disease	4 (5.6%)	20 (7.9%)	0.514
Ischaemic heart disease	18 (25.4%)	43 (17.1%)	0.116
Peripheral arterial obstructive disease	**11 (15.5%)**	**14 (5.6%)**	**0.006**
Stroke	8 (11.3%)	15 (6.0%)	0.125
Neuropathy	**18 (25.4%)**	**11 (4.4%)**	**<0.001**
Chronic renal failure	5 (7.0%)	11 (4.4%)	0.359
Chronic hepatic failure	2 (2.8%)	6 (2.4%)	0.835
Chronic obstructive lung disease	5 (7.0%)	26 (10.3%)	0.409
Solid organ malignancy (not in remission)	11 (15.5%)	33 (13.1%)	0.603
Haematological malignancy (not in remission)	3 (4.2%)	13 (5.2%)	0.749
Neutropenia	1 (1.4%)	2 (0.8%)	0.634
Humoral immunodeficiency[a]	1 (1.4%)	8 (3.2%)	0.425
Cellular immunodeficiency[b]	8 (11.3%)	24 (9.5%)	0.664
Smoking	16 (22.5%)	72 (28.6%)	0.314
Alcohol abuse	4 (5.6%)	20 (7.9%)	0.514
Intravascular drug use	0	5 (2.0%)	0.232
Others	4 (5.6%)	6 (2.4%)	0.163

NOTE. Data are no. (%).
[a] Humoral immunodeficiency: HIV infection any stage, chronic lymphatic leukaemia, lymphoma, multiple myeloma, uraemia, nephrotic syndrome, splenectomy.
[b] Cellular immunodeficiency: HIV infection A3-C3, corticosteroids (>25 mg/d prednisone for at least one month or 700 mg cumulative dose), other immunosuppressive drugs, transplantation.

Table 3
Microorganisms isolated from blood cultures.

Microorganism	Diabetics (n = 71)[a]	Non-diabetics (n = 252)[b]	p
Escherichia coli	20 (28.2%)	94 (37.3%)	0.156
Staphylococcus aureus	17 (23.9%)	40 (15.9%)	0.117
Klebsiella pneumoniae	**13 (18.3%)**	**13 (5.2%)**	**<0.001**
Streptococcus pneumoniae	6 (8.5%)	31 (12.3%)	0.369
Enterococcus faecalis	4 (5.6%)	4 (1.6%)	0.053
Candida albicans	2 (2.8%)	4 (1.6%)	0.499
Klebsiella oxytoca	2 (2.8%)	2 (0.8%)	0.174
Bacteroides spp.	1 (1.4%)	6 (2.4%)	0.620
Coagulase-negative staphylococci	0 (0%)	12 (4.8%)	0.061
Other	10 (14.1%)	59 (23.4%)	0.091
Polymicrobial infection	4 (5.6%)	13 (5.2%)	0.874

NOTE. Data are no. (%).
[a] 79 microorganisms, therefore total >100%.
[b] 265 microorganisms, therefore total >100%.

in diabetics than in non-diabetics (18.3% vs. 5.2%; p <0.001).

Clinical presentation, complications, outcome

In the first three days after diagnosis of bloodstream infection there was no significant difference regarding vital signs between the two groups (data not shown). A similar fraction of patients required treatment in the ICU. As shown in Table 4, secondary foci of infection (p = 0.04) and disseminated intravascular coagulation (p = 0.030) were significantly more common in diabetic than non-diabetic patients.

The median duration of hospital stay until discharge or transfer to another institution was 1.6 times longer for diabetics (21 and 13 days respectively: p <0.0001). In contrast, no difference in the median duration of hospital stay was noticed in patients who died. Significantly more diabetics required transfer to another institution and were therefore less commonly discharged home. Mortality was similar between the two groups; however, the death rate per 1,000 admissions was 5.6 times higher in diabetic than non-diabetic patients.

Table 4
Complications and outcome.

Complication[a]	Diabetics (n = 71)	Non-diabetics (n = 252)	p
None	39 (54.9%)	160 (63.5%)	0.190
ICU stay	21 (29.6%)	63 (25.0%)	0.438
Mechanical ventilation	5 (7.0%)	13 (5.2%)	0.542
Secondary foci	**13 (18.3%)**	**24 (9.5%)**	**0.040**
Septic shock	9 (12.7%)	28 (11.1%)	0.715
Disseminated intravascular coagulation	**5 (7.0%)**	**5 (2.0%)**	**0.030**
Acute respiratory distress syndrome	0	4 (1.6%)	0.560
Acute renal failure	0	2 (0.8%)	0.608
Median duration of hospital stay (days)			
– until discharge	**21**	**13**	**<0.0001**
– until death	8	9	0.916
Discharged			
– home	**41 (57.7%)**	**186 (73.8%)**	**<0.01**
– transfer to other institution	**17 (23.9%)**	**30 (11.9%)**	**0.025**
Mortality rate	13 (18.3%)	36 (14.3%)	0.97
Death rate/1,000 admissions	**4.7**	**0.84**	**<0.0001**

NOTE. Data are no. (%) unless otherwise indicated.
[a] Several patients had more than one (up to six) different complications; therefore the sum of complications exceeds 100%.

Table 5
Univariate analysis of risk factors for fatal outcome of bloodstream infection in 71 diabetic patients.

Characteristic	No. (%) of fatal episodes in presence vs. absence of characteristic	Relative risk (95% CI)
Age ≥75 years	6/33 (18.2%) vs. 7/38 (18.4%)	0.98 (0.29–3.29)
Male sex	7/38 (18.4%) vs. 6/33 (18.2%)	1.02 (0.3–3.4)
HbA_{1c} >7%	6/38 (15.8%) vs. 2/19 (10.5%)	1.59 (0.29–8.77)
Cardiovascular disease[a]	8/27 (29.6%) vs. 5/44 (11.4%)	3.28 (0.95–11.40)
Neuropathy	4/18 (22.2%) vs. 9/53 (17.0)	1.40 (0.37–524)
Chronic renal/hepatic failure	**4/7 (57.1%) vs. 9/64 (14.1%)**	**8.15 (1.56–42.62)**
Malignancy	3/14 (21.4%) vs. 10/57 (17.6%)	1.28 (0.30–5.45)
Smoking[b]	4/16 (25.0%) vs. 1/12 (8.3%)	3.67 (0.36–38.03)
Alcoholism	1/4 (25.0%) vs. 12/67 (17.9%)	1.53 (0.15–15.98)
Nosocomial infection	5/20 (25%) vs. 8/51 (15.7%)	1.79 (0.51–6.33)
Unknown focus	3/10 (30%) vs. 10/61 (16.4%)	2.19 (0.48–9.92)
Urinary tract infection	2/22 (9.1%) vs. 11/49 (22.4%)	0.35 (0.07–1.71)
Lower respiratory tract infection	3/8 (37.5%) vs. 10/63 (15.9%)	3.18 (0.65–15.40)
Surgical site infection	2/7 (28.6%) vs. 11/64 (17.2%)	1.93 (0.33–11.24)
Glycaemia >20 mmol/L	**8/20 (40%) vs. 5/50 (10%)**	**3.94 (1.66–21.71)**
ICU stay	**8/21 (38.1%) vs. 5/63 (7.9%)**	**7.14 (2.01–25.39)**
Mechanical ventilation	**3/5 (60%) vs. 10/66 (15.2%)**	**8.4 (1.24–56.82)**

[a] Congestive heart failure, ischaemic heart disease, valvular heart disease, stroke, peripheral arterial occlusive disease.
[b] Data on smoking missing in 43 patients (among them 8 died).

Factors associated with death

Table 5 shows the univariate analysis of risk factors for death in diabetics. Four factors were associated with a significantly increased relative risk. Among them, mechanical ventilation was the most significant risk factor. Poor control of glycaemia at the time of bloodstream infection was associated with a significantly increased risk of death, whereas poor long-term control (HbA1c) did not correlate with poor prognosis. Chronic renal or hepatic failure increased the risk of death more than 8-fold. In the multivariate analysis, hyperglycaemia at the time of diagnosis of sepsis (RR = 4.3 [3.4–5.2]) and ICU stay (RR = 3.3 [1.9.–4.9]) remained significant.

Table 6 shows the univariate analysis of risk factors for death in non-diabetics. Six factors were significantly more often associated with death, the most important being ICU stay, mechanical ventilation and underlying neuropathy. In contrast, patients with urinary tract infection as the source of bacteraemia had a factor significantly less often associated with death than those with other primary foci. In the multivariate analysis, age ≥75 years (RR = 2.9 [1.8–4.2]), neuropathy (RR = 4.2 [3.3–5.1]) and ICU-stay (RR = 2.9 [1.8.–4.0]) remained significant.

Discussion

A quarter of a century ago Rayfield et al. [15] showed that 14% of all deaths in diabetics were caused by infection and that the infection-associated death rate was approximately twice as high as in non-diabetic patients. Whether the higher death rate was due to an increased infection-associated mortality rate or the result of a higher host susceptibility to infection remained unclear. With the introduction of novel oral antidiabetic drugs and long-acting insulins the management of diabetes mellitus and glycaemia control has made significant progress. However, the effect of these novel treatment modes on susceptibility to and outcome of infection in diabetic patients has not yet been quantified [24–26]. It is conceivable that diabetes mellitus has faded as a risk factor for fatal outcome of infection because, thanks to improved metabolic control, host defence in diabetic patients is no longer compromised.

The association between diabetes mellitus and increased susceptibility to infection is a common belief supported by few data [1]. In the largest and most recent study, patients with type 1 and type 2 diabetes mellitus were shown to be at increased risk of lower respiratory tract infection, urinary tract infection and skin and mucous membrane infection compared with control hypertensives [10]. In this study data were obtained from general practitioners and bloodstream infection was not included as an outcome measure.

In our study the incidence of bloodstream infection was evaluated among hospitalised patients with and without diabetes and factors associated with death. The incidence of bloodstream infection was 4.4 times higher in patients with diabetes than in non-diabetics. This finding was also reported in several previous studies, but in our study this difference was higher than that reported by

Table 6

Univariate analysis of risk factors for fatal outcome of bloodstream infection in 252 non-diabetic patients.

Characteristic	No. (%) of fatal episodes in presence vs absence of characteristic	Relative risk (95% CI)
Age ≥75 years	**23/99 (39.2%) vs. 13/153 (8.5%)**	**3.26 (1.56–6.80)**
Male sex	21/133 (15.8%) vs. 15/119 (12.6%)	1.3 (0.64–2.66)
ICU stay	**22/63 (34.9%) vs. 14/189 (7.4%)**	**6.71 (3.16–14.22)**
Mechanical ventilation	**9/13 (69.2%) vs. 27/239 (11.3%)**	**17.67 (5.09–61.3)**
Nosocomial infection	**19/89 (21.3%) vs. 17/163 (10.4%)**	**2.33 (1.14–4.76)**
Unknown	3/16 (18.8%) vs. 33/236 (14.0%)	1.42 (0.48–5.25)
Urinary tract infection	**2/85 (2.4%) vs. 34/167 (20.4%)**	**0.09 (0.02–0.40)**
Surgical site infection	2/13 (15.4%) vs. 34/239 (14.2%)	1.10 (0.23–5.16)
Cardiovascular disease[a]	16/78 (20.5%) vs. 20/174 (11.5%)	1.99 (0.97–4.08)
Neuropathy	**5/11 (45.5%) vs. 31/241 (12.9%)**	**5.65 (1.63–19.61)**
Chronic renal/hepatic failure	4/16 (25.0%) vs. 32/236 (13.6%)	2.13 (0.65–6.99)
Malignancy	**13/46 (28.3%) vs. 23/206 (11.2%)**	**3.13 (1.44–6.80)**
Smoking[b]	9/72 (12.5%) vs. 7/47 (14.9%)	0.82 (0.28–2.37)
Alcoholism	6/20 (30.0%) vs. 30/132 (22.7%)	1.46 (0.52–4.12)

[a] Congestive heart failure, ischaemic heart disease, valvular heart disease, stroke, peripheral arterial occlusive disease.

[b] Data on smoking missing in 133 patients (among them 20 died).

Bryan et al. [27] (2-fold), McFarlane et al. [28] (2.9-fold), and Carton et al. [29] (1.7-fold).

In our study bacteraemia with an unknown focus was 2.3 times more common in diabetics than non-diabetics, whereas the frequency of urosepsis was similar in the two groups. This is in contrast to the study of Leibovici et al. [30], in which urosepsis was 1.3 times more common in diabetics than in non-diabetics, whereas the primary site of infection remained unknown in a similar fraction in both groups. This difference may be explained by the fact that the primary focus was detected in >90% of episodes in our study, but only in 70% of the episodes in the study by Leibovici et al. Carton et al. [29] reported a fraction of 14% of skin/soft tissue infection in bacteraemic diabetic patients. In our study only 2.9% of the diabetic patients had skin infection as the primary focus, suggesting that complicated diabetic foot infection has become less frequent.

Comorbidity was the rule in diabetic patients. More than 97% of the diabetic patients with bacteraemia had at least one underlying condition, chiefly hypertension (54.9%), neuropathy (25.4%), ischaemic heart disease (25.4%), and smoking (22.5%). Hypertension, peripheral artery obstructive disease and neuropathy were significantly more prevalent in diabetic than in non-diabetic patients. However, from our data it cannot be concluded that these comorbidities predispose for bloodstream infection, since a control population of hospitalised diabetic patients without bacteraemia was not analysed. Interestingly, skin and bone infections were rare in our study, despite the large fraction of patients with neuropathy and peripheral artery obstructive disease. Foot care, which has gained increasing importance in primary care, thus seems to prevent bloodstream infection, given that infection of the extremities was an important primary source in older studies.

E. coli and *S. aureus* were the most common microorganisms in both groups of patients. This is similar to studies of patients with bloodstream infection in general [31]. The only difference was the 3.5-fold higher frequency of *K. pneumoniae* bacteraemia in diabetic as compared to non-diabetic patients. Similarly, in the study of Leibovici et al. [30], *Klebsiella* was also overrepresented in diabetics (13.5% vs.9.3%). In a study dealing with the epidemiology of bacteraemia due to *Klebsiella* as compared to *E. coli*, diabetes mellitus was a significant risk factor for the former microorganism [32]. Similarly, among 160 patients with *K. pneumoniae* liver abscess, 75% of the patients had diabetes compared to 4.5% of the patients with polymicrobial liver abscess [33]. The reason for the high incidence of *K. pneumoniae* in diabetic patients remains unclear. In the study mentioned above, an impaired Kupffer's cell function in diabetic patients may explain the increased incidence of *K. pneumoniae*, since this microorganism seeds via haematogenous route whereas polymicrobial abscesses result from cholangitis. However, this hypothesis does not explain the entire difference, since *Klebsiella* was also overrepresented in diabetic patients with urosepsis (25% vs. 8%) in the study by Leibovici et al. [30]. Hence increased adhesion of *Klebsiella* to epithelial cells of diabetic patients may be an additional factor resulting in more *Klebsiella* infection in this population. Increased adhesion to epithelial cells of diabetics has been shown for two fimbriated strains of *E. coli*, but has not yet been analysed for *Klebsiella* [34]. Both hypotheses remain to be tested.

Secondary foci were almost twice as frequent in diabetic as in non-diabetic patients in our study. This finding indicates that impaired host defence favours haematogenous bacterial seeding in diabetic patients. The death rate due to bacteraemia per 1000 hospital admissions was >5 times higher in diabetic than in non-diabetic patients. However, the mortality rate was similar in both populations. This indicates that the susceptibility of diabetics to bloodstream infection is increased, but the prognosis is similar once the infection is diagnosed [35]. The difference between the frequency of infections in diabetic and non-diabetic patients may be due to different health-seeking behaviour. Diabetic patients have frequent healthcare contacts, and this may lead to more common and/or earlier diagnosis of infections. However, this hypothesis may only explain the differences in uncomplicated infections [10]. As bloodstream infections are chiefly treated in an inpatient setting, a possible difference in incidence or outcome is due rather to different susceptibility or prognosis than to different health-seeking behaviour.

In non-diabetic patients, factors associated with death were similar to those in other studies on bloodstream infection [8, 35, 36]. Most factors indicate severe infection (ICU stay, mechanical ventilation) or comorbidity (advanced age, malignancy). In diabetic patients two factors remained significant in the multivariate analysis, ICU stay and hyperglycaemia. HbA1c >7% was not a factor significantly associated with death. Hence hyperglycaemia does not necessarily indicate a poor baseline diabetes but could also be the result of severe sepsis. Poor glucose control has been demonstrated as a risk factor in critically ill patients regardless of whether they were diabetics or not [37].

The main limitation of our study is its retrospective design. However, thanks to our electronic patient chart and laboratory system, the quality of the data can be regarded as reliable. Only 10 screened patients had to be excluded because of missing clinical documentation. Our study has two main clinical implications. First, in diabetic patients with sepsis, empiric antibiotic therapy should include efficacy against *K. pneumoniae*. Further, secondary foci should be actively sought in order to avoid failure due to lack of drainage and/or of prolonged antimicrobial therapy.

In conclusion, diabetics are at increased risk of bloodstream infection but have a similar mortality. The increased risk of complications means a significantly prolonged hospital stay.

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