Chapter 22

Infection and Diabetes

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SUMMARY

To summarize the evidence for and against a higher infection risk in diabetic subjects, several terms will be used. "Probable" means that the data support the presence of this association, "possible" indicates that presence or absence of an association cannot be established from current data, and "doubtful" indicates that data argue for no association.

Diabetic subjects probably have a higher risk of the following infections: asymptomatic bacteriuria, lower extremity infections, reactivation tuberculosis in American Indians, infections in surgical wounds after sternotomy and total hip replacement, and group B streptococcal. Support for these associations comes from controlled observational studies in all cases, except for lower extremity infections, where the magnitude of the association between foot and ankle infection and diabetes from hospital-based data appears too great to be explained by detection, selection, or other potential biases. Local and systemic immunologic defects probably account for higher infection rates in diabetic patients. Autonomic and sensory neuropathy probably account for higher bacteriuria and lower extremity infection rates, while systemic immunologic effects of diabetes may be responsible for the increased propensity to surgical wound infection and tuberculosis reactivation. Population-based data support a probable higher influenza/pneumonia mortality rate in patients with diabetes.

There is a possible association between diabetes and prevalence of the following infections: cystitis, pyelonephritis, candida vulvovaginitis and cystitis, pneumonia, influenza, chronic bronchitis, bacteremia, primary tuberculosis, reactivation tuberculosis in non-American Indians, mucormycosis, malignant otitis externa, and Fournier's gangrene. Doubtful associations exist between diabetes and prevalence of chronic sinusitis or *S. aureus* colonization.

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INTRODUCTION

Clinicians often express the belief that diabetic patients are at higher risk for various infections than nondiabetic patients. Reviews of this subject have concluded that data supporting a higher risk for many infections in diabetes are inadequate[1-3] . Immunologic research has, however, demonstrated several defects in host immune defense mechanisms in diabetic subjects. Phagocytic capabilities of polymorphonuclear leukocytes (PMN) are adversely affected by hyperglycemia in rat models[4]. Several PMN defects occur in diabetic subjects, including impaired migration, phagocytosis, intracellular killing, and chemotaxis[5], which may be due to decreased PMN membrane fluidity[6]. Generalized immunologic defects such as these raise the suspicion that diabetic patients may be at an overall increased risk for infection.

Besides generalized impairments of immunity, other nonimmunologic, anatomically specific factors may contribute to an increased infection risk. Macrovascular disease and microvascular dysfunction may result in compromised local circulation leading to delayed response to infection[7] and impaired wound healing[8]. Unawareness of lower extremity trauma due to sensory neuropathy may result in inadequate attention to minor wounds and subsequent increased infection risk[9]. Incomplete bladder emptying due to autonomic neuropathy permits urinary colonization by microorganisms[10,11]. High glucose concentration in the urine promotes the growth of some microorganisms[12].

Although these immunologic and anatomical factors would seem to put diabetic subjects at higher risk for infection, only a few infectious diseases have been shown to occur more frequently in diabetic subjects on the basis of studies that used a nondiabetic control group.

GENITOURINARY INFECTION

Several types of urinary tract infections occur more commonly in diabetic patients. These include, in increasing clinical severity, asymptomatic bacteriuria, cystitis, emphysematous cystitis, pyelonephritis, emphysematous pyelonephritis, and perinephric abscess. Asymptomatic bacteriuria is usually considered to be significant if $\geq 10^5$ microorganism colonies per ml grow in urine culture in the absence of cystitis symptoms (dysuria, frequency, urgency). Since upper urinary tract infection (pyelonephritis) is thought to usually occur by bladder organisms ascending the ureters, one would suspect higher rates of bladder colonization or infection to be associated with higher rates of pyelonephritis. Several severe and less common urinary tract infections are thought to occur more frequently in diabetes. Emphysematous infections refer to those complicated by gas formation due to bacterial fermentation[13]. This may occur in the bladder (cystitis) or in the renal pelvis or parenchyma

Table 22.1
Studies on the Association Between Diabetes and Bacteriuria

Outcome definition	Description of subjects: Diabetic	Description of subjects: Nondiabetic	Outcome prevalence (%): Diabetic	Outcome prevalence (%): Nondiabetic	Adjustment factors	Comments	Ref.
Asymptomatic bacteriuria	Outpatients; F=54, M=37	Outpatients; F=337, M=102	F=18.0 M=5.0	F=6.0 M=4.0	None		15
Bacteriuria	Outpatients; F=91, M=59	Casualty dept.; F=91, M=59	F=19.8 M=3.3	F=18.7 M=1.7	Similar age and sex distribution	Nondiabetic subjects presented to casualty department with minor trauma; friends and relatives of nondiabetic subjects also selected for the nondiabetic group	21
Asymptomatic bacteriuria	Outpatients; F=81, M=67	Outpatients; F=81, M=67	F=18.5 M=7.5	F=7.5 M=3.0	Age and sex matched	Subjects with recent antibiotic use were excluded	19
Bacteriuria	Consecutive outpatients; F=128, M=141	Casualty dept.; F=114, M=146	F=18.8 M=0.7	F=7.9 M=2.1	Similar age and sex distribution		25
Asymptomatic bacteriuria	Outpatients; F=97, M=149	Outpatients; n=100 (sex not specified)	F=11.3 M=10.7	Combined M&F=3.0	None		18
Asymptomatic bacteriuria	Outpatients; F=60, M=40	Outpatients; F=36 (all age >60 years)	F>60yrs=20 F<60yrs=0 M=2.5	F=2.8	None		20
Asymptomatic bacteriuria	Outpatients; F=152, M=154	Outpatients; F=152, M=159	F=15.8 M=1.3	F=4.6 M=0.7	Matched on age in decades, sex, and parity	Subjects with diastolic blood pressure ≥100mm were excluded; subjects with known renal disease were excluded from the nondiabetic group	22
Bacteriuria	Outpatients; F=111, M=87	Outpatients; F=79, M=68	F=27.0 M=8.0	F=11.4 M=2.9	None	Subjects with known urinary tract disease were excluded from the nondiabetic group	23
Asymptomatic bacteriuria	Not specified; F=47, M=53	Not specified; F=48, M=52	F=10.6 M=3.8	F=8.3 M=1.9	Age and sex matched	Subjects with urinary symptoms were excluded	26
Asymptomatic bacteriuria	Outpatients; F=100, M=90	Outpatients; F=100, M=90	F=9.0 M=3.3	F=8.0 M=2.5	Matched on age by decade and sex	Subjects with urinary complaints or known renal diseases were excluded from the nondiabetic group; all subjects with antibiotic use in the past month were excluded	17
Bacteriuria	Outpatients; F=341, M=411	Outpatients; F=100, M=100	F=9.1 M=1.0	F=5.0 M=0	None		24
Chemstrip LN	Population-based diabetic sample; n=206 (sex not specified)	Population-based nondiabetic sample; n=418 (sex not specified)	M&F= 5.8	M&F= 1.7	Age, ethnicity, sex, county of residence	Chemstrip LN used to assess presumptive bacteriuria prevalence; antibiotic use was an exclusion criterion	16

Source: References are listed within the table

(pyelonephritis). Perinephric abscess occurs when kidney infection extends into surrounding tissues. Renal papillary necrosis may result from an infectious etiology.

BACTERIURIA

More controlled studies have examined the prevalence of bacteriuria in diabetic compared with nondiabetic subjects than any other infection (Table 22.1)[14-26]. Bacteriuria (defined above) predisposes to cystitis and upper urinary tract infection[27]. Of the 12 studies in Table 22.1, 75% reported a higher (two- to fourfold increase) bacteriuria prevalence in diabetic subjects. Nearly all these studies chose cases from diabetic subjects attending outpatient clinics. Since clinic attendance is probably related to underlying disease severity, it is possible that these studies included diabetic subjects with more severe illness and comorbid conditions, who were thus at higher risk for bacteriuria. One study that sampled diabetic (including those previously undiagnosed) and control nondiabetic subjects from a defined community still found a higher bacteriuria prevalence associated with diabetes[16]. These data therefore support a higher prevalence of bacteriuria in diabetic subjects. No data exist on the incidence of bacteriuria associated with diabetes.

Several uncontrolled case series demonstrate a low prevalence of bacteriuria in children with insulin-dependent diabetes mellitus (IDDM). In two such studies, bacteriuria prevalences of 1.6-2.0% were found in 266 girls age 6-15 years attending a diabetes summer camp[28], and 1% in 304 girls and 0% in 337 boys attending regular follow-up appointments at a diabetes clinic[29]. Although these female rates may exceed those of nondiabetic children, the data suggest that bacteriuria in girls and boys with IDDM occurs very infrequently.

Longer duration of diabetes, but not glucose control, is associated with bacteriuria prevalence. A statistically significant longer diabetes duration was found for diabetic subjects with bacteriuria than without (9.9 versus 5.4 years)[24]. Bacteriuria prevalence increased 1.9-fold with each 10-year increase in diabetes duration[16]. However, there was no association between long-term glucose control, as reflected by glycosylated hemoglobin level, and bacteriuria prevalence[16,24].

CYSTITIS

Significant bacteriuria associated with lower urinary tract symptoms is thought to occur more commonly in diabetic subjects, but few studies have addressed

Table 22.2
Frequency of Infectious or Possibly Infectious Conditions by Diabetes Status, U.S., 1989

	Nondiabetic		All diabetic		IDDM		NIDDM, taking insulin		NIDDM, not taking insulin	
Condition and age (years)	No.	%	No.	%	No.	%	No.	%	No.	%
≥1 urinary tract infection in past 12 months (women)										
18-44	6,417	14.8	205	30.0	47	18.6	72	37.4	84	30.1
45-64	2,656	8.9	537	23.3			230	23.6	293	23.4
≥65	2,457	10.4	651	20.8			237	26.0	412	18.2
≥18	11,530	12.6	1,393	23.2			539	26.5	789	21.3
								All NIDDM		
Chronic sinusitis								No.	%	
18-44	1,921	18.4	58	28.4	21	34.1		37	25.1	
45-64	793	18.7	173	17.6				169	18.0	
≥65	632	15.4	159	14.7				159	14.7	
≥18	3,346	18.0	390	18.0				365	17.2	
Chronic bronchitis										
18-44	1,921	4.5	58	6.6	21	4.5		37	7.9	
45-64	793	6.1	173	7.6				169	7.7	
≥65	632	5.9	159	8.7				159	8.7	
≥18	3,346	5.2	390	7.9				365	8.2	

The table shows self-reported data from the 1989 National Health Interview Survey; No., total number of subjects surveyed; %, percentage reporting the condition, adjusted for survey sampling scheme; nondiabetic subjects include people who reported no medical history of diabetes; IDDM includes people who reported a medical history of diabetes diagnosed by a physician at age <30 years, who were taking insulin since diagnosis, and whose percent desirable weight was <120; all other subjects with physician-diagnosed diabetes were classified as NIDDM; data for IDDM for age ≥45 years is not shown due to small numbers of subjects surveyed.

Source: 1989 National Health Interview Survey

this question. The 1989 National Health Interview Survey (NHIS) Diabetes Supplement obtained population-based self-reported data on the prevalence of symptomatic urinary tract infection (Table 22.2). One or more self-reported infections occurred more frequently over the previous 12 months in diabetic women, compared with nondiabetic women. Since most urinary tract infections occur in the lower tract, these data probably reflect largely cystitis prevalence. This difference was seen in each of the three age strata examined (18-44, 45-64, ≥65 years). Both women with IDDM and women with non-insulin-dependent diabetes mellitus (NIDDM) appeared to have higher rates of urinary tract infection over the past 12 months, although the rate was highest in NIDDM women. In the 1976-80 Second National Health and Nutrition Examination Survey (NHANES II), diabetic men and women age 20-44 years more frequently reported bladder and urinary tract infections, compared with nondiabetic subjects (Table 22.3). At age

Table 22.3

Prevalence of Self-Reported Medical History of Infections by Diabetes Status, U.S., 1976-80

	Age 20-44 years		Age 45-54 years		Age 55-64 years		Age 65-74 years		Age 45-74 years	
Infection and diabetes status	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
Bladder infection					Percent with self-reported infection					
Diagnosed diabetes	3.1*	37.3	9.7	20.3	6.7	16.4	5.3	14.9	7.0	16.8
Undiagnosed diabetes	0.0*	44.3*	0.0*	9.1*	0.0*	35.5	0.0	12.9	0.0	21.4
IGT	2.1	27.1	1.9	17.2	3.0	22.1	4.4	10.4	3.1	16.2
Normal glucose tolerance	2.2	21.0	1.5	20.3	4.5	22.5	5.4	20.1	3.3	21.1
Bladder infection (physician diagnosed)										
Diagnosed diabetes	3.2*	34.4	11.2	27.0	6.0	17.3	4.4	16.5	6.9	19.4
Undiagnosed diabetes	0.0*	44.3*	0.0*	16.9*	2.2*	31.0	0.0	14.6	0.6	22.3
IGT	2.1	32.5	1.9	15.8	1.3	20.8	5.4	12.1	2.8	15.9
Normal glucose tolerance	2.6	21.9	1.9	21.4	4.7	22.8	5.3	18.4	3.6	21.2
Urinary tract infection										
Diagnosed diabetes	9.1*	24.0	5.5	14.2	9.1	11.3	2.4	10.6	5.6	11.8
Undiagnosed diabetes	0.0*	0.0*	0.0*	16.9*	2.3*	8.0	7.0	7.2	3.8	10.1
IGT	11.6	14.4	1.9	10.5	2.6	4.2	5.3	4.8	3.2	6.7
Normal glucose tolerance	5.1	13.2	3.3	12.6	5.3	8.9	5.1	8.6	4.4	10.4
Urinary tract infection (physician diagnosed)										
Diagnosed diabetes	6.3*	26.7	4.6	17.4	6.3	8.5	4.0	14.4	4.9	12.9
Undiagnosed diabetes	0.0*	24.9*	0.0*	13.7*	2.2*	14.9	6.9	4.8	3.8	11.5
IGT	11.6	13.6	1.9	10.5	1.2	5.6	8.1	5.0	3.7	7.2
Normal glucose tolerance	4.6	14.0	2.9	13.2	4.7	8.5	5.5	6.6	4.0	10.0
Kidney infection										
Diagnosed diabetes	29.2*	27.0	3.1	26.5	6.8	13.5	8.8	12.7	6.5	16.4
Undiagnosed diabetes	0.0*	6.4*	21.6*	19.7*	2.6*	27.7	1.0	10.2	7.1	20.2
IGT	7.6	15.9	4.2	8.7	1.3	10.3	2.8	8.5	2.7	9.1
Normal glucose tolerance	5.1	17.8	5.6	13.4	7.3	12.2	5.0	15.3	6.1	13.4
Kidney infection (physician diagnosed)										
Diagnosed diabetes	18.4*	22.9	8.4	33.2	4.2	16.5	9.4	16.8	7.4	20.7
Undiagnosed diabetes	0.0*	14.5*	21.6*	19.7*	2.8*	30.0	1.0	15.1	7.1	22.8
IGT	7.6	22.3	4.2	11.9	1.3	15.0	5.7	8.7	3.6	11.7
Normal glucose tolerance	5.3	19.7	4.9	17.1	6.5	13.5	6.6	17.4	5.8	15.9
Bronchitis (physician diagnosed)										
Diagnosed diabetes	6.5*	13.8	21.5	14.4	4.5	11.4	7.4	9.1	10.6	11.3
Undiagnosed diabetes	0.0*	14.1*	0.0*	6.0*	2.8*	8.7	9.2	3.6	4.9	6.4
IGT	0.0	6.0	0.0	11.9	5.9	6.5	10.7	9.6	5.6	9.6
Normal glucose tolerance	4.0	6.7	3.0	7.1	4.8	8.0	11.3	9.9	5.2	8.1
Tuberculosis (physician diagnosed)										
Diagnosed diabetes	0.0*	4.2	1.5	5.6	3.9	1.6	1.5	0.6	2.3	2.2
Undiagnosed diabetes	0.0*	0.0*	0.0*	0.0*	0.0*	6.1	3.5	0.0	1.6	2.7
IGT	0.0	0.0	3.7	4.8	0.6	0.0	2.6	1.8	2.2	2.4
Normal glucose tolerance	0.2	0.5	0.2	0.6	2.4	1.0	1.5	0.5	1.2	0.7

*Indicates unstable prevalence estimate due to small number of subjects. Diagnosed diabetes defined as medical history of diabetes diagnosed by a physician; undiagnosed diabetes defined as no medical history of diabetes with fasting plasma glucose ≥140 mg/dl or plasma glucose ≥200 mg/dl at 2 hours after a 75-g glucose challenge; IGT, impaired glucose tolerance, defined as no medical history of diabetes and fasting plasma glucose <140 mg/dl and 2-hour plasma glucose 140-199 mg/dl; normal glucose tolerance defined as no medical history of diabetes and fasting plasma glucose <140 mg/dl and 2-hour plasma glucose <140 mg/dl.

Source: 1976-80 Second National Health and Nutrition Examination Survey

45-74 years, diabetic men more frequently reported bladder and urinary tract infections than nondiabetic men, while diabetic women reported a lower frequency of bladder infection but a higher frequency of urinary tract infection, compared with nondiabetic women (Table 22.3). Although validation of reported urinary tract infection was not performed by medical record review, these data support other evidence for a higher cystitis prevalence in diabetic subjects. No prospective incidence data are available for cystitis in diabetic subjects. Emphysematous cystitis is purported to occur more frequently in diabetic subjects, but no direct comparison of the incidence or prevalence of this disorder in persons with and without diabetes has been performed. A high proportion of subjects with diabetes, ranging from 49%-79%, has been noted in case series that have included more than five patients[13,30,31].

OTHER URINARY TRACT INFECTION

Few population-based data exist on pyelonephritis, emphysematous pyelonephritis, perinephric abscess, or renal papillary necrosis incidence or prevalence in diabetic persons compared with a suitable nondiabetic control group. Diabetic men and women in the NHANES II survey reported a higher prevalence of kidney infection than nondiabetic subjects in the 20-44 year and 45-74 year age groups (Table 22.3). An autopsy study found acute pyelonephritis in 6.8% of diabetic subjects versus 1.6% of nondiabetic subjects, suggesting a higher prevalence of this disorder in diabetes[32].

Hospital discharge data from the 1989-91 National Hospital Discharge Surveys (NHDS) permit estimation of the proportion of hospitalizations due to a particular diagnosis in persons who have and do not have diabetes listed as a discharge diagnosis (Table 22.4). These data do not permit direct comparison of disease prevalence by diabetes status, because no information is present in these data on the number of persons with and without diabetes. The only denominator available in the NHDS is total number of hospitalizations by diabetes status. This denominator may lead to biased estimates of relative disease prevalence for several reasons. Higher number of hospitalizations in diabetes, as would be expected in a group with an important chronic disease, would bias comparisons of prevalence by inflating the diabetic denominator. Since ~10% of all hospital discharges have an associated diabetes mellitus discharge diagnosis, it is clear that people known to have diabetes (who comprise ~6% of adults in the U.S. population) are admitted to hospital more frequently than nondiabetic subjects. Other potential biases include overcounting of diagnoses when one person has multiple admissions in a given year for the same problem, overascertainment of diabetes status in patients presenting with infections thought to be diabetes-associated, misclassification of diabetes status based on discharge summary information, and different hospitalization rates for the condition of interest by diabetes status. As shown in Table 22.4, a higher proportion of diabetic, compared with nondiabetic, discharge summaries noted acute pyelonephritis (diabetic, 0.401%; nondiabetic, 0.295%). The relative frequency of acute pyelonephritis as a proportion of all hospital discharges in diabetic patients increased with increasing age, but the opposite trend was noted for nondiabetic patients (Table 22.4). Because of the potential biases noted above, one cannot conclude from these data that acute pyelonephritis occurs more frequently in diabetic subjects.

Case series of subjects with emphysematous pyelonephritis have reported that 72%-89% of these subjects have diabetes[33,34]. Similarly, 37% of subjects with perinephric abscess have been reported to have diabetes[35]. Renal papillary necrosis occurs as a result of an infectious or noninfectious insult to the kidney interstitium. It is thought to occur more frequently in diabetes, with ~30% of subjects with this condition reported to have diabetes[36-42]. Whether diabetes predisposes to a higher risk for these conditions cannot be determined from available data due to the lack of controlled studies. Since detection of all these conditions requires imaging technology or direct inspection via surgery or autopsy, seemingly higher proportions of diabetes among persons with these conditions may be the result of detection bias (when diabetes status is known).

CANDIDA VULVOVAGINITIS AND CYSTITIS

Many physicians believe that diabetes increases the risk of vulvovaginitis due to *Candida albicans* and other *Candida* species[43]. Hyperglycemia promotes yeast adhesion and diminishes its phagocytosis[44]. Despite these laboratory-based results, no clinical data demonstrate a higher risk for this condition in diabetes[45]. Incidence and prevalence of vulvovaginitis in diabetic women are unknown. Vulvovaginal candidiasis would rarely cause hospital admission for treatment but might be listed on a discharge summary as an associated condition. A discharge diagnosis of candida vaginitis occurred 5.6 times more frequently in diabetic than nondiabetic hospital discharges in the 1989-91 NHDS (Table 22.4, 0.356% versus 0.064%), with the greatest difference noted in the youngest age

Table 22.4

Average Annual Frequency of Infection Diagnoses in Hospital Discharge Summaries, U.S., 1989-91

Infection diagnosis, ICD9-CM code and age (years)	Diabetic hospitalizations Unweighted no.	Diabetic hospitalizations Weighted no.	Diabetic hospitalizations Weighted %	Nondiabetic hospitalizations Unweighted no.	Nondiabetic hospitalizations Weighted no.	Nondiabetic hospitalizations Weighted %	Relative hospitalization frequency
Acute pyelonephritis, 590.10							
Total	228	11,724	0.401	562	80,098	0.295	1.4
Age 18-44	37	1,393	0.362	364	53,174	0.407	0.9
Age 45-64	71	3,320	0.388	96	11,811	0.219	1.8
Age ≥65	120	7,011	0.417	102	15,113	0.174	2.4
Candida vaginitis (females), 112.1							
Total	129	5,971	0.356	99	10,660	0.064	5.6
Age 18-44	64	3,147	1.407	76	7,322	0.082	17.2
Age 45-64	39	1,294	0.286	10	1,012	0.038	7.5
Age ≥65	26	1,531	0.153	13	2,326	0.048	3.2
Urogenital candidiasis, 112.2							
Total	69	2,737	0.094	79	10,290	0.038	2.5
Age 18-44	11	484	0.126	16	2,488	0.019	6.6
Age 45-64	19	739	0.086	9	1,053	0.020	4.3
Age ≥65	39	1,514	0.090	54	6,749	0.078	1.2
Osteomyelitis							
Acute, leg, 730.06	8	265	0.009	19	1,991	0.007	1.3
Acute, ankle or foot, 730.07	152	6,497	0.222	31	5,216	0.019	11.7
Chronic, leg, 730.16	8	126	0.004	29	3,229	0.012	0.3
Chronic, ankle or foot, 730.17	92	4,552	0.156	29	4,892	0.018	8.7
NOS, leg, 730.26	17	318	0.011	45	6,092	0.022	0.5
NOS, ankle or foot, 730.27	317	14,111	0.483	65	7,784	0.029	16.7
Cellulitis, 681.0-682.9	2,575	119,915	4.104	2,790	351,189	1.294	3.2
Finger, 681.00	38	2,363	0.081	90	11,254	0.041	2.0
Leg, 682.6	925	43,626	1.493	1,222	144,368	0.532	2.8
Foot, 682.7	789	35,218	1.205	334	36,376	0.134	9.3
Toe, 681.10	267	12,120	0.415	79	7,912	0.029	13.7
Viral (excluding influenza) and bacterial pneumonias, 480-83, 485, 486							
Total	3,148	160,920	5.507	9,925	1,356,227	4.998	1.1
Age 18-44	237	11,195	2.911	3,057	382,662	2.930	1.0
Age 45-64	698	32,785	3.835	1,561	218,836	4.056	1.0
Age ≥65	2,213	116,940	6.951	5,307	754,729	8.693	0.8
Bacteremia, 36.2-38.9							
Total	1,609	77,290	2.645	2,989	380,532	1.402	1.9
Age 18-44	102	4,687	1.219	625	79,009	0.605	2.0
Age 45-64	395	18,283	2.138	533	68,815	1.275	1.7
Age ≥65	1,112	54,320	3.229	1,831	232,708	2.680	1.2
Tuberculosis, 10.0-18.9							
Total	75	3,616	0.124	236	32,246	0.119	1.0
Age 18-44	14	721	0.187	126	17,546	0.134	1.4
Age 45-64	35	1,808	0.211	55	7,780	0.144	1.5
Age ≥65	26	1,087	0.065	55	6,920	0.080	0.8
Mucormycosis, 117.7	3	48	0.0016	3	202	0.0007	
Malignant otitis externa, 380.14							
Total	6	97	0.003	4	1,098	0.004	
Total male	5	91	0.007	2	304	0.003	
Total female	1	6	0.000	2	794	0.005	
Age 18-44	0			3	781	0.006	
Age 45-64	3	68	0.008	1	317	0.006	
Age ≥65	3	29	0.002	0			

ICD9-CM, 9th Edition of the *International Classification of Diseases, Clinical Modification*; NOS, not otherwise specified; Diabetes hospitalizations are those in which any of the following diabetes conditions were listed on the hospital record: ICD9-CM codes 250, 251.3, 357.2, 362.0, 366.41, 648.0, and 775.1. Nondiabetic hospitalizations were hospitalizations in which these codes were not listed. Unweighted number refers to actual number of hospitalizations counted, while weighted number is adjusted to represent all discharges from U.S. short-stay hospitals. The relative hospitalization frequency refers to the weighted frequency in diabetic versus nondiabetic hospitalizations. Diabetic discharges are pooled from 1989 through 1991 survey data, while nondiabetic numbers are derived from 1990 data only. Therefore "Diabetic weighted number" has been divided by 3 to reflect an average annual number of discharges. Weighted total number of discharges are: diabetes, 8,766,194 in 1989-91 (3 years, 2,922,065 annually on average); nondiabetic, 27,137,276 in 1990. Note that the percent columns are percentages and not proportions. For example, 0.401% of diabetes discharges had acute pyelonephritis recorded on the hospital discharge summary, compared with 0.295% of hospitalizations that did not mention diabetes. Where data are not entered for relative hospitalization frequency, the ratio was not calculated due to the small number of discharges.

Source: 1989-91 National Hospital Discharge Surveys

group (18-44 years, 1.407% versus 0.082%, Table 22.4). Of the annual number of 16,631 discharges listing candida vaginitis in women, 36% also listed diabetes.

Candidal urinary tract infection due to *Torulopsis glabrata* is frequently mentioned in the literature as an infectious complication of diabetes. The proportion of subjects with clinically important infection due to this microorganism who have diabetes ranges from 18-82%[46,47]. Comparative studies of the rate of this infection in diabetic and nondiabetic subjects have not been performed. A discharge diagnosis of urogenital candidiasis occurred 2.5 times more frequently in diabetic than nondiabetic hospital discharges in the 1989-91 NHDS (0.094% versus 0.038%). Differences diminished with increasing age (Table 22.4). These data suggest a higher candidal infection prevalence in diabetes patients.

LOWER EXTREMITY INFECTION

Diabetes results in a number of foot and lower extremity disorders that are described in greater detail in Chapter 18. These disorders are believed to lead to a higher risk of infection of skin, soft tissue, and bone. Although no study has directly compared lower extremity skin, soft tissue, and bone infection incidence or prevalence in diabetic versus nondiabetic subjects, a plausible case for more frequent infection in diabetic subjects can be made from available data. Diabetic subjects have a ~15-fold higher rate of lower extremity amputation than nondiabetic subjects[48]. About 59% of diabetic lower extremity amputations are preceded by an infected foot ulcer[8]. Infection was the second most frequent indication (next to gangrene) for diabetic lower extremity amputation in a review of 31 published studies on the topic[49]. It was cited by 71% of authors as a criterion for amputation. Given that diabetes increases risk of lower extremity amputation and that infection frequently leads to limb loss, it is plausible that diabetes predisposes to lower extremity infection.

The microbiology of diabetic lower extremity infection varies depending on the patient population studied. Among hospitalized patients, infections are often polymicrobial, with aerobic gram-positive and gram-negative organisms, as well as obligate anaerobes[9]. Most of these patients have limb- or life-threatening infection and have received antibiotics prior to hospitalization. Among diabetic outpatients with lower extremity infection who have not received antibiotics, cultures yielded a mean of only 2.1 different microorganisms per case[9]. Aerobic gram-positive cocci were isolated as the sole pathogen in 42% of cases, while anaerobes and aerobic gram-negative bacilli were infrequently recovered[9]. Thus, infection severity appears related to number and type of infecting organism.

Hospital discharge data support more frequent lower extremity skin and bone infections in diabetic subjects. Table 22.4 contains the number and relative frequency of hospital admissions involving osteomyelitis and cellulitis by whether diabetes was mentioned on the discharge summary from the 1989-91 NHDS. Osteomyelitis at more distal lower extremity locations (ankle or foot) accounted for a greater proportion of all diabetic hospitalizations, compared with this infection at a more proximal location (leg). For example, the relative proportion of all hospitalizations with mention of acute ankle or foot osteomyelitis was 11.7 times greater in diabetic than nondiabetic hospitalizations, whereas acute leg osteomyelitis comprised a similar proportion of hospitalizations in diabetic and nondiabetic patients (relative frequency = 1.3, Table 22.4). Similarly, the relative hospitalization frequency for cellulitis in diabetic compared with nondiabetic patients increases in a seemingly linear fashion as one proceeds from finger (relative frequency = 2.0) to toe (relative frequency = 13.7). These data support higher osteomyelitis and cellulitis prevalence of the distal lower extremity in diabetic subjects.

Colonization by pathogenic bacteria in diabetic patients has been investigated as a potential mechanism for their probable higher rate of lower extremity skin infection. Colonization, also referred to as carriage, refers to the presence of microorganisms in specified bodily locations. Most study has focused on *Staphylococcus aureus* carriage, which is associated with a higher rate of postoperative infection, and infections associated with peritoneal and hemodialysis[50-53]. Six studies have compared the prevalence of *S. aureus*

Table 22.5
Staphylococcus aureus Carriage (Colonization) Rates, by Diabetes Status

	Diabetic, insulin-treated		Diabetic, not insulin-treated		Nondiabetic	
Ref.	No.	%	No.	%	No.	%
55	144	53	180	35	254 healthy adults	34
56	29	24	30	27	44 clinic patients	9
54	35	23	36	8	55 medical students	4
57	19	53	11	36	30 clinic patients	17
59	71	47	0		116 medical students	50
58	83	27	105	27	363 population-based nondiabetic subjects	21

Source: References are listed within the table

carriage in the anterior nares or elsewhere in diabetic subjects with nondiabetic subjects (Table 22.5)[54-59]. Four outpatient clinic-based studies reported a significant 1.6- to 6.3-fold higher carriage rate in diabetes[54-57]. The only population-based study that addressed this question found no significant differences in *S. aureus* nasal carriage in diabetic subjects, either treated or not treated with insulin, and community-based nondiabetic controls[58]. These data suggest that diabetic clinic attendees have a higher carriage rate for this microorganism. Thus, clinic-based studies of *S. aureus* nasal colonization may lead to biased conclusions about carriage frequency. Since population-based studies are generally more credible than studies of clinic patients, the data do not support a higher *S. aureus* colonization rate in persons who have diabetes. Therefore, one would not expect diabetic subjects to experience a higher rate of staphylococcal infections, particularly of lower extremity skin, soft tissues, or bone, due to higher colonization with this microorganism.

RESPIRATORY INFECTION

PNEUMONIA AND INFLUENZA

Few controlled data exist comparing pneumonia incidence in diabetic and nondiabetic subjects. Diabetes was examined as a potential risk factor for pneumococcal infection in a case-control study in male veterans[60]. Pneumonia was the most frequent type of pneumococcal infection (92% of cases), and pneumococcal infection risk was virtually identical in diabetic and nondiabetic subjects. Diabetic subjects were 15.8-25.6 times more likely to be hospitalized for pneumonia during the influenza season (the first 13 weeks) of 4 consecutive years[61]. These data suggest a higher pneumonia incidence in diabetic patients but do not exclude a lower threshold for hospitalization for treatment of complicated pneumonia in diabetic subjects. Also, it is not clear whether the nondiabetic control group, comprising patients with duodenal ulcer, reflects the population from which the diabetic subjects were derived with regard to either pneumonia incidence or severity. In the 1989-91 NHDS, pneumonia of bacterial or viral (excluding influenza) etiology accounted for a nearly identical proportion of hospitalizations in patients discharged with diabetes, compared with nondiabetic hospitalizations (Table 22.4). Relative hospitalization frequency ranged from 0.8-1.0 in diabetic versus nondiabetic patients. Thus, no data strongly suggest a higher pneumonia incidence or prevalence in diabetic versus nondiabetic subjects.

No direct comparison of influenza incidence in diabetic subjects versus nondiabetic controls has been performed. The incidence of hospitalization for influenza has been compared for diabetic and nondiabetic patients hospitalized for duodenal ulcer[61]. During influenza epidemic years, the relative risk of hospitalization for influenza was 5.7-6.2 times greater in diabetic than nondiabetic subjects. Higher in-hospital mortality rates for influenza and ketoacidosis were seen for diabetic patients during epidemic years, and higher relative mortality in diabetic subjects occurred during influenza epidemics[62,63]. Whether this mortality increase is directly attributable to influenza or to some other factor is not clear. Good evidence for higher influenza and pneumonia mortality in diabetic subjects comes from a Wisconsin prospective population-based study that established cause of death by death certificate data[64]. Mortality due to pneumonia and influenza for 1,772 subjects who had diabetes diagnosed at age ≥30 years was 1.7 times higher than for nondiabetic subjects. Younger-onset patients with diabetes (age <30 years) were 7.6 times more likely to die from these infections over an average follow-up period of 8.5 years. It cannot be determined from these data whether this increased mortality from pneumonia/influenza is attributable to higher disease incidence, higher case-fatality rate, or both.

BRONCHITIS AND SINUSITIS

No controlled comparisons have been published on the incidence or prevalence of acute bronchitis or sinusitis in diabetic versus nondiabetic subjects. Data from the 1989 NHIS and the 1976-80 NHANES II included questions about the presence of chronic bronchitis and sinusitis (Tables 22.2 and 22.3), which may or may not be of infectious etiology. No validation was made of self-reported chronic bronchitis or sinusitis. In the NHIS, 5.2% of nondiabetic subjects, compared with 7.9% of diabetic subjects, reported a history of chronic bronchitis. A higher self-reported prevalence of this condition was also seen in persons with diagnosed diabetes compared with persons with normal glucose tolerance in the NHANES II survey (Table 22.3). These data suggest a higher chronic bronchitis prevalence in diabetes, but further research is required to confirm these associations. These data do not consider potential confounding by smoking habit or increased medical surveillance and greater likelihood of disease detection in diabetic subjects. The overall prevalence of self-reported chronic sinusitis was identical for diabetic and nondiabetic subjects age ≥18 years in the 1989 NHIS (18.0%), although at age 18-44 years those with diabetes more frequently reported this condition than nondiabetic subjects

(28.4% versus 18.4%) (Table 22.2).

BACTEREMIA

Many reports have considered whether diabetes predisposes to a higher incidence or case fatality rate for bacteremia, but few have employed adequate study designs. In 1968, a diabetes prevalence of 14% was found in a case series of 185 subjects with *S. aureus* bacteremia[65]. It is not clear whether diabetic persons were overrepresented in this series, since the proportion with diabetes in nonbacteremic subjects was not stated. The mortality rate due to bacteremia in the diabetic patients (69%) exceeded that of the nondiabetic patients (38%). A more recent study included all cases of bacteremia in four major metropolitan hospitals, with diabetes status determined by medical record information[66]. The prevalence of bacteremia caused by *S. aureus* and enteric organisms in diabetic subjects exceeded that in nondiabetic subjects by a large margin (3.0% versus 0.12% for *S. aureus*; 1.0% versus 0.3% for enterobacteriaceae). Similar mortality rates were seen in diabetic and nondiabetic patients (13.0% versus 14.9%). This comparison is subject to several potential biases, including reliance on the medical record to assess diabetes status, which probably underestimated diabetes prevalence, and inability to include nonhospitalized cases of bacteremia that occurred in the geographic area studied. Mortality rates due to *S. aureus* bacteremia were compared in 27 diabetic and 34 nondiabetic patients at one medical center[67]. Mortality rates were somewhat lower in those with diabetes (25.9% versus 44.1%), but the difference was not statistically significant. A significantly higher mortality in diabetic patients was found in 612 bacteremic patients ($p<0.05$), but actual mortality rates were not provided[68]. Similar mortality rates occurred in 124 episodes of bacteremia in diabetic patients and 508 episodes in nondiabetic patients (28% and 29%)[69].

A few studies have addressed relative rates of bacteremia by diabetes status using adequately controlled study designs. A review was conducted of 18 months of hospitalization data to identify all diabetic and nondiabetic subjects undergoing an operative procedure[70]. Postoperative gram-negative shock developed in 7.1% (7/98) of diabetic and 0.4% (17/4,207) of nondiabetic subjects, for a relative risk of 18. Diabetic and nondiabetic subjects had identical median age (72 years). Using NHDS data on 5,457 nosocomial infections that occurred in eight hospitals, the gram-negative bacteremia rate without a known primary site in diabetic patients was 0.003 per hospital admission, compared with 0.001 in nondiabetic patients[71]. It is unclear whether accurate denominator data were used to estimate incidence rates by diabetes status. A significantly higher ($p=0.040$) proportion of febrile patients admitted to an internal medicine inpatient service had bacteremia if they had diabetes (44%, 23/52) than if they did not (6%, 12/192)[72]. The contribution of diabetes became nonsignificant in a multivariate model, but this was likely due to insertion of intervening variables in the regression model (urinary tract infection, renal failure) that were likely to have been related to diabetes. For 880 adults evaluated for acute fever in an emergency room, diabetes was related to a 2.5-fold increased risk of bacteremia[73]. These studies indicate that there is an increased risk of bacteremia due to diabetes, but a relatively higher hospitalization rate in febrile diabetic patients with bacteremia cannot be excluded as the source of the difference.

Bacteremia is found in a 1.9-fold higher proportion of diabetic versus nondiabetic hospitalizations in the 1989-91 NHDS (Table 22.4). The greatest difference was seen in the youngest age group (18-44 years, relative frequency = 2.0), with a gradual decline as age increased (Table 22.4).

TUBERCULOSIS

An extensive literature review indicates a higher risk of tuberculosis (TB) in people with diabetes. Several controlled studies of this subject have been conducted, but for the most part the choice of the nondiabetic control group was not optimal by current standards for observational research. A cumulative incidence for TB of 1.6% was found for 1,126 diabetic patients age <15 years, compared with 0.12% in a school survey of 140,000 children, for a relative prevalence of ~14. The selection process was not adequately described for either diabetic or TB cases. It is not clear if a defined cohort of diabetic subjects was followed, or if diabetic subjects were added to a case series. In the latter instance, the presence of TB might have increased chances for inclusion and thereby falsely elevated the prevalence. A survey of 3,029 diabetic subjects in the Philadelphia, PA area was conducted in 1945-47 using chest radiography[75]. TB prevalence in this group was compared with results of a survey of 71,767 Philadelphia industrial workers conducted in 1942-45, and TB prevalence in those with diabetes was approximately twofold higher than nondiabetic subjects. The definition of TB included fibro-calcific pulmonary lesions that may have represented inactive disease. The prevalence of radiographic features of active pulmonary disease, present in only 30.7% of

diabetic subjects, was not provided for the nondiabetic controls. Also, the industrial worker control group probably enjoyed better health and living standards than the average population and may underrepresent TB prevalence.

Pulmonary TB prevalence by chest radiograph screening was 3.6% of all known diabetic subjects in a defined community, compared with an overall rate of 0.88%[76]. The screening methods were similar for the two groups, but the nondiabetic subjects had been screened earlier. Screening was conducted in 96% of the diabetic subjects but in an unspecified proportion of those without diabetes. The higher prevalence in diabetes may therefore represent an overestimate due to differences in TB screening intensity.

In 1957, the TB prevalence in 1,851 diabetic first-time clinic attendees at University College Hospital, London, UK who routinely received a screening chest radiograph, was compared with nondiabetic control subjects who were referred when entering the hospital or from practitioners for a chest radiograph[77]. The pulmonary TB rate in the controls was 4.9% (290/58,867), compared with 18.2% (40/1,851) in diabetic subjects. A higher TB prevalence was seen across all age and sex strata. This control group may overestimate TB prevalence because they may have been referred for evaluation of symptoms. Even so, the prevalence of TB in diabetic subjects was higher. The literature therefore suggests a higher TB prevalence in association with diabetes, although optimal study designs have not been used to address this question.

A recent case-control study examined diabetes as a risk factor for reactivation of TB in tuberculin-positive American Indians[78]. Forty-six active TB cases were compared with an identical number of controls who all tested tuberculin positive. A relative odds of 4.9 (95% confidence interval 1.3-15.5) was found for TB reactivation in association with diabetes. This study suggests that diabetes (or an associated condition) is strongly related to higher risk of TB reactivation in American Indians but does not address the question of whether primary TB incidence differs by diabetes status.

The NHANES II survey inquired about TB history and determined diabetes status by medical history and oral glucose tolerance test (Table 22.3). The interview did not clearly distinguish between active tuberculosis and tuberculin skin test positivity. Rates of TB are somewhat higher in those with diabetes, but this may be due to more frequent skin testing in a group considered by clinicians to be at higher risk for this infection. This could not explain the somewhat higher TB prevalence in undiagnosed diabetes, who presumably would not have been more intensively scrutinized. In the 1989-91 NHDS, TB had an overall relative hospitalization frequency of 1.04 in diabetic compared with nondiabetic hospital discharges (Table 22.4). TB accounted for a higher proportion of diabetic hospitalizations in the younger age groups (Table 22.4).

In sum, no convincing data exist to argue that people with diabetes are at higher risk for TB, except that diabetic American Indians are at higher risk for TB reactivation[78].

MUCORMYCOSIS

Mucormycosis (also referred to as zygomycosis or phycomycosis) is usually caused by the fungal species *Mucor* or *Rhizopsus*, but *Absidia* and *Cunninghamella* species are occasionally implicated. Several distinct patterns of infection occur, including rhinocerebral infection and invasive pulmonary or gastrointestinal disease.

Diabetes, particularly ketoacidosis, is frequently mentioned as a risk factor for this disease, but incidence and prevalence of mucormycosis in diabetic and nondiabetic populations is unknown and no controlled research has been performed. Of all 33 cases of mucormycosis in the past 50 years at Johns Hopkins Hospital in Baltimore, MD, 42% had diabetes[79]. A comprehensive literature review found a total of 179 cases of mucormycosis in 109 publications[80]. Prevalence of diabetes in these cases was 70.4%. Overall mortality was 50%, with a somewhat lower rate in the 126 subjects with diabetes (40.5%). An even lower mortality rate was observed in the 67 diabetic subjects who received amphotericin B treatment (20.9%). Immunologic research has demonstrated that human alveolar macrophages from patients with diabetes have decreased ability to attach to the hyphae of the fungus *Rhizopsus oryzae*, which might impair immune responses directed against this microorganism[81]. Data strongly suggest an increased risk in diabetes for these infections but do not exclude the possibility that selection bias may account for the high proportion of diabetes in these subjects. Mortality due to this infection appears to be no greater, and perhaps may be lower, in diabetic than nondiabetic subjects. In the 1989-91 NHDS, mucormycosis (zygomycosis) was listed in only 16 per million diabetic hospitalizations and 7 per million of nondiabetic hospitalizations (Table 22.4).

MALIGNANT EXTERNAL OTITIS

Extension of external ear infection to adjacent soft tissue, mastoid bone, and central nervous system produces malignant or invasive external otitis. It is caused almost exclusively by *Pseudomonas aeruginosa* and rarely by *Aspergillius*[82-84].

Incidence and prevalence of this condition in diabetic and nondiabetic populations is unknown. In 151 reported cases, prevalence of diabetes was 89%[83]. The mean age of infected patients was 68.5 years, and 65% were male. Mortality ranged from 23%-75%[85]. Data strongly suggest an increased risk in diabetes for this infection but do not exclude the possibility of selection bias.

Malignant external otitis accounted for a very small proportion in the NHDS of diabetic hospitalizations (3 per 100,000) and nondiabetic hospitalizations (4 per 100,000) (Table 22.4).

SURGICAL WOUND INFECTION

Unlike most infections, several controlled studies have addressed the issue of whether patients with diabetes experience higher surgical wound infection rates. The National Academy of Sciences-National Research Council Cooperative Study found a similar age-adjusted rate of surgical wound infection in 354 diabetic subjects (7.2%), compared with nondiabetic subjects (7.1%)[86]. Similar infection rates were noted for clean orthopedic operations performed on 203 diabetic and 3,414 nondiabetic subjects matched on age, sex, and operation duration (3.4% versus 3.6%)[87]. On the other hand, in a study of 23,649 surgical wounds from a variety of operative procedures, the unadjusted clean wound infection rate was 10.7% for diabetes, compared with 1.8% overall[88]. The wound infection rate for subjects who underwent total hip replacement was 11% of 42 diabetic patients, compared with 2% of 1,180 similarly aged nondiabetic patients[89]. A higher combined sternal, leg, or vascular access wound infection rate was found in 146 diabetic patients who had undergone coronary artery bypass grafting (CABG), compared with 565 nondiabetic subjects (7.5% versus 0.9%)[90]. These two groups were similar with respect to mean age, but mean body mass index (a measure of obesity) was slightly higher in diabetic subjects (28.7 versus 26.6). Other studies on the increased incidence of leg and sternal infection in diabetes following CABG or open heart surgery are shown in Table 22.6[91-93].

A twofold increased risk of median sternotomy infection associated with diabetes was reported in a case-control study of 1,704 patients matched on age and type of operation[94]. A nonsignificant diabetes-associated increase (relative risk=1.24, p=0.80) in risk of severe bacterial infection (mediastinitis, septicemia, or pneumonia) was found in 162 patients (17% diabetic) who underwent CABG surgery[95]. Diabetes was not reported to be related to the 29 cases of mediastinitis that occurred in 2,031 patients who underwent median sternotomy at the National Heart, Lung, and Blood Institute during 1956-81, but actual infection rates in diabetic and nondiabetic patients were not shown[96].

Most controlled research supports a higher post-sternotomy wound infection rate in diabetic patients, either of sternum or leg vein graft site, after operations requiring sternotomy. Controlled data also suggest a higher wound infection rate in diabetic individuals who undergo total hip replacement.

OTHER INFECTIONS

FOURNIER'S GANGRENE

This uncommon polymicrobial necrotizing infection

Table 22.6
Incidence of Sternal or Leg Wound Infection After Open Heart Surgery or Coronary Artery Bypass Grafting

	Combined infections				Sternal infection				Leg infection			
	Diabetic		Nondiabetic		Diabetic		Nondiabetic		Diabetic		Nondiabetic	
Ref.	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
91					21	19.0	288	2.1	21	14.3	288	12.8
92					412	2.4	3,295	0.5				
93	35	17.1	135	5.9								

Data from Reference 92 are for coronary artery bypass graft patients only.

Source: References are listed within the table

of the genitalia, which occurs mostly in men (86% of cases) is associated with a high mortality rate (22%)[97]. Incidence and prevalence of this disorder by diabetes status is not available. In 66 articles published during 1979-88, 449 cases were reported[97]. Of the 364 cases in which an underlying medical condition was reported, diabetes was mentioned as the most frequent condition (10%). Diabetic patients are thought to have a higher mortality rate due to this infection, but convincing data on either relative infection risk or mortality in diabetes is not available[98,99].

GROUP B STREPTOCOCCAL INFECTIONS

Group B streptococcal infections in adults unrelated to pregnancy or the postpartum state have been reported to occur more commonly in diabetes[3]. Case series of persons with bacteremia due to this organism have demonstrated varying proportions of associated diabetes: 37.9% (11/29), 9.4% (3/32), and 45.8% (11/24)[100-102]. In a controlled study of group B streptococcus infection in eight metropolitan Atlanta, GA counties with 2.3 million persons, 41 persons had bacteremia due to this organism[103]. Diabetes was not mentioned as an underlying condition that increased risk for bacteremia, although it was associated with higher overall risk of serious infection (relative risk 3.7-30.0, depending on age). Diabetes was associated as an underlying condition with skin, soft tissue, and bone infection (grouped together) and with urosepsis. These infections were the first and third most commonly occurring group B streptococcus infections (36% and 14%, respectively), with bacteremia the second most common (30%). One review of the subject concluded that group B streptococcus bacteremia frequently originated from the urinary tract or foot ulcers[3]. Therefore, the apparent higher group B streptococcus infection rate in diabetes[103] may reflect higher local infection rates by this microorganism, as opposed to a systemic immune defect that renders them more susceptible to infections by this microorganism.

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REFERENCES

1. Kaslow RA: Infections in diabetics. In *Diabetes in America*. Harris MI, Hamman RF, eds. NIH publ. no. 85-1468, 1985, p. XIX 1-18
2. Edwards JE, Tillman DB, Miller ME, Pitchon HE: Infection and diabetes mellitus. *West J Med* 130:515-21, 1979
3. Wheat LJ: Infection and diabetes mellitus. *Diabetes Care* 3:187-95, 1980
4. Drachman RH, Root RK Jr, WB Wood: Studies on the effect of experimental nonketotic diabetes on antibacterial defense— I. Demonstration of a defect in phagocytosis. *J Exp Med* 124:227-40, 1966
5. Valerius NH, Eff C, Hansen NE, Karle H, Nerup J, Soeberg B, Sorenson SF: Neutrophil and lymphocyte function in patients with diabetes mellitus. *Acta Med Scand* 211:463-67, 1982
6. Masuda M, Markami T, Egawa H, Murata K: Decreased fluidity of polymorphonuclear leukocyte membrane in streptozocin-induced diabetic rats. *Diabetes* 39:466-70, 1990
7. Goodson III WH, Hunt TK: Wound healing and the diabetic patient. *Surg Gynecol Obstet* 149:600-08, 1979
8. Pecoraro RE, Ahroni JH, Boyko EJ, Stensel VL: Chronology and determinants of tissue repair in diabetic lower-extremity ulcers. *Diabetes* 40:1305-13, 1991
9. Lipsky BA, Pecoraro RE, Ahroni JH: Foot ulceration and infection in elderly diabetics. *Clin Geriatr Med* 6:747-69, 1990
10. Ellenberg M, Weber H: The incipient asymptomatic diabetic bladder. *Diabetes* 16:331-35, 1967
11. Hosking DJ, Bennett T, Hampton JR: Diabetic autonomic neuropathy. *Diabetes* 27:1043-54, 1978
12. Murphy DP, Tan JS, File TM: Infectious complications in diabetic patients. *Primary Care* 8:695-714, 1981
13. Ankel F, Wolfson AB, Stapczynski JS: Emphysematous cystitis: A complication of urinary tract infection occurring predominantly in diabetic women. *Ann Emerg Med* 19:404-06, 1990
14. Kass EH: Bacteriuria and the diagnosis of infections of the urinary tract. *Arch Int Med* 100:709-14, 1957
15. Kass EH: Asymptomatic infections of the urinary tract. *Trans Assoc Am Phys* 69:56-64, 1956
16. Keane EM, Boyko EJ, Reller LB, Hamman RF: Prevalence of asymptomatic bacteriuria in subjects with NIDDM in San Luis Valley of Colorado. *Diabetes Care* 11:708-12, 1988
17. Abu-Bakare A, Oyaide SM: Asymptomatic bacteriuria in Nigerian diabetes. *J Trop Med Hyg* 89:29-32, 1986
18. Bahl AL, Chugh RN, Sharma KB: Asymptomatic bacteriuria in diabetics attending a diabetic clinic. *Indian J Med Sci* 24:1-6, 1970
19. Hansen RO: Bacteriuria in diabetic and non-diabetic outpatients. *Acta Med Scand* 176:721-30, 1964
20. Joffe BL, Seftel HC, Distiller LA: Asymptomatic bacteriuria in diabetes mellitus. *S Afr Med J* 1306-08, 1974
21. O'Sullivan DJ, Fitzgerald MG, Meynell MJ: Urinary tract infection: Comparative study in the diabetic and normal populations. *Br Med J* 1:786-88, 1961
22. Ooi BS, Chen BTM, Yu M: Prevalence and site of bacteriuria in diabetes mellitus. *Postgrad Med J* 50:497-99, 1974
23. Jaspan JB, Mangera C, Krut LJ: Bacteriuria in black diabetics. *S Afr Med* 51:374-76, 1977
24. Schmitt JK, Fawcett CJ, Gullickson G: Asymptomatic bacteriuria and hemoglobin A1. *Diabetes Care* 9:518-20, 1986
25. Vejlsgaard R: Studies on urinary infections in diabetics. I. Bacteriuria in patients with diabetes mellitus and in control subjects. *Acta Med Scand* 179:172-82, 1966
26. Vigg B, Rai V: Asymptomatic bacteriuria in diabetics. *J Assoc Physicians* 1977
27. Kunin CM: *Detection, Prevention, and Management of Urinary Tract Infections, 4th Edition.* Philadelphia, PA, Lea and Febiger, 1987
28. Pometta D, Rees SB, Younger D, Kass EH: Asymptomatic bacteriuria in diabetes mellitus. *N Engl J Med* 276:1118-21, 1967
29. Lindberg U, Bergstrom AL, Carlsson E, Dahlquist G, Hermansson G, Larsson Y, Nilsson KO, Samuelsson G, Sjoblad S, Thalme B: Urinary tract infection in children with type I diabetes. *Acta Paediatr Scand* 74:85-88, 1985
30. Bailey H: Cystitis emphysematosa. *Am J Roentgenol* 86:850-62, 1961
31. Holesh S: Gas in the bladder: Cystitis emphysematosa. *Clin Radiol* 20:234-36, 1969
32. Robbins SL, Tucker AW: The cause of death in diabetes: A report of 307 autopsied cases. *N Engl J Med* 231:868, 1944
33. Schainuck LI, Fouty R, Cutier RE: Emphysematous pyelonephritis. *Am J Med* 44:134-39, 1968
34. Yasumoto R, Iseki T, Nishio S, Kishimoto T, Tsujita M, Maekawa M: Emphysematous pyelonephritis: Report of two cases and review of literature. *Osaka City Med* 26:73-80, 1980
35. Thorely JD, Jones SR, Sanford JP: Perinephric abscess. *Medicine* 53:441-51, 1974
36. Whitehouse FW, Root HF: Necrotizing renal papillitis and diabetes mellitus. *JAMA* 162:444-47, 1956
37. Mujais SK: Renal papillary necrosis in diabetes mellitus. *Semin Nephrol* 4:40-47, 1984
38. Mandel EE: Renal medullary necrosis. *Am J Med* 13:322-27, 1952
39. Lauier DP, Schreiner GE, David A: Renal medullary necrosis. *Am J Med* 29:132-56, 1960
40. Eknoyan G, Quinibi WY, Grissom RT, Tuma SN, Ayus JC: Renal papillary necrosis: An update. *Medicine* 61:53-73, 1982
41. Edmonson HA, Reynolds TB, Jacobson HG: Renal papillary necrosis with special reference to chronic alcoholism. A report of 20 cases. *Arch Intern Med* 118:255-64, 1966
42. Abdulhayoghlu S, Marble A: Necrotizing renal papillitis (papillary necrosis in diabetes mellitus). *Am J Med Sci* 248:623-32, 1964
43. Murphy DP: Primary Care. *Am J Obstet Gynecol* 1985
44. Hostetter MK: Perspectives in diabetes: Effects of hyperglycemia on CD and Candida albicans. *Diabetes* 39:271, 1990
45. Reed BD: Risk factors for candida vulvovaginitis. *Obstet & Gynecol Sur* 47:551-60, 1992
46. Kaufman CA, Tan JS: Torulopis glabrata renal infection. *Am J Med* 57:217-24, 1974

47. Marks MI, Langston C, Eickhoff TC: Torulopsis glabrata—an opportunistic pathogen in man. *N Engl J Med* 283:1131-35, 1970

48. Most RS, Sinnock P: The epidemiology of lower extremity amputations in diabetic individuals. *Diabetes Care* 6:87-91, 1983

49. Fylling CP, Knighton DR: Amputation in the diabetic population: Incidence, causes, cost, treatment, and prevention. *J Enterostam Ther* 16:247-55, 1989

50. Luzar MA, Coles GA, Faller B, Slingeneyer A, Dah G Dah, Briat C, Wone C, Knefati Y, Kessler M, Peluso F: Staphylococcus aureus nasal carriage and infection in patients on continuous ambulatory peritoneal dialysis. *N Engl J Med* 322:505-09, 1990

51. Miller DL, McDonald JC, Jevons MP, Williams REO: Staphylococcal disease and nasal carriage in the Royal Air Force. *J Hyg* 60:451-65, 1962

52. Weinstein H: The relation between the nasal staphylococcal carrier state and the incidence of postoperative complications. *N Engl J Med* 260:1303-08, 1959

53. Yu VL, Goetz A, Wagener M, Smith PB, Rihs JD, Hanchett J, Zuravleff JJ: Staphylococcus aureus nasal carriage and infection in patients on hemodialysis. *N Engl J Med* 315:91-96, 1986

54. Tuazon CU, Perez A, Kishaba T, Sheagren JN: Staphylococcus aureus among insulin-injecting diabetic patients. *JAMA* 231:1272, 1975

55. Smith JA, O'Conner JJ, Willis AT: Nasal carriage of Staphylococcus aureus in diabetes mellitus. *Lancet* 2:776-77, 1966

56. Lipsky BA, Pecoraro RE, Chen MS, Koepsell TD: Factors affecting staphylococcal colonization among NIDDM outpatients. *Diabetes Care* 10:483-86, 1987

57. Chandler PT, Chandler SD: Pathogenic carrier rate in diabetes mellitus. *Am J Med Sci* 273:259-65, 1977

58. Boyko EJ, Lipsky BA, Sandoval R, Keane EM, Monahan JS, Pecoraro RE, Hamman RF: Non-insulin-dependent diabetes mellitus does not increase the prevalence of nasal Staphylococcus aureus colonization. *Diabetes Care* 189-193, 1989

59. Berman DS, Schaefler S, Simberkoff MS, Rahal JJ: Staphylococcus aureus colonization in intravenous drug abusers, dialysis patients, and diabetics. *J Infect Dis* 155:829-31, 1987

60. Lipsky BA, Boyko EJ, Inui TS, Koepsell TD: Risk factors for acquiring pneumococcal infections. *Arch Intern Med* 146:2179-85, 1986

61. Bouter KP, Diepersloot RJ, Romunde LK van, Uitslager R, Masurel N, Hoekstra JB, Erkelens DW: Effect of epidemic influenza on ketoacidosis, pneumonia and death in diabetes mellitus: A hospital register survey of 1976-79 in the Netherlands. *Diabetes Res Clin Pract* 12:61-68, 1991

62. Cameron AS, Roder DM, Esterman AJ, Moore BW: Mortality from influenza and allied infections in South Australia during 1968-81. *Med J Aust* 142:14-17, 1985

63. Diepersloot RJA, Bouter KP, Hoekstra JBL: Influenza infection and diabetes mellitus. Case for annual vaccination. *Diabetes Care* 13:876-82, 1990

64. Moss SE, Klein R, Klein BE: Cause specific mortality in a population-based study of diabetes. *Am J Public Health* 81:1158-62, 1991

65. Cluff LE, Reynolds RC, Page DL: Staphylococcal bacteremia and altered host resistance. *Ann Intern Med* 69:85-93, 1968

66. Bryan CS, Reynods KL, Metzger WT: Bacteremia in diabetic patients: Comparison of incidence and mortality with nondiabetic patients. *Diabetes Care* 8:244-49, 1985

67. Cooper G, Platt R: Staphylococcus aureus bacteremia in diabetic patients: Endocarditis and mortality. *Am J Med* 73:658-62, 1982

68. Kreger BE, Craven DE, McCabe WR: Gram-negative bacteremia. IV. Re-evaluation of clincal features and treatment in 612 patients. *Am J Med* 68:344-55, 1980

69. Leibovici L, Samra Z, Konisberger H, Kalter-Leibovici O, Pitlik SD, Drucker M: Bacteremia in adult diabetic patients. *Diabetes Care* 14:89-94, 1991

70. Ariyan S, Halasz NA: The incidence of postoperative gram-negative shock in diabetes. *Am J Med Sci* 25:808-15, 1967

71. Stamm WE, Martin SM, Bennett JV: Epidemiology of noscomial infections due to gram-negative bacilli: Aspects relevant to development and use of vaccines. *J Infect Dis* 136:S151-60, 1977

72. Leibovici L, Greenshtain S, Cohen O, Mor F, Wysenbeek AJ: Bacteremia in febrile patients—a clinical model for diagnosis. *Arch Intern Med* 151:1801-06, 1991

73. Mellors JW, Horwitz RI, Harvey MR, Horwitz SM: A simple index to identify occult bacterial infection in adults with acute unexplained fever. *Arch Intern Med* 147:666-71, 1987

74. Root HF, WR Bloor: Diabetes and pulmonary TB. *Am Rev Tuberc* 39:714-37, 1939

75. Boucot KR, Dillon ES, Cooper DA, Meier P, Richardson R: Tuberculosis among diabetics: The Philadelphia Survey. *Am Rev Tuberc* 65 (part II):1-50, 1952

76. Oscarsson PN, Silwer H: Incidence of TB among diabetics. *Acta Med Scand* 161:23-48, 1958

77. Warwick MT: Pulmonary tuberculosis and diabetes mellitus. *Q J Med* 26:31-42, 1957

78. Mori MA, Leonardson G, Welty TK: The benefits of isoniazid chemoprophylaxis and risk factors for TB among Oglala Sioux Indians. *Arch Intern Med* 152:547-50, 1992

79. Parfrey NA: Improved diagnosis and prognosis of mucormycosis. A clinicopathologic study of 33 cases. *Medicine (Baltimore)* 65:113-23, 1986

80. Blitzer A, Lawson W, Meyers BR, Biller HF: Patient survival factors in paranasal sinus mucromycosis. *Laryngoscope* 90:635-48, 1980

81. Waldor AR, Ruderman N, Diamond RD: Specific susceptibility to Mucormycosis in murine diabetes and bronchoalveolar macrophage defense against Rhizopsus. *J Clin Inves* 74:150-60, 1984

82. Cunningham M, Yu VL, Turner J, Curtin H: Necrotizing otitis externa due to Aspergillus in an immumocompetent patient. *Arch Otolaryngol Head Neck Surg* 114:554-56, 1988

83. Doroghazi RM, Nadol JB, Hyslop NE, Baker AS, Axelrod L: Invasive external otitis: Report of 21 cases and review of the literature. *Am J Med* 71:603-14, 1981

84. Phillips P, Bryce G, Shepherd J, Mintz D: Invasive external otitis caused by Aspergillus. *Rev Inf Dis* 12:277-81, 1990

85. Timon CI, O'Dwyer T: Diagnosis, treatment, and complications of malignant otitis externa. *Ir Med J* 82:30-31, 1989

86. National Academy of Sciences-National Research Council: Post-operative wound infections: The influence of ultraviolet irradiation of the operating room and of various other factors. *Ann Surg* 160:1-192, 1964

87. Lidgren L: Postoperative orthopedic infections in patients

with diabetes mellitus. *Acta Orthop Scan* 44:149-51, 1973

88. Cruse PJE, Foord R: A five-year prospective study of 23,649 surgical wounds. *Arch Surg* 107:206-09, 1973
89. Vannini P, Ciaverella A, Olmi R, Flammini M, Moroni A, Galuppi V, Giunti A: Diabetes as a pro-infective risk factor in total hip replacement. *Acta Diabetol Lat* 21:275-79, 1984
90. Fietsam R Jr, Bassett J, Glover JL: Complications of coronary artery surgery in diabetic patients. *AmSurg* 57:551-57, 1991
91. Farrington M, Webster M, Fenn A, Phillips I: Study of cardiovascular wound infection at St. Thomas' Hospital. *Br J Surg* 72:759-62, 1985
92. Salomon NW, Page US, Okies JE, Stephens J, Krause AH, Bigelow JC: Diabetes mellitus and coronary artery bypass. *J Thorac Cardiovasc Surg* 85:264-71, 1983
93. Shuhaiber H, Chugh T, Portoian-Shuhaiber S, Ghosh D: Wound infection in cardiac surgery. *J Cardiovasc Surg* 28:139-42, 1987
94. Lilienfeld DE, Engin MS, Vlahov D, Tenney JH, McLaughlin JS: Obesity and diabetes as risk factors for postoperative wound infections after cardiac surgery. *Am J Infect Control* 16:3-6, 1988
95. Miholic J, Hudec M, Domanig E, Hiertz H, Klepetko W, Lackner F, Wolner E: Risk factors for severe bacterial infections after valve replacement and aortocoronary bypass operations: Analysis of 246 cases by logistic regression. *Ann Thorac Surg* 40:224-28, 1985
96. Rutledge R, Appelbaum RE, Kim BJ: Mediastinal infection after open heart surgery. *Surgery* 97:88-92, 1985
97. Stephens BJ, Lathrop JC, Rice WT, Gruenberg JC: Fournier's gangrene: Historic (1764-1978) versus contemporary (1979-1988) differences in etiology and clinical importance. *Am Surg* 59:149-54, 1993
98. Paty R, Smith AD: Gangrene and Fournier's gangrene. *Urol Clin North Am* 19:149-62, 1992
99. Edmondson RA, Banerjee AK, Rennie JA: Fournier's gangrene: An aetiological hypothesis. *Br J Urol* 69:543-4, 1992
100. Opal SM, Cross A, Palmer M, Almazan R: Group B streptococcal sepsis in adults and infants. *Arch Intern Med* 148:641-45, 1988
101. Lerner P, Gopakadrishna K, Wolinsky E: Group B streptococcus (S agalactiae) bacteremia in adults: Analysis of 32 cases and review of the literature. *Medicine* 56:457-73, 1977
102. Bayer AS, Chow AW, Anthoney BF: Serious infections in adults due to group B streptococci: Clinical and serologic characteristics. *Am J Med* 61:498-503, 1976
103. Farley MM, Harvey RC, Stull T, Smith JD, Schuchat A, Wenger JD, Stephens DS: A population-based assessment of invasive disease due to group B streptococcus in nonpregnant adults. *N Engl J Med* 328:1807-11, 1993