

Diabetes and Risk of Community-Acquired Respiratory Tract Infections, Urinary Tract Infections, and Bacteremia

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Abstract: This review provides an update on the risk of several important community-acquired infections seen in patients with diabetes: respiratory tract infections, urinary tract infections, and bacteremia. *Respiratory tract infections:* Recent epidemiological evidence shows a modest (1.25 to 1.75-fold) risk increase for hospitalization with pneumonia associated with diabetes. The increase of risk for tuberculosis is of similar magnitude in highly developed countries, and possibly higher in low-income countries. Poor glycemic control and long diabetes duration predict higher risk for both pneumonia and tuberculosis. Limited data is available for diabetes and influenza, yet both influenza and pneumococcal vaccination is recommended in patients with diabetes.

Urinary tract infections: The risk of asymptomatic bacteriuria and cystitis is 1.5 to 2 times increased in diabetes patients, while their risk of pyelonephritis may be 2 to 4 times increased. Treatment of asymptomatic bacteriuria in diabetes is generally not recommended. Diabetes duration and chronic complications including cystopathy appear to be more important risk factors than current glycemic control, but further evidence is needed. Modifiable risk factors for urinary tract infection are the same as in persons without diabetes.

Bacteremia: The risk of bacteremia due to pneumococci is approximately 1.5 times increased in diabetes, similar to the increased risk for pneumonia. In comparison, diabetes is associated with 2.5 to 3 times increased risk for bacteremia due to *E. coli* and other enterobacteria, often due to a urinary tract focus. Diabetes is also associated with a 2 times increased risk for hemolytic streptococcal bacteremia, and 3 times increased risk for invasive group B streptococcal infection. Limited data is available for staphylococcal bacteremia.

Conclusions: Increased infection surveillance and unmeasured confounding factors among diabetic patients may contribute to the observed increased infection risk, yet outcomes following infection are similar or worse in diabetes patients. In conclusion, there is epidemiological evidence that individuals with diabetes have a substantially increased risk of a number of important infections. Clinicians should remain vigilant for infections in this increasing group of patients.

Keywords: Diabetes, hyperglycemia, infection, risk, epidemiology, bacteremia, sepsis, urinary tract infection, pneumonia, risk.

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 major and increasing public health and clinical problem [1-3]. Prevalence of diabetes has tripled in the last 3 decades, and according to the World Health Organization approximately 346 million people are now living with diabetes worldwide. According to an estimate the world prevalence of diabetes among adults will increase to 7.7% or 439 million adults by 2030, with a 69% increase in numbers of adults with diabetes in developing countries and a 20% increase in developed countries [4]. Diabetes affects the function of multiple organ systems and thus imposes a tremendous burden on the individual with diabetes and on health care systems. Individuals with diabetes have a two- to fourfold increased risk of cardiovascular and cerebrovascular disease [5], 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 [6]. Diabetes was responsible for 6.8% of total global deaths in all age groups in 2010 [7]. A multi-center observational study showed that only 13% of diabetic patients died solely due to diabetes whereas 87% died of diabetes complications, including infections [8].

It has long been a common clinical belief that diabetes increases the risk of infections [9-11]. Until the 2000s, this

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belief was not supported by much epidemiological evidence, as stated in a review of the issue in the *New England Journal of Medicine* in 1999 [12]. During the last decade however, there has been an increasing amount of new evidence and research interest in important infections amongst those with diabetes [13, 14], although in some areas the evidence is still scant and of poor quality. There is also new evidence that hyperglycemia is associated with inflammation, altered immune function, and increased severity of infection [15, 16]. Rare infections that occur almost exclusively in diabetic patients, such as malignant otitis externa due to *P. aeruginosa*, rhinocerebral mucormycosis, the fungal infection zygomycosis, certain infections with gas-forming microorganisms e.g. emphysematous pyelonephritis and cholecystitis [17], and the tropical diabetic hand syndrome [18] are covered in more detail elsewhere [12, 19].

DIABETES AND THE RISK OF COMMUNITY-ACQUIRED RESPIRATORY TRACT INFECTIONS

Respiratory Tract Infection (RTI) is a leading cause of morbidity, mortality, and cost of care worldwide. Combined with influenza, pneumonia is the eighth leading cause of death in United States and the most frequent cause of death due to infectious disease [20]. During the past decade, hospitalizations with pneumonia have increased by 20-50% in Western populations [21-24], possibly related to an increasing population prevalence of comorbidities such as cancer, heart failure, chronic obstructive pulmonary disease (COPD), and diabetes. On the population level, patients with diabetes may be more susceptible to RTIs due to a number of mechanisms. These include higher age, unhealthy lifestyle such as smoking and alcohol overuse, a generally decreased immune function, increased risk of aspiration due to diabetic gastroparesis, possibly impaired lung function and pulmonary microangiopathy, and frequent comorbidity like renal failure, stroke sequelae, and chronic heart failure [25, 26]. In their 2011 Standards of Medical Care in Diabetes [27], the American Diabetes Association states that there are limited studies reporting the morbidity and mortality of influenza and pneumococcal pneumonia specifically in people with diabetes, citing an 11 year old review of this topic [28]. However, new evidence has accumulated during the last decade.

Diabetes and Pneumonia

Five cohort studies since 2003 found that diabetes is a risk factor for pneumonia, with relative risks (RRs) ranging from 1.26 to 1.75 [26, 29-33], while three older studies had failed to find an association [34-36]. A Dutch cohort study compared diabetic patients with an age-matched control group of hypertensive patients in 195 general practices. The authors found that diabetic patients had a greater risk of lower respiratory tract infections diagnosed in primary care, including pneumonia, acute bronchitis, influenza, pleuritis, and exacerbations of chronic lung disease (adjusted odds ratio (OR) for patients with type 1 diabetes = 1.42 (95% CI 0.96-2.08) and for patients with type 2 diabetes = 1.32 (95% CI, 1.13-1.53)) [32]. In a large Canadian cohort study, Shah *et al.* compared all persons with diabetes in Ontario to matched nondiabetic persons ($n = 513,749$ in each group) [29]. Persons with diabetes had an increased risk of pneumonia-related hospitalization or physician claims for

pneumonia treatment (RR = 1.46; 99% CI 1.42-1.49), yet comorbidity adjustment was not possible in that study. Jackson *et al.* reported that the adjusted RR for hospitalizations for community-acquired pneumonia was 1.52 (95% CI 1.29-1.78) among persons with diabetes compared to persons without diabetes, based on 46,237 persons aged ≥ 65 years enrolled in a single health maintenance organization in Washington State [30]. Kornum *et al.* did a case-control study of 34,239 patients with a pneumonia-related hospitalization and 342,390 population controls in Denmark [26]. The adjusted RR for pneumonia-related hospitalization among persons with diabetes was 1.26 (95% confidence interval (CI) 1.21-1.31). The adjusted RR was larger for type 1 diabetes: 4.43 (95% CI 3.40-5.77), vs 1.23 (95% CI 1.19-1.28) for persons with type 2 diabetes. In a recent large analysis of individual-participant data from 97 prospective studies that had information about diabetes or fasting blood-glucose level at baseline, the age-, smoking-, and BMI-adjusted hazard ratio for death from pneumonia associated with presence of diabetes was 1.67 (95% CI 1.45-1.92) (compared with hazard ratio for infections other than pneumonia: 2.39 (95% CI 1.95-2.93)) [37]. In conclusion, there is evidence that diabetes is associated with a moderately (25%-75%) increase in the relative risk of pneumonia-related hospitalization. Several studies show that longer duration of diabetes and poor glycaemic control increase the risk of pneumonia-related hospitalization [26, 33]. Moreover, several studies report an increased risk of death associated with pneumonia hospitalization in patients with diabetes or hyperglycemia [38-41]. Yende *et al.* analysed two different cohorts and found that diabetes was associated with a 1.3 to 1.9 times higher risk of death within the first year following CAP [39]. One of their cohort analyses suggested that increased mortality from diabetes was not due to an altered immune response, but rather to worsening of pre-existing cardiovascular and kidney disease. In a Danish population-based study, mortality among type 2 diabetic vs other patients was 19.9% vs 15.1% in other patients 30 days after pneumonia admission and 27.0% vs 21.6% after 90 days, corresponding to adjusted 30- and 90-day mortality rate ratios (MRRs) of 1.16 (95% CI 1.07-1.27) and 1.10 (95% CI 1.02-1.18). In contrast, presence of type 2 diabetes did not predict pulmonary complications or bacteremia [40].

Diabetes and Influenza

Few epidemiologic studies provide data specifically on influenza risk in diabetes. As mentioned above, a Dutch cohort study found that diabetic patients in general practice had a 1.3 to 1.4 higher risk of lower respiratory tract infection including influenza [32]. Obesity and type 2 diabetes are closely associated [1], and in the recent influenza A (H1N1) pandemic, both diabetes and obesity have been highly prevalent among patients with very severe episodes of influenza A (H1N1) [42] and among those with bacterial pneumonia in fatal influenza A (H1N1) cases [43]. Obese individuals may have increased susceptibility to lower respiratory tract infection due to impaired T and B cell-mediated immune responses, a higher risk of aspiration, reduced lung volume, and an altered ventilation pattern [44-46]. Notwithstanding, a recent large cohort study using the UK General Practice Research Database found

approximately 20% decreased rates of any influenza-associated pneumonia diagnosis among overweight and obese individuals, whereas women with type 2 diabetes in contrast had 1.37 times (95% CI 1.08-1.72) increased rates, and even more (1.47 times) if they were also obese [47]. A recent Danish cohort study found that moderate obesity (body mass index (BMI) 30.0-34.9) was associated with a 1.4-fold (95% CI 1.2-1.7) higher risk of a pneumonia-related hospitalization among men, while severe obesity (BMI \geq 35.0) was associated with a 2.0-fold (1.4-2.8) higher risk; only weak associations were observed among women [48]. Importantly, adjustment for chronic diseases including diabetes diagnosed during follow-up eliminated the associations between obesity and pneumonia risk [48]. These UK and Danish results suggest that the apparently increased influenza and pneumonia risk associated with obesity may be explained by the occurrence of diabetes and other comorbidity. On the other hand, it remains uncertain to which degree severe obesity may explain any apparent association between diabetes and severe influenza or pneumonia, since confounder or mediator data on anthropometric measures are often not available in large diabetes database studies.

Influenza and Pneumococcal Vaccination in Diabetes – Recommendations and Effectiveness

The above data may emphasize the value of influenza and pneumococcal immunization in diabetic patients, particularly for those with long diabetes duration and associated obesity, and the importance of good glycemic control. The Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices recommends influenza vaccination for all children and adults with diabetes (<http://www.cdc.gov/vaccines/recs/>) [49]. In their 2011 Standards of Medical Care in Diabetes [27], the American Diabetes Association (ADA) recommends annually influenza vaccine to all diabetic patients at least 6 months of age, and pneumococcal polysaccharide vaccine to all diabetic patients \geq 2 years of age. A one-time revaccination is recommended for individuals >64 years of age if the vaccine was administered >5 years ago. It is generally believed that people with diabetes have appropriate serologic responses to these vaccinations [27]. However, Nam and colleagues recently studied the humoral immune response to the inactivated influenza A (H1N1) 2009 monovalent vaccine in patients with Type 2 diabetes mellitus in Korea, and suggested to consider a two-dose vaccination for older patients and those with long duration of diabetes as they appeared to have low seroconversion rates [50].

A Dutch nested case-control study found that influenza vaccination was associated with a 54-58% risk reduction of any acute cardiopulmonary hospitalization or death among adults with diabetes [51]. However, there is a high risk of uncontrolled healthy vaccine user bias in observational studies [52]. As noted in two recent Cochrane reviews from 2010, influenza vaccines have a modest effect in reducing influenza symptoms and working days lost in healthy adults [53], whereas there are no adequately powered randomized controlled trials to assess the effectiveness of influenza vaccines in preventing influenza-related hospital admissions, complications and mortality in individuals aged 65 years or

older [54]. Polysaccharide pneumococcal vaccines appear effective in preventing invasive pneumococcal disease, although the efficacy may be poorer in adults with comorbidity. The efficacy of pneumococcal vaccines against pneumonia or death in adults with or without chronic illness including the elderly is inconclusive [55].

Diabetes and Tuberculosis

In the pre-insulin era, tuberculosis used to be a very frequent cause of death in diabetic patients [56-58]. In 1928, Jacobsen reviewed the clinical course of the first 251 diabetic patients ever treated with insulin in Denmark [59]. Of 34 early deaths within four weeks after treatment was started, 14 diabetic patients died of infection (among these five of tuberculosis, and three of pneumonia). Early studies of the association of diabetes and tuberculosis were hampered by selection problems and lack of control groups, but more recent studies provide some evidence that an association is truly present. A systematic review from 2007 included 9 case-control and cohort studies and found that diabetes was consistently associated with an increased risk of tuberculosis, however with widely differing relative risk estimates between 1.5 and 7.8 [60]. A more recent meta-analysis from 2008 included 13 epidemiologic studies [61]. This review found that diabetes was associated with a 3.1 (2.3-4.3) times elevated risk of tuberculosis in three cohort studies, and with odds ratios between 1.16 and 7.83 in ten case-control or cross-sectional studies. Odds ratios were 1.50, 1.61, and 1.65, respectively, in the three largest case-control studies, and odds ratios increased with decreasing study size, indicating some publication bias. Most of the studies did not properly adjust for confounding factors. In a case-control analysis of 5,290 hospitalized TB cases by Pablos-Mendez *et al.* [62] among ethnic groups in California, adjusted TB ORs from diabetes were 0.93 (0.78-1.09) among Blacks, 1.31 (1.19-1.45) among Whites, and 2.95 (2.61-3.33) among Hispanics, respectively. Recently, Leung *et al.* [63] followed a cohort of 42,116 patients aged 65 years or more in Hong Kong; diabetes was associated with adjusted TB hazard ratios of 1.77 (1.41-2.24) for any active TB and 1.89 (1.48-2.42) for pulmonary TB. Interestingly, diabetic subjects with hemoglobin A1c $<7\%$ at enrollment were not at increased risk. Even newer results from highly developed countries suggest that any tuberculosis risk increase from diabetes may be lower than previously thought in this setting [64]. Dobler *et al.* compared the incidence of active TB in Australia between 2001 and 2006 among 802,087 people with diabetes and close to 20 million people in the general population, and found an adjusted RR of TB of 1.48 (95% CI 1.04-2.10) in those with diabetes [64]. In a Danish population-based case-control study including 2,950 patients with tuberculosis and 14,274 matched population controls, the adjusted OR for active TB in diabetic versus nondiabetic individuals was only 1.18 (95% CI 0.96-1.45) [65]. Unfortunately, epidemiological studies of the diabetes-tuberculosis association are sparse in Africa, where the increasing prevalence of (often poorly controlled) diabetes may fuel a surge in tuberculosis in a region which already has the highest global incidence rate of tuberculosis [66]. Faurholt-Jepsen *et al.* recently conducted a case-control study in Tanzania, and examined diabetes among 803 confirmed

pulmonary TB patients and 350 neighborhood controls. Diabetes was associated with a TB OR of 2.2 (95% CI 1.5-3.4), and this association was restricted to HIV uninfected individuals [67]. Goldhaber-Fiebert *et al.* undertook a cross-sectional analysis using the World Health Survey (n = 124,607; 46 countries) and estimated that in lower-income countries, individuals with diabetes are 1.8 (1.4-2.4) times more likely than non-diabetic individuals to have TB [68]. It is currently not clear if diabetes makes individuals more susceptible to initial tuberculosis infection or increases the development of active tuberculosis from latent infection [66]. Diabetes may also affect the nature and severity of tuberculosis, including infectivity and responsiveness to treatment [60, 66]. Finally, several studies have reported a highly increased risk of multi-drug resistant tuberculosis among diabetic persons [69, 70]. In conclusion, there is growing evidence that diabetes is associated with a moderately to highly (RRs between 1.5 and 3.0 in most studies) increased relative risk of tuberculosis, in particular if diabetes is poorly controlled. In particular for settings such as sub-Saharan Africa, where diabetes diagnosis, treatment and control is hampered by limited infrastructure and health care systems [71], it is feared that this association may exert a significant “double burden” of communicable and non-communicable disease in the future [72-76].

Conclusions on Diabetes and Community-Acquired Respiratory Tract Infections

In conclusion, there is now much evidence that the risk of (in particular hospitalized) pneumonia is 1.3 to 1.5 times increased in diabetic patients, and their risk of tuberculosis may be 1.5 to 2 times or even more increased, depending on glycemic control and diabetes-associated comorbidity.

Influenza and pneumococcal vaccination is recommended in these patients. Treating physicians should be aware of the modestly increased risk of death in diabetic patients with lower respiratory tract infections. As in other patients, choice of antibiotic therapy should integrate local sensitivity patterns of the infecting organism, as well as place of acquisition and severity of disease.

DIABETES AND THE RISK OF COMMUNITY-ACQUIRED URINARY TRACT INFECTIONS

Urinary tract infections (UTIs) are among the most frequent community-acquired infections, with a self-reported yearly incidence of about 10% in adult women [77]. UTIs seem to be a common clinical problem in diabetic patients [78-80], but formal evidence for any association has been scarce until recently.

Diabetes and Asymptomatic Bacteriuria

As reviewed by Boyko and Lipsky in 1995 [10], 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 in the Netherlands (ASB 26% in diabetic vs 6% in non-diabetic females) and in Africa (32% in diabetic vs 11% in non-diabetic) confirmed these findings [81, 82], whereas another study from Italy found similar prevalences of ASB (18% in both) in female type 2 diabetes outpatients when compared with female non-diabetic outpatients visiting a cardiology

clinic [83]. In a prospective cohort study, Boyko *et al.* found a 2.3 times (95% CI: 1.3-3.9) increased ASB risk for diabetic compared with nondiabetic women [84]. The spectrum of uropathogens and the profile of antibiotic resistance has shown to be similar in diabetic and nondiabetic patients with ASB [85]. Although ASB is a well-known predictor of symptomatic UTI, a randomized controlled trial in 2002 demonstrated that antibiotic treatment of ASB in women with diabetes does not reduce the risk of later UTI episodes [86].

Diabetes and Cystitis

For symptomatic urinary tract infections, not until recently have epidemiologic studies convincingly proven an association with diabetes [87, 88]. 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) [89]. A doubled incidence rate of UTI associated with diabetes has been confirmed in different prospective cohort studies including thousands of postmenopausal women, for example by Brown *et al.* [90] (OR 1.8, 95% CI 1.4-2.3) and Boyko *et al.* [84] (RR = 1.8, 95% CI: 1.2-2.7) in the U.S. A large Canadian cohort study found that the RR of a hospitalization or physician claim for UTI associated with DM was 1.39 (95% CI: 1.36-1.42) for cystitis and 1.95 (95% CI: 1.78-2.13) for pyelonephritis [29]. Muller *et al.* [32] in general practice in Holland found UTI ORs of 2.0 (95% CI 1.5-2.6) for T1 diabetes and 1.2 (95% CI 1.1-1.4) for type 2 diabetes. Others have suggested that the cystitis relative risk may be lower in T1 than T2 diabetic persons. In a recent study of 550 primarily premenopausal women with T1 diabetes, 15% reported at least one diagnosis of cystitis in the preceding 12 months; this prevalence was similar to that among nondiabetic women participants in the U.S. National Health and Nutrition Examination Survey III (NHANES III) [87]. Sexual activity rather than diabetes duration, glycemic control and diabetic complications appeared to be the main risk factor for UTI in this cohort.

Diabetes and Pyelonephritis

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 [91]. A population-based case-control study from Washington corroborated a highly increased (adjusted OR 4.1, 95% CI 1.6-10.9) risk of pyelonephritis associated with diabetes among healthy women aged 18 to 49 years [92]. Diabetes is also associated with worsened prognosis among elderly patients hospitalized with pyelonephritis [93, 94].

The Role of Hyperglycemia in UTI Risk

The biological mechanisms of increased UTI risk among diabetic patients remain uncertain but are likely to include immune mechanisms responsive to the quality of glycemic control [14, 95]. The few clinical studies addressing the impact of baseline glycemic level on subsequent UTI risk had conflicting results [33, 84, 89, 90, 96, 97]. Two case-control

studies did not find significantly more UTIs among diabetic patients with a baseline HbA1c level over or under 8.0% and 9.0%, respectively [89, 96]. Three cohort studies reported no major differences in relative risk estimates for UTI according to glycemic control [84, 90, 97]. Risk estimates were provided only in the study conducted by Boyko *et al.* [84] and tended to be increased with worse glycemic control; adjusted UTI hazard ratios for baseline HbA1c values of $\leq 7.5\%$, 7.6–8.5% and $> 8.5\%$ were 1.3 (95% CI 0.7–2.3), 1.8 (95% CI 0.9–3.3) and 1.9 (95% CI 0.7–4.8), respectively. A recent cohort study by Benfield *et al.* found a 10% increased risk for hospitalizations with UTI diagnoses over 7 years of follow-up for each 1 mmol/L increase in baseline plasma-glucose [33]. In contrast, Czaja *et al.* found that neither HbA1c nor intensive glycemic therapy during the Diabetes Control and Complications Trial was associated with cystitis risk in Type 1 diabetic women [87]. Very few studies have provided data on UTI risk associated with changing glycemic control in diabetic patients. A recent Danish prescription study determined the risk of antibiotic-treated UTI episodes in a population-based cohort of 2737 Type 2 diabetic patients who switched from oral antidiabetic drug (OAD) to insulin therapy. Each patient was observed for 365 days before and after the switch-to-insulin date. The annual risk of antibiotic-treated UTI was high both on oral therapy (16.0%) and insulin therapy (16.3%), and no evidence was found that switch to insulin therapy with or without tightened glycemic control decreased the risk of UTI episodes [88].

The role of hyperglycemia is thus still unclear at present but does not seem as crucial as once thought. The evidence suggests that long diabetes duration and diabetic complications may be more important than current glycemic control, including diabetic cystopathy with retention of urine, incontinence, and an increased likelihood of instrumentation of the urinary tract [84, 88, 98]. Other important biological mechanisms may include a general predilection for certain microorganisms in diabetes, including *Escherichia coli* and *Klebsiella* species [84, 99, 100]. Geerlings *et al.* showed that virulent type 1-fimbriated *E. coli* adhere much more to the uroepithelial cells of diabetic women than other women [99]. The authors suggested that the increased binding to diabetic uroepithelial cells is caused by a difference between the type 1 fimbriae receptor on diabetic and nondiabetic uroepithelial cells.

Conclusions on Diabetes and Community-Acquired Urinary Tract Infections

In conclusion, there is much evidence that the risk of ASB and cystitis is 1.5 to 2 times increased in diabetic patients, and their risk of pyelonephritis may be 2 to 4 times increased. Treatment of ASB is generally not recommended. As in other individuals, history of previous UTI is a strong predictor for subsequent UTIs, and sexual activity and use of certain contraceptives are important modifiable UTI risk factors [87, 101]. Choice of antibiotic therapy should integrate local sensitivity patterns of the infecting organism, and rare complications as emphysematous cystitis and pyelonephritis should always be kept in mind [98].

DIABETES AND THE RISK OF COMMUNITY-ACQUIRED BACTEREMIA AND SEVERE SEPSIS

Bacteremia constitutes the most severe end of the spectrum of frequent community-acquired infections such as pneumonia and UTI, and the prevalence and thus disease

burden of bacteremia has increased during the last decades analogous with diabetes. In 2003, Martin *et al.* reported that the annual prevalence of discharge diagnoses of septicemia, bacteremia or disseminated fungal infections in U.S hospitals had increased from 0.8 discharges/1,000 inhabitants in 1979 to 2.4 discharges /1,000 inhabitants in 2000 [102]. In 2006, septicemia was ranked the 10th leading cause of death in the United States, constituting the largest group of severe infections with known microbial etiology [20]. In Denmark, the incidence rate of microbiologically confirmed bacteremia has increased by 46% from 1992 through 2006 (from 114 to 166 episodes per 100,000 person-years). This bacteremia increase is not explained by changing demographics, but possibly explained by more frequent blood cultures and more prevalent comorbidity in the background population, including increasing prevalence of diabetes [103].

Diabetes and Bacteremia/Sepsis Due to Various Pathogens

In two early studies from the 1990s in North Carolina and Spain, the authors compared the prevalence of mixed bacteremia among all their hospitalized patients with and without diabetes over several years in a cross-sectional design [104, 105]. 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. In the large population-based Canadian cohort study of more than 500,000 diabetic persons and non-diabetic comparisons, the risk ratio for hospitalization with sepsis among diabetic patients was 2.5 (95% CI: 2.2–2.7) [29]. A 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 [106]. Standardized mortality rates for septicemia in diabetic patients compared with the general 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. These results mixed incidence and case fatality of septicemia in diabetes, however. Most studies in the 1980s and 1990s reported a similar in-hospital case-fatality following bacteremia in diabetic and non-diabetic patients, which was corroborated in recent cohort studies from Taiwan [107] and Switzerland [108]. These findings may be related to a larger proportion of diabetic cases having (prognostically more benign) urosepsis. It therefore becomes pertinent to examine the association between diabetes and specific important groups of community-acquired bacteremia due to pneumococci, enterobacteria, streptococci, and staphylococci.

Diabetes and Pneumococcal Bacteremia

S. pneumoniae accounts for at least 50% of microbiologically confirmed community-acquired pneumonias [109–112]. Pneumococcal bacteremia is probably a common feature of pneumococcal pneumonia, though it may be detected in less than ten percent of hospitalized cases [113–115]. Conversely, 80% of patients with pneumococcal bacteremia have a RTI focus [116, 117]. The increased risk of RTIs in persons with diabetes has been discussed above. As reviewed by Smith and Poland in 2000 [28], data about diabetes as risk factor for pneumococcal

bacteremia at that time came primarily from case series. Diabetes prevalence in these studies 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 [105], the prevalence of bacteremia with *S. pneumoniae* was two times increased, whereas the similar U.S. study found no increase for this group of bacteremia [104]. 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 [114], suggesting that diabetes is a risk factor for bacteremic pneumococcal pneumonia. In a much-cited 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.* [118] 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 association was no longer statistically significant (risk estimates not given). A population-based case-control study from Denmark included 598 adults with pneumococcal bacteremia and ten matched controls per case [119]. 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). In comparison, a similar subsequent case-control study found an adjusted OR of 1.3 (95% CI: 1.2-1.3) for pneumonia hospitalization associated with diabetes [26]. Among the pneumonia patients, a similar proportion of diabetic and nondiabetic individuals were blood cultured (60% in both groups); the adjusted RRs for having any bacteremia in cultured diabetic vs non-diabetic patients was 1.02 (95% CI 0.78-1.33); and for pneumococcal bacteremia was 1.17 (95% CI 0.84-1.62). In conclusion, recent evidence suggests that diabetes is associated with a moderately (approximately 1.5-fold) increased risk of pneumococcal bacteremia, and that this risk increase is comparable with, or slightly higher than, the risk increase for pneumonia.

Diabetes and Enterobacterial Bacteremia

Although previous studies have reported an increased risk of UTI and in particular pyelonephritis, associated with diabetes (see above), there are few studies of the association with the most life-threatening consequence of UTI, bacteremia caused by gram-negative bacilli such as *E. coli* and other enterobacteria. Case-series from the beginning of the 2000s reported a diabetes prevalence of 20-30% among patients with enterobacterial bacteremia [120], and up to 40% among patients with community-acquired *Klebsiella pneumoniae* bacteremia [121]. East Asian cases series have reported a diabetes prevalence of approximately 75% among pyogenic liver abscess patients infected with *Klebsiella pneumoniae* [122, 123], and diabetes has since been confirmed as strong risk factor for pyogenic liver abscess in European and North American studies [124, 125].

Early cross-sectional studies of diverse bacteremias have estimated that the prevalence of enterobacterial bacteremia in diabetic patients was two- to threefold increased [105, 126].

In 2005, Jackson *et al.* [127] conducted a nested case-control study including 184 seniors with community-acquired *E. coli* bacteraemias and 769 matched controls. The prevalence of diabetes in bacteremia cases vs controls was 21% vs 18% among men and 20% vs 9% among women. The authors stated that diabetes mellitus was associated with an increased risk of *E. coli* bacteremia from a urinary source in women in an age-adjusted model (OR 2.42, 95% CI 1.40–4.17), yet diabetes was not selected for the final multivariate model [127]. In 2005, diabetes was examined as a risk and prognostic factor for community-acquired bacteremia caused by *E. coli* and other enterobacteria in Denmark [128]. This population-based case-control included 1,317 adult case patients and ten population controls per case and found that persons with diabetes had a substantially increased risk for enterobacterial bacteremia (adjusted odds ratio = 2.9, 95% CI: 2.4-3.4). Among bacteremia patients, diabetes was furthermore associated with a poorer prognosis [128], whereas another cohort study from Spain found that diabetes was not associated with worse prognosis following Enterobacteriaceae bacteremia [129]. Laupland *et al.* conducted a population-based surveillance of *E. coli* bacteremia in a large Canadian region during 2000–2006 [130]. They estimated the approximate number of persons with diabetes and other risk factors based on Canadian survey data, suggesting that diabetic individuals may have a crude incidence rate ratio of 7.2 (6.4–8.0) for *E. coli* bacteremia, not taking into account possible confounding by age and other comorbidity however.

In conclusion, there is strong evidence that diabetes is associated with at least 2.5 to 3 times increased risk for bacteremia due to *E. coli* and other enterobacteria, which compares to the 2 times increased risk of cystitis and the up to 4 times increased risk of pyelonephritis discussed above, given that the majority of community-acquired bacteremias with enterobacteria are due to an UTI focus [128, 130].

Diabetes and Streptococcal Bacteremia

Hemolytic streptococci (HS) are an increasingly common cause of severe bacteremia and sepsis worldwide [131-133]. These infections are most often community-acquired and derived from a skin or soft-tissue or an unknown focus. In the U.S., the incidence of adult invasive group B streptococcal (GBS) infection has more than doubled between 1990 and 2007 to 7.3 cases per 100,000 persons in 2007, and now approaches the incidence of invasive pneumococcal infections in elderly people [134]. The increasing prevalence of adults with chronic medical conditions remains the most plausible explanation for the increasing incidence of adult invasive HS disease. In particular, several studies have indicated a strikingly high prevalence of diabetes among patients with invasive HS disease [135]. For GBS invasive disease, many case series from both North America, Asia and Europe have reported diabetes prevalences of approximately 30% [136-143]. Among patients with severe GAS infections, 8% (with a wide range of 0% to 22%) had diabetes in a recent 2-year prospective surveillance study in 11 European countries [132]. In Denmark in 1999-2002, Ekelund *et al.* found comparable prevalences of diabetes in patients with invasive infection due to GAS (11%), GBS (14%) and GGS (16%) [131]. Only two case-control studies of HS invasive disease

have reported on the role of diabetes among a variety of risk factors. In Factor *et al*'s GAS case-control study including 139 patients with invasive GAS disease in the US and Canada [144] the relative risk associated with diabetes was 2.1 among persons 18-44 years old (crude odds ratio (OR), 2.1; 95% confidence interval (CI), 0.6-7.1) (adjusted OR not reported). Among persons 45+ years old the crude OR was 2.3 (95% CI, 1.2-4.5) and the adjusted OR 2.3 (95% CI, 1.1-4.8). In Jackson *et al*'s GBS case-control study of 219 nonpregnant adult GBS cases the adjusted OR for diabetes was 3.0 (95% CI, 1.9-4.7) [145].

Thus, there is increasing epidemiological evidence that bacteremia risk due to hemolytic streptococci may be increased 2 times in diabetes, and at least 3 times specifically for GBS bacteremia.

Diabetes and Staphylococcal Bacteremia

Staphylococcus aureus is a major cause of community-acquired bacteremia and severe sepsis worldwide, although most cases are health care related [146]. As for hemolytic streptococcal bacteremia, skin and soft tissue is an important focus for *S. aureus* bacteremia.

Laupland *et al.* conducted a population-based surveillance of *Staphylococcus aureus* bacteremia in a large Canadian region during 2000–2006 [146]. As in an earlier *E. coli* study [130], they estimated the approximate number of persons with diabetes and other risk factors based on Canadian survey data. They suggested diabetes may have a crude incidence rate ratio as high as 10.6 (95% CI 9.3–11.9) for any *S. aureus* bacteremia, and 14.7 (10.4-20.6) for methicillin-resistant *S. aureus* (MRSA) bacteremia, not taking into account confounding by age and other comorbidity however. A survey study of all cases of invasive *S. aureus* infections in western Sweden from March 2003 to February 2005 used similar methods, estimating the number of individuals in the background population with diabetes. The authors suggested that the incidence of invasive *S. aureus* infections may be 8.2 (95% CI 6-12) times increased. No formal large population-based epidemiologic case-control or cohort studies, to our knowledge, have focused on diabetes as risk factor for *S. aureus* bacteremia.

Diabetic persons may have increased susceptibility to community-acquired streptococcal and staphylococcal bacteremia for several reasons, including tissue hyperglycemia and decreased oxygenation, and generally decreased immunity (see later). Mechanisms may also include shared risk factors for diabetes and skin or soft tissue infections, such as physical inactivity and obesity, which may lead to venous oedema and/or lymphoedema followed by relapsing erysipelas/cellulitis and ulcers of the leg [135, 147]. Moreover, diabetes *per se* may lead to peripheral vascular disease and neuropathy, and at least 15% of patients with diabetes will develop a foot ulcer in their lifetime [148, 149]. Moreover, diabetes is a major risk factor for chronic heart failure [150] that subsequently may lead to venous oedema, leg ulcers and infections. Correspondingly, the risk ratio for cellulitis (=1.8; 95% CI, 1.8-1.9) was among the highest for a range of examined infections among diabetic individuals in Ontario, Canada [29]. Cellulitis is a major focus of infection for GAS and GGS bacteraemia [131, 132, 151]. The risk of foot ulcers is known to increase with

diabetes duration and poor glycemic control [148]. Some studies have suggested an increased prevalence of colonization with *S. aureus* in diabetic individuals [152], and colonization may be a risk factor for infection [153]. Insulin injections and blood glucose self monitoring may theoretically increase bacterial colonization, yet manifest infections after such penetrating traumas (“finger sepsis”) are rarely reported [154].

METHODOLOGICAL CHALLENGES WHEN EXAMINING THE ASSOCIATION BETWEEN DIABETES AND COMMUNITY-ACQUIRED INFECTIONS

Increased Surveillance of Diabetic Patients for Infections

Infection as a diabetic complication is still not mentioned much even in updated diabetes guidelines [27]. Yet, it is likely that patients with diabetes are generally more closely followed for development of infections by their caregivers, due to clinical experience and anticipated problems with glycemic regulation [119]. In some settings, diabetic patients have been provided with information leaflets and education about UTI and RTI risk and management, and this has been found to positively influence their health-seeking behavior in a Dutch randomized trial [155]. Also, physicians may be more likely to admit a diabetic patient with infection to the hospital, due to anticipated dysregulation, dehydration and worsening of diabetic complications [27]. Such bias would lead to overestimation of the relative risk of infection associated with diabetes in infection hospitalization studies. There is some evidence in the literature for increased hospitalization versus outpatient treatment of diabetic individuals with infection. 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 in primary or secondary care, but 2.01 (99% CI: 1.96-2.06) for infections requiring hospitalization. A U.S. cohort study suggested that diabetic persons who develop pneumonia are more likely to be hospitalized than nondiabetic persons (hospitalizations for pneumonia, adjusted RR = 1.52; outpatient visits for pneumonia, adjusted RR = 0.90) [30]. These findings may be either due to hospitalization of a higher proportion of diabetic than non-diabetic persons with the same severity of infection, or may be due to increased severity of infection caused by diabetes, or both. For example, several studies found that compared with non-diabetes, diabetes confers a lower relative risk increase for URTI (which in many instances precedes LRTI) than for LRTI [29, 32]. Similar considerations may apply to the continuum of cystitis -> pyelonephritis -> urosepsis and Gram-negative bacteremia, or wound infection -> cellulitis -> streptococcal bacteremia. For the worst category in the infectious disease spectrum, bacteremia, there might furthermore be detection bias by more frequent blood cultures done in diabetic persons. However, earlier population-based studies of diabetes patients hospitalized with pneumococcal bacteremia [156] or pneumonia [40] showed that both pre-admission prescriptions of antibiotics, levels of inflammatory markers on admission, and proportions of patients with at least one blood culture were similar among patients with diabetes and nondiabetic patients. This suggests that there was no severe bias associated with surveillance and treatment of infected patients with diabetes in a population-based setting [40,

156]. In conclusion, some surveillance bias is likely to be present, but it is unlikely to fully explain risk ratios of 1.5 to 2 or more as seen for many of the infections discussed above.

Misclassification of Diabetes

The risk of missing undetected diabetes may be greater for non-infected controls than for infected case patients in some studies [119], and stress hyperglycemia may be misinterpreted as diabetes in some cases, both leading to an overestimation of the relative risk of infection from diabetes. It may be preferable to collect data on diabetes exposure and possible confounding factors before the date of contact with infection [26].

Uncontrolled Confounders

Uncontrolled confounding may have affected relative risk estimates in many studies. In general, this may have led to an overestimation of the relative risk of infection from diabetes, since many factors predictive of infection are expected to be more prevalent in diabetic than other persons. These diabetes-associated factors include increased age and associated immunosenescence, ethnicity, lifestyle factors such as smoking and alcohol overuse, socioeconomic factors including poorer housing, number of children in the household and crowding, possibly hygiene and sexual habits, a range of comorbidities as mentioned above, immunosuppressive therapies including glucocorticoids, and genetic immunodeficiencies such as mannose-binding lectine. Importantly, direct effects of diabetes should not be considered confounders in any study assessing the impact of diabetes on infection risk [157]. Such mediators of diabetes effect on infection risk may include diabetes complications such as cardiovascular or renal comorbidity, or drug treatment as a consequence of diabetes. Mediators may also include economic or lifestyle factors, e.g. alcohol overuse or inability to work, that may be negatively affected by receiving a chronic and sometimes invalidating diagnosis as diabetes. On the other hand, diabetic patients may also receive more infection-prophylactic interventions such as smoking cessation and immunizations [27], tending to decrease their risk of infection.

SUGGESTED BIOLOGICAL MECHANISMS THAT MAY PLAY A ROLE IN THE ASSOCIATION BETWEEN DIABETES AND COMMUNITY-ACQUIRED INFECTIONS

The Impact of Diabetes and Hyperglycemia on Inflammation and Immune Function

Unlike type 2 diabetes which is often associated with hyperinsulinemia, type 1 diabetes is characterized by reduced or totally absent insulin secretion. It is well-known that insulin exerts anti-inflammatory signaling [158-160]. In contrast, hyperglycemia triggers robust proinflammatory responses demonstrable *in vivo* and *in vitro* [161, 162]. Since a variable proportion of type 2 diabetic patients and all type 1 diabetic patients are treated with external insulin to reduce their hyperglycemia, the net effect of these exposures becomes complicated to elucidate. It is well-substantiated however, that diabetes is associated with chronic low-grade inflammation. Elevated levels of C-reactive protein and interleukin 6 (IL-6) predict development of type 2 diabetes

in healthy individuals [163], and manifest diabetes is associated with increased levels of circulating proinflammatory cytokines such as IL-6 [164].

Parallel with the chronic low-intensity inflammation, cytokine responses to an acute infectious challenge seem to be reduced in patients with diabetes. In a mice model of experimental sepsis, diabetic mice had a profound and wide-ranging suppression of systemic cytokine release compared to non-diabetic mice [161]. Among women with asymptomatic bacteriuria, those with diabetes had a lower concentration of IL-6 in the urine compared with non-diabetic women, and their monocytes secreted less pro-inflammatory cytokines after stimulation with lipopolysaccharide *in vitro* [165]. Andreasen *et al.* exposed type 2 diabetic patients and healthy controls to an intravenous injection of *E. coli* lipopolysaccharide. They found that type 2 diabetes was associated with less pronounced lipopolysaccharide-induced increases in TNF and several other cytokine responses [166]. Others have hypothesized that deficiencies in the innate immune system may underly both increased diabetes risk and increased infection risk. For example, mannose-binding lectin deficiency has been associated with increased risk of type 1 diabetes, insulin resistance, and obesity [167]. Because mannose-binding lectin deficiency is associated with decreased inherent ability to sense and buffer environmental substances, it may lead to both increased low-grade chronic inflammation and increased risk of infection [168].

Concerning prognosis of infection, it has been speculated that diabetic patients with sepsis may be protected from severe complications, such as ARDS, *via* a less active inflammatory cascade [156, 169]. Recently, Esper *et al.* examined the impact of pre-existing diabetes on organ dysfunction among 12.5 million sepsis patients [170]. They concluded that diabetes patients, relative to non-diabetic individuals, were less likely to develop respiratory failure during the course of sepsis. On the other hand, diabetic patients were more likely to develop renal failure [170]. Also, while hyperglycemia is associated with decreased acute inflammation in humans with endotoxemia, hyperglycemia at the same time potentiates coagulation and may thus make diabetic patients especially vulnerable to prothrombotic events [15]. Cohort studies from Denmark [40] and Canada [41] have clearly demonstrated the association between glucose levels of more than 11 mmol/L on admssion and increased mortality following pneumonia, as discussed above. Interestingly, several studies have found that acutely high initial glucose levels on admission with severe infection are much stronger predictors of death in nondiabetic than in diabetic individuals, for example among patients with pneumonia [40, 41, 171] and sepsis [172].

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* [173]. 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 [174]. Others demonstrated that

hyperglycemia impairs the generation in leukocytes of oxygen free radicals and hydrogen peroxide required for intracellular killing of microorganisms [175]. The clinical significance of these findings remains uncertain.

Thirty years ago, 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 [176]. The evidence from newer studies suggests that severely dysregulated diabetes increases a number of specific infections more than well-regulated diabetes does, this evidence is discussed in more detail above. Randomized trials have shown that surgical patients who are fed parenterally experience more infections as compared to patients on enteral nutrition, potentially associated with development of severe hyperglycemia [177, 178]. 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 in certain groups of diabetic and non-diabetic patients [179, 180]. It is debated whether this observed effect may be due to reduced harm of hyperglycemia, or beneficial anti-inflammatory effects of insulin [158]. Intensive glucose control increased mortality among adults in the ICU in the large international randomized NICE-SUGAR trial [181]. Therefore, very tight glycemic control in critical illness including severe sepsis is not recommended in updated guidelines, and more moderate recommendation to target a blood glucose concentration between 144 mg/dL and 180 mg/dL (8-10 mmol/L) in critical illness is currently advocated [182].

Infections Causing Metabolic Derangement in Diabetes

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 type 2 diabetes) 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 [183]. 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. It has been known for long that infection and ketoacidosis frequently co-occur [184, 185], whereas it may be difficult to determine if hyperglycemia caused the infection or vice versa. During periods of influenza epidemics, an increased prevalence of hospitalizations with ketoacidosis has been observed [186]. 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 [187]. 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 [188].

CONCLUSIONS

There is now epidemiological evidence that individuals with diabetes have increased risk of some of the most frequent and severe community-acquired infections in society: respiratory tract infections, urinary tract infections, and bacteremia. This association is of major clinical and public health importance as the number of persons with diabetes is rapidly increasing. Compared with vascular diseases and other "classic" diabetes complications, infections have been a rather neglected area of diabetes research. Thus, the exact underlying mechanisms for the increased infection risk in patients with diabetes (including hyperglycemia, comorbidity, obesity, late diabetes complications, impaired immune function, and lifestyle factors) remain uncertain. In addition to prevention of diabetes, new research may focus on the relative importance of vaccines, patient and caregiver education, and modifiable risk factors among diabetic individuals, including good glycemic control, lifestyle factors, and existing antidiabetic drug therapies of which some (e.g. statins, metformin, insulin) may have beneficial effects against infections.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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