CHAPTER 30

INFECTIONS ASSOCIATED WITH DIABETES

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SUMMARY

Evidence supporting the notion that diabetes predisposes to an increased risk of infection continues to be inconclusive. In fact, in patients with diabetes, the percentage of outpatient visits to a physician because of an infection ranges from 1.6% to 5.1%, whereas individuals without diabetes average 2.6%–3.6% outpatient visits to physicians as a result of an infection. Additionally, compared to the general population, the percentage of deaths due to infection in those diagnosed with diabetes ranges from 2.7% to 3.4% compared to a range of 4.1% to 4.6% in individuals without diabetes. In individuals with diabetes, the mechanisms have not been clearly elucidated but are partly attributed to the effect of hyperglycemia on the immune system, increased risk of local tissue ischemia, and neuropathy. The available evidence suggests that individuals with diabetes are more likely to develop certain infections, including asymptomatic bacteriuria (especially women), urinary tract infection, pyelonephritis, renal and perinephric abscess, lower extremity infections, deep subcutaneous tissue infections, postoperative sternal wound infections, and tuberculosis compared to individuals without diabetes. In 2010, 2.8% of hospital discharges for persons diagnosed with diabetes were due to foot ulcers, a stark contrast when compared to only 0.6% of discharges due to foot ulcers in individuals without diabetes.

There is inadequate evidence linking diabetes to an increased risk of pneumonia or influenza. The case fatality rate among individuals with diabetes who are diagnosed with a respiratory tract infection, such as influenza, sinusitis, and bronchitis, ranges from 1% to 1.4% compared to a range of 1.9% to 2.4% in individuals without diabetes. Most clinical guidelines recommend persons with diabetes receive the pneumonia and influenza vaccines. Similar to the evidence linking diabetes to respiratory tract infections, the evidence linking diabetes to an increased risk of fungal infections, superficial bacterial skin and soft tissue infections, sinusitis, or bronchitis, is weak.

However, there are infections that occur almost exclusively among individuals with diabetes, including: emphysematous pyelonephritis and emphysematous cholecystitis, malignant otitis externa, and rhinocerebral mucormycosis. Additionally, diabetes has been identified as a risk factor for invasive group B streptococcal infections in nonpregnant adults. Immunological defects, microangiopathy, and autonomic and sensory neuropathy have all been implicated as risk factors for the aforementioned infections in individuals with diabetes. This chapter summarizes the body of evidence on the relationship between diabetes and infectious disease risks and outcomes.

INTRODUCTION AND OVERVIEW

The link between diabetes and infections, such as tuberculosis, has been clinically observed for centuries (1), and the compilation of scientific evidence has been an ongoing work. Before the invention of medications such as insulin and antibiotics, infections were shown to contribute considerably to diabetes-associated morbidity and mortality (2). Diabetes is associated with reduced response of T cells, diminished neutrophil function, and impaired humoral immunity (3). As a result, susceptibility to infections increases in patients with diabetes, not only for common infections in the general population, including respiratory, urinary tract, and skin and connective tissue infections, but also for infections commonly associated with diabetes, such as rhinocerebral mucormycosis and emphysematous cholecystitis (Table 30.1). However, few specific infections occur almost exclusively in individuals with diabetes. The longstanding question regarding whether diabetes is a risk factor for many infections has not been resolved satisfactorily.

Based on data from the National Vital Statistics System (NVSS) analyzed for *Diabetes in America, 3rd edition,* in the United States in 1999–2010, the percent of deaths with infections ranged from 2.7% to 3.4% in persons with diabetes and 4.1% to 4.6% in persons without diabetes (Appendix 30.1), with respiratory tract infections accounting for the highest percentage of deaths in both groups (Figure 30.1). Based on a new analysis of data from the National Hospital Discharge Surveys (NHDS) during the same period, the age-standardized percent of hospital

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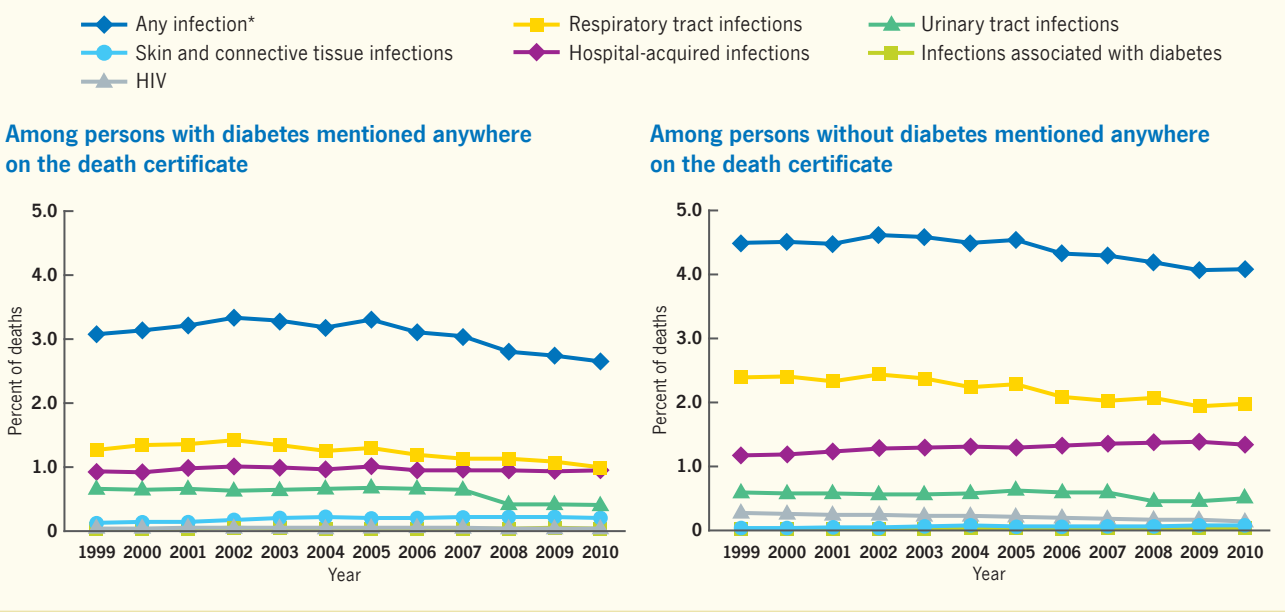
TABLE 30.1. Summary of Infections in Diabetes

INFECTIONS	COMMON PATHOGENS (REF.)	CLINICAL FEATURES (REF.)	DIAGNOSIS (REF.)
Respiratory tract infections			
Influenza		Fever, body ache, cough	
Pneumonia	*Staphylococcus aureus*, *Streptococcus pneumoniae, Haemophilus influenzae,* other gram-negative rods, and atypical pathogens (18)	Cough, fever	Chest radiogram
Sinusitis		Fever, headache, nasal discharge	Clinical diagnosis, CT
Bronchitis		Cough	Clinical diagnosis
Urinary tract infections			
Asymptomatic bacteriuria	*Escherichia coli*, *Proteus* species, *Staphylococcus saprophyticus, Klebsiella*, *Enterococci* (19)	No symptoms	Urine culture
Cystitis	*Escherichia coli, Proteus* species (18)	Dysuria, increased urinary frequency, suprapubic pain (18)	Urine analysis and culture (18)
Pyelonephritis	*Escherichia coli*, *Proteus* species (18), *Staphylococcus saprophyticus*, *Klebsiella, Enterococci* (19)	Flank pain, fever (18)	Urine analysis and culture (18)
Emphysematous pyelonephritis	*Escherichia coli* and other gram-negative rods (18)	Flank pain, fever, poor response to antibiotics (18)	Radiography or CT (18)
Perinephric abscess	*Escherichia coli* and other gram-negative rods (18)	Flank pain, fever, poor response to antibiotics (18)	Ultrasound or CT (18)
Skin and connective tissue infections			
Oral and vaginal candidiasis; Intertrigo	*Candida albicans*	Thrush, rash, discharge	Clinical diagnosis, microscopic examination, culture
Onychomycosis	*Trichophyton rubrum, Trichophyton mentagrophytes*	Nail discoloration	Clinical diagnosis
Cellulitis and impetigo	*Staphylococcus aureus, Staphylococcus pyogenes* (2)	Redness, pain, skin lesion (2)	Clinical diagnosis
Foot ulcers	Cellulitis without an open skin wound β-hemolytic *Streptococcus* and *Staphylococcus aureus* Infected ulcer and antibiotic naïve *Staphylococcus aureus* and β-hemolytic *Streptococcus* Chronic infected ulcer or was previously treated with antibiotics *Staphylococcus aureus,* β-hemolytic *Streptococcus, Enterobacteriaceae* Macerated ulcer (due to soaking) *Pseudomona aeruginosa* (often with other organisms) Long-duration nonhealing ulcer with prolonged antibiotic therapy aerobic gram-positive cocci, diphtheroids, *Enterobacteriaceae*, *Pseudomonas* species, fungi Extensive necrosis and gangrene mixed aerobic gram-positive cocci, *Enterobacteriaceae*, non-fermenting gram-negative rods, obligate anaerobes (53)	See Table 30.4.	Clinical examination, radiology, CT, culture
Necrotizing fasciitis	Gram-negative rods, anaerobes (type 1) or group A *Streptococci* (type 2) (18)	Pain, redness, crepitus, skin lesion (18)	Radiology, CT
Fournier's gangrene	Gram-negative rods, anaerobes (type 1) or group A *Streptococci* (type 2) (18)	Pain, redness, crepitus, skin lesion (18)	Radiology, CT
Osteomyelitis	See "foot ulcers"	Chronic, nonhealing ulcers, leukocytosis, fever	Radiology, MRI, radioisotope scans, bone biopsy
Infections associated with diabetes			
Malignant otitis externa	*Pseudomonas aeruginosa*	Ear pain, hearing loss, cellulitis, discharge (18)	Clinical examination, MRI (18)
Mucormycosis	*Mucor* and *Rhizodus* species (18)	Facial or ocular pain, fever, black nasal eschar (18)	Clinical examination, MRI, pathology (18)
Emphysematous cholecystitis	Gram-negative bacilli, anaerobes (18), most commonly polymicrobial (19)	Right upper quadrant abdominal pain, fever, systemic toxicity (18)	Radiology, CT (18)
Group B Strep infections	Group B *Streptococcus*	Skin and soft tissue (cellulitis, abscess, necrotizing fasciitis, sternal wound infections), bacteremia without clear cause, urinary tract (cystitis, pyelonephritis), pneumonia, osteomyelitis, septic arthritis, endocarditis, meningitis	Culture

CT, computed tomography; MRI, magnetic resonance imaging.

SOURCE: References are listed within the table.

FIGURE 30.1. Percent of Deaths With Infections, by Diabetes Status, U.S., 1999–2010

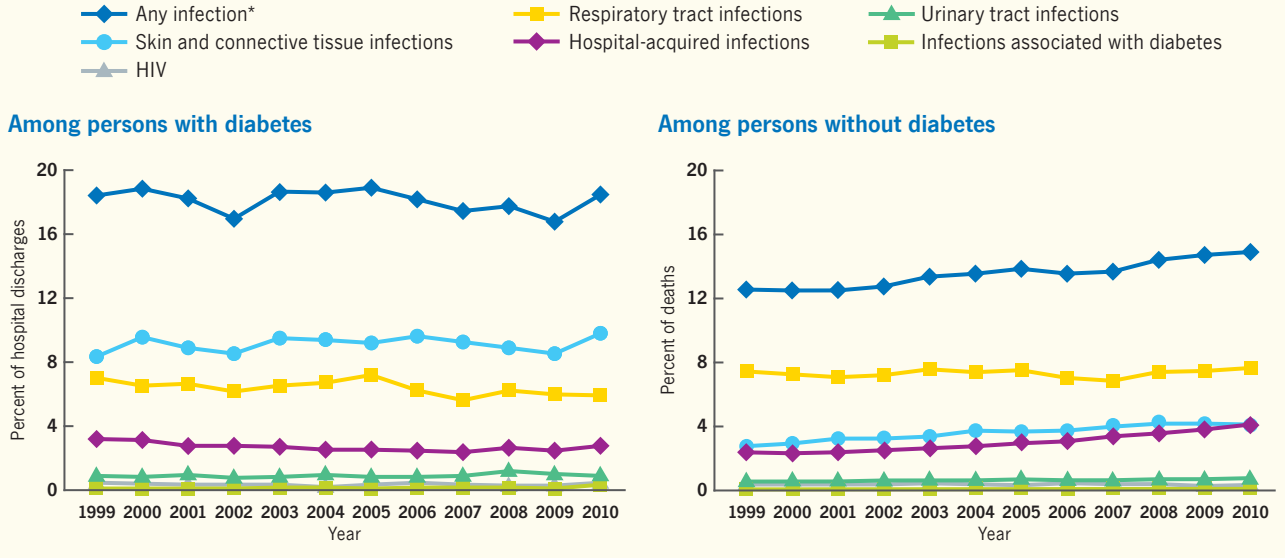


Diabetes is defined using ICD-10 codes: E10–E14, O24.0–O24.3, and P70.2. ICD-10 codes used to define infections are as follows: respiratory tract infections, including influenza (J10.1, J18.9), and sinusitis and bronchitis (J32.9, J40); urinary tract infections, including asymptomatic bacteriuria (N39.0), cystitis (N30.9), pyelonephritis (N10), and perinephric abscess (N15.1); skin and connective tissue infections, including oral and vaginal candidiasis (B37.0, B37.3), onychomycosis (B35.1), intertrigo (L30.4), cellulitis and impetigo (L3.9, L1.0), foot ulcers (L97), necrotizing fasciitis (M72.6), and osteomyelitis (M86.9); hospital-acquired infections, including sepsis (A41.9); infections associated with diabetes, including malignant otitis externa (H60.2), mucormycosis (B46.5), and emphysematous cholecystitis (K81.0); and HIV (B20). Tuberculosis (A15.9) and Fournier's gangrene (N49.3) were not in the data set. HIV, human immunodeficiency virus; ICD-10, The International Classification of Diseases, Tenth Revision, is the standard diagnostic tool for epidemiologic, health management, and clinical purposes, including the analysis of the general health situation of population groups. It is used to monitor the incidence and prevalence of diseases and other health problems, proving a picture of the general health situation of countries and populations.

* Any infection includes respiratory, urinary tract, skin and connective tissue, hospital-acquired, infections associated with diabetes, or HIV.

SOURCE: National Vital Statistics System 1999–2010

FIGURE 30.2. Age-Standardized Percent of Hospital Discharges Listing Infection, by Diabetes Status, U.S., 1999–2010



Diabetes is defined using ICD-9 codes: 250, 357.2, 362.0, 366.41, 648.0, and 775.1. ICD-9 codes used to define infections are as follows: respiratory tract infections, including influenza (480–488) and sinusitis and bronchitis (461, 466); urinary tract infections, including asymptomatic bacteriuria (791.9), cystitis (595.0), pyelonephritis (590.1, 590.8), and perinephric abscess (590.2); skin and connective tissue infections, including oral and vaginal candidiasis (112.0–112.3), onychomycosis (110.1), intertrigo (695.89), cellulitis and impetigo (682, 684), foot ulcers (707.1), necrotizing fasciitis (728.86), Fournier's gangrene (785.4), and osteomyelitis (730.2); hospital-acquired infections, including sepsis (038) and postoperative wound infections (998.59); infections associated with diabetes, including malignant otitis externa (380.14), mucormycosis (117.7), and emphysematous cholecystitis (575.0); and HIV (042–044). Data are age-standardized to the overall National Hospital Discharge Survey 2010 using age categories <44, 45–64, and ≥65 years. HIV, human immunodeficiency virus; ICD-9, The International Classification of Diseases, Ninth Revision, is the official system of assigning codes to diagnoses and procedures associated with hospital utilization in the United States.

* Any infection includes respiratory, urinary tract, skin and connective tissue, hospital-acquired, infections associated with diabetes, and HIV.

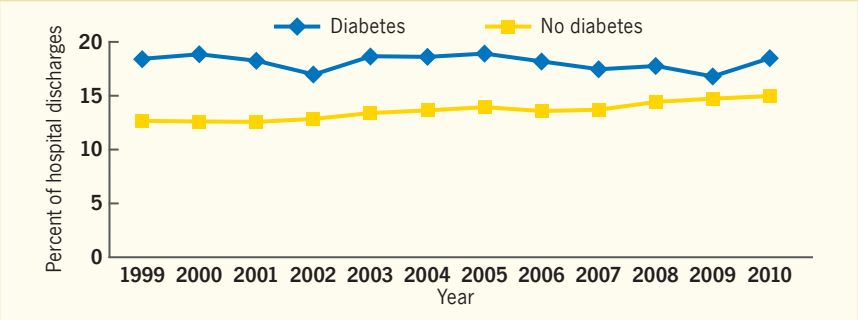
SOURCE: National Hospital Discharge Surveys 1999–2010

discharges listing infections ranged from 16.8% to 18.9% in persons with diabetes and 12.5% to 14.9% in persons without diabetes (Appendix 30.2); skin and connective tissue infections were the most common infections in those with diabetes, followed by respiratory tract infections, while respiratory tract infections accounted for the highest percentage of hospital discharges in those without diabetes (Figures 30.2–30.7). Physician office visits for infection ranged from 1.6% to 5.1% in persons with diabetes and from 2.6% to 3.6% in persons without diabetes over the same time period (Appendix 30.3) based on a new analysis of data from the National Ambulatory Medical Care Surveys (NAMCS) (Figure 30.8).

A new analysis of data from the National Nursing Home Surveys (NNHS) 1999 and 2004 for *Diabetes in America* showed the age-standardized percent of nursing home residents with infections among persons with diabetes increased from 6.1% in 1999 to 10.3% in 2004, while the change in persons without diabetes over the same two time points was from 6.0% to 8.5% (Table 30.2). Overall, these data suggest that a greater proportion of hospitalizations and physician office visits among persons with diabetes compared to persons without diabetes involve the care of infection, especially among older adults (nursing home residents).

Various host/organism-specific factors capable of increasing an individual's susceptibility to infection have been investigated. These studies found that individuals with diabetes are more likely to develop peripheral vascular disease and microangiopathy, which can cause local tissue ischemia. In turn, ischemia can result in delayed wound healing and tissue necrosis due to decreased oxygen, nutrient, and activated leukocyte delivery, as well as poor tissue penetration of antibiotics (4). Tissue ischemia may be further compounded by an increased venous and tissue pressure due to arteriovenous shunting occurring in patients with autonomic neuropathy and peripheral sympathetic denervation (4). Autonomic neuropathy can also cause urine retention

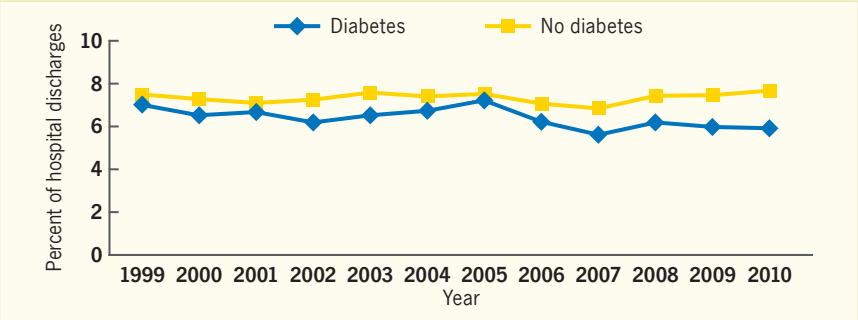
FIGURE 30.3. Age-Standardized Percent of Hospital Discharges Listing Any Infection, by Diabetes Status, U.S., 1999–2010



Any infection includes respiratory, urinary tract, skin and connective tissue, hospital-acquired, infection associated with diabetes, or HIV. Diabetes is defined using ICD-9 codes: 250, 357.2, 362.0, 366.41, 648.0, and 775.1. ICD-9 codes used to define infections are as follows: respiratory tract infections, including influenza (480–488) and sinusitis and bronchitis (461, 466); urinary tract infections, including asymptomatic bacteriuria (791.9), cystitis (595.0), pyelonephritis (590.1, 590.8), and perinephric abscess (590.2); skin and connective tissue infections, including oral and vaginal candidiasis (112.0–112.3), onychomycosis (110.1), intertrigo (695.89), cellulitis and impetigo (682, 684), foot ulcers (707.1), necrotizing fasciitis (728.86), Fournier's gangrene (785.4), and osteomyelitis (730.2); hospital-acquired infections, including sepsis (038), and postoperative wound infections (998.59); infections associated with diabetes, including malignant otitis externa (380.14), mucormycosis (117.7), and emphysematous cholecystitis (575.0); and HIV (human immunodeficiency virus) (042–044). Data are age-standardized to the overall National Hospital Discharge Survey 2010 using age categories <44, 45–64, and ≥65 years. ICD-9, The International Classification of Diseases, Ninth Revision, is the official system of assigning codes to diagnoses and procedures associated with hospital utilization in the United States.

SOURCE: National Hospital Discharge Surveys 1999–2010

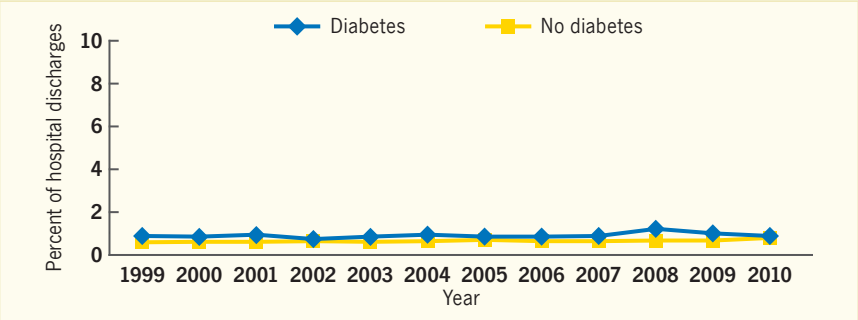
FIGURE 30.4. Age-Standardized Percent of Hospital Discharges Listing Respiratory Tract Infections, by Diabetes Status, U.S., 1999–2010



Respiratory tract infections include influenza and sinusitis and bronchitis. Diabetes is defined using ICD-9 codes: 250, 357.2, 362.0, 366.41, 648.0, and 775.1. ICD-9 codes used to define respiratory tract infections are as follows: influenza (480–488) and sinusitis and bronchitis (461, 466). Data are age-standardized to the overall National Hospital Discharge Survey 2010 using age categories <44, 45–64, and ≥65 years. ICD-9, The International Classification of Diseases, Ninth Revision, is the official system of assigning codes to diagnoses and procedures associated with hospital utilization in the United States.

SOURCE: National Hospital Discharge Surveys 1999–2010

FIGURE 30.5. Age-Standardized Percent of Hospital Discharges Listing Urinary Tract Infections, by Diabetes Status, U.S., 1999–2010



Urinary tract infections include asymptomatic bacteriuria, cystitis, pyelonephritis, and perinephric abscess. Diabetes is defined using ICD-9 codes: 250, 357.2, 362.0, 366.41, 648.0, and 775.1. ICD-9 codes used to define urinary tract infections are as follows: asymptomatic bacteriuria (791.9), cystitis (595.0), pyelonephritis (590.1, 590.8), and perinephric abscess (590.2). Data are age-standardized to the overall National Hospital Discharge Survey 2010 using age categories <44, 45–64, and ≥65 years. ICD-9, The International Classification of Diseases, Ninth Revision, is the official system of assigning codes to diagnoses and procedures associated with hospital utilization in the United States.

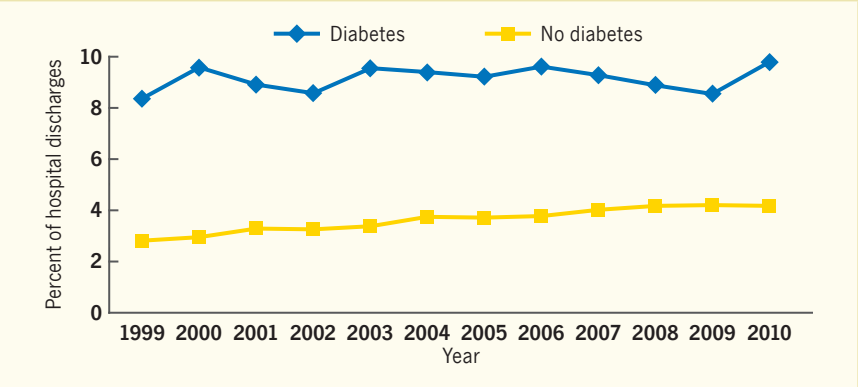
SOURCE: National Hospital Discharge Surveys 1999–2010

that can predispose the patient to urinary tract infections (UTIs) (5). C fiber dysfunction can result in a decrease of local and systemic inflammatory signs (4), and peripheral neuropathy causes a loss of sensation. Due to these factors, skin lesions in diabetic patients can go unnoticed.

The effects of hyperglycemia on the immune system have been studied, showing a reduction in the activity of polymorphonuclear cells in the presence of hyperglycemia, mostly due to impaired chemotaxis, adherence to vascular walls, phagocytosis, opsonization, and defects in oxidation (4,6). Several pathogens have been shown to proliferate in the presence of hyperglycemia. Hyperglycemia promotes the adhesion of *Candida albicans* to the mucosal epithelium, and *Rhizopus* species produce an enzyme, ketone reductase, that allows them to thrive in hyperglycemic acidic conditions (7).

Though clinical observation of anatomic, immunologic, and pathogenic related factors suggest that individuals with diabetes are more likely to suffer from infections, scientific data are lacking, with few infections demonstrated to occur more frequently in individuals with diabetes compared to individuals without diabetes.

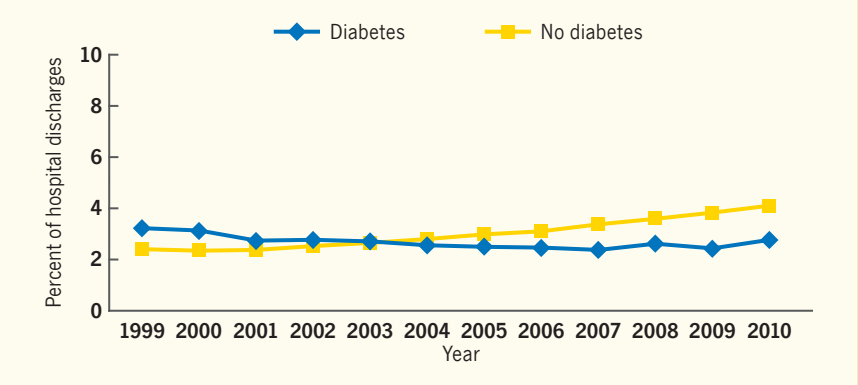
FIGURE 30.6. Age-Standardized Percent of Hospital Discharges Listing Skin and Connective Tissue Infections, by Diabetes Status, U.S., 1999–2010



Skin and connective tissue infections include oral and vaginal candidiasis, onychomycosis, intertrigo, cellulitis and impetigo, foot ulcers, necrotizing fasciitis, Fournier's gangrene, and osteomyelitis. Diabetes is defined using ICD-9 codes: 250, 357.2, 362.0, 366.41, 648.0, and 775.1. ICD-9 codes used to define skin and connective tissue infections are as follows: oral and vaginal candidiasis (112.0–112.3), onychomycosis (110.1), intertrigo (695.89), cellulitis and impetigo (682, 684), foot ulcers (707.1), necrotizing fasciitis (728.86), Fournier's gangrene (785.4), and osteomyelitis (730.2). Data are age-standardized to the overall National Hospital Discharge Survey 2010 using age categories <44, 45–64, and ≥65 years. ICD-9, The International Classification of Diseases, Ninth Revision, is the official system of assigning codes to diagnoses and procedures associated with hospital utilization in the United States.

SOURCE: National Hospital Discharge Surveys 1999–2010

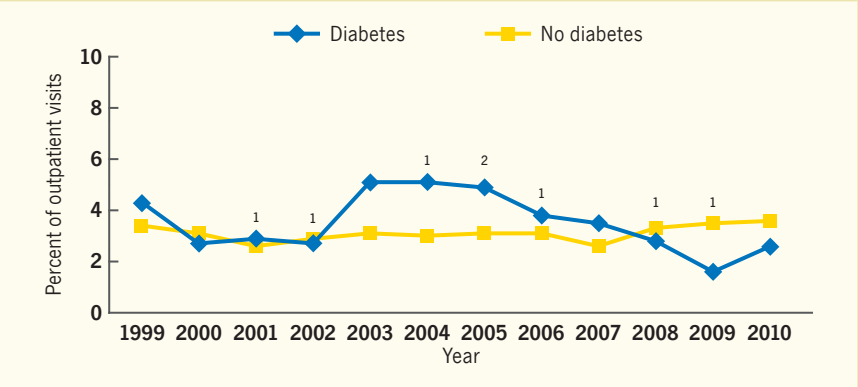
FIGURE 30.7. Age-Standardized Percent of Hospital Discharges Listing Hospital-Acquired Infections, by Diabetes Status, U.S., 1999–2010



Hospital-acquired infections include sepsis and postoperative wound infections. Diabetes is defined using ICD-9 codes: 250, 357.2, 362.0, 366.41, 648.0, and 775.1. ICD-9 codes used to define hospital-acquired infections are as follows: sepsis (038) and postoperative wound infections (998.59). Data are age-standardized to the overall National Hospital Discharge Survey 2010 using age categories <44, 45–64, and ≥65 years. ICD-9, The International Classification of Diseases, Ninth Revision, is the official system of assigning codes to diagnoses and procedures associated with hospital utilization in the United States.

SOURCE: National Hospital Discharge Surveys 1999–2010

FIGURE 30.8. Age-Standardized Percent of Outpatient Visits to a Physician Pertaining to Infections, by Diabetes Status, U.S., 1999–2010



Diabetes is defined using ICD-9 codes: 250, 357.2, 362.0, 366.41, 648.0, and 775.1. ICD-9 codes used to define infections are as follows: influenza (480–488), sinusitis and bronchitis (461, 466), asymptomatic bacteriuria (791.9), cystitis (595.0), pyelonephritis (590.1, 590.8), perinephric abscess (590.2), oral and vaginal candidiasis (112.0–112.3), onychomycosis (110.1), intertrigo (695.89), cellulitis and impetigo (682, 684), foot ulcers (707.1), necrotizing fasciitis (728.86), Fournier's gangrene (785.4), osteomyelitis (730.2), sepsis (038), postoperative wound infections (998.59), malignant otitis externa (380.14), mucormycosis (117.7), emphysematous cholecystitis (575.0), HIV (human immunodeficiency virus) (042–044), and tuberculosis (010–018). Data are age-standardized to the overall National Ambulatory Medical Care Survey 2010 using age categories <45, 45–64, and ≥65 years. ICD-9, The International Classification of Diseases, Ninth Revision, is the official system of assigning codes to diagnoses and procedures associated with hospital utilization in the United States.

[1] Relative standard error >30%–40%

[2] Relative standard error >40%–50%

SOURCE: National Ambulatory Medical Care Surveys 1999–2010

TABLE 30.2. Age-Standardized Percent of Nursing Home Residents With Infections, by Diabetes Status, U.S., 1999 and 2004

	PERCENT (STANDARD ERROR)	
	1999	2004
Diabetes	6.1 (0.68)	10.3 (0.67)
No diabetes	6.0 (0.30)	8.5 (0.37)

Diabetes is defined using ICD-9 codes: 250, 357.2, 362.0, 366.41, 648.0, and 775.1. ICD-9 codes used to define infections are as follows: influenza (480–488), sinusitis and bronchitis (461, 466), asymptomatic bacteriuria (791.9), cystitis (595.0), pyelonephritis (590.1, 590.8), perinephric abscess (590.2), oral and vaginal candidiasis (112.0–112.3), onychomycosis (110.1), intertrigo (695.89), cellulitis and impetigo (682, 684), foot ulcers (707.1), necrotizing fasciitis (728.86), Fournier's gangrene (785.4), osteomyelitis (730.2), sepsis (038), postoperative wound infections (998.59), malignant otitis externa (380.14), mucormycosis (117.7), emphysematous cholecystitis (575.0), HIV (human immunodeficiency virus) (042–044), tuberculosis (010–018). Data are age-standardized to the overall National Nursing Home Survey 2004 using age categories <65, 65–74, 75–84, and ≥85 years. ICD-9, The International Classification of Diseases, Ninth Revision, is the official system of assigning codes to diagnoses and procedures associated with hospital utilization in the United States.

SOURCE: National Nursing Home Surveys 1999 and 2004

DATA SOURCES AND LIMITATIONS

Numerous data sources are used in this chapter, including but not limited to:

NATIONAL VITAL STATISTICS SYSTEM 1999–2010

The NVSS is the oldest and most successful example of intergovernmental data sharing in public health, and the shared relationships, standards, and procedures form the mechanism by which the National Center for Health Statistics (NCHS) collects and disseminates the Nation's official vital statistics. These data are provided through contracts between NCHS and vital registration systems operated in the various jurisdictions legally responsible for the registration of vital events—births, deaths, marriages, divorces, and fetal deaths.

NATIONAL HOSPITAL DISCHARGE SURVEYS 1999–2010

NHDS data are collected from a sample of inpatient records acquired from a national probability sample of hospitals. Because persons with multiple discharges during the year can be sampled more than once, NHDS produces estimates for discharges, not persons. Only hospitals with an average length of stay of fewer than 30 days for all patients, general hospitals, or children's general hospitals are included in the survey. Federal, military, and Department of Veterans Affairs hospitals, as well as hospital units of institutions (such as prison hospitals) and hospitals with fewer than six beds staffed for patient use, are excluded.

NATIONAL AMBULATORY MEDICAL CARE SURVEYS 1999–2010

The NAMCS is a national survey designed to meet the need for objective, reliable information about the provision and use of ambulatory medical care services in the United States. Findings are based on a sample of visits to non-federal employed, office-based physicians who are primarily engaged in direct patient care.

NATIONAL NURSING HOME SURVEYS 1999 AND 2004

The NNHS is a continuing series of national sample surveys of nursing homes, their residents, and their staff. Although each of these surveys emphasized different topics, they all provided some common basic information about nursing homes, their residents, and their staff. All nursing homes included in this survey had at least three beds and were either certified (by Medicare or Medicaid) or had a state license to operate as a nursing home.

There are several limitations that must be mentioned. First, with large, national data sets, it is important to recognize that underreporting and/or misreporting of data can occur. For example, compared to those who do not have diabetes, the death certificate data on infections for individuals with diabetes may not be reported accurately. Similarly, hospital discharge data may not reflect all appropriate diagnoses upon release after inpatient hospitalizations. Additionally, long-term and federal hospitals are often excluded from national data, such as the NHDS; therefore, hospitalizations involving persons with diabetes may be underestimated. Second, the sample size associated with some of the medical conditions analyzed may be small; therefore, estimates may be limited and not generalizable to all subpopulations. Third, because national data sets provide aggregate data on a group of individuals rather than individuals, rates of diabetes-related infections may not reflect risks for individual persons. Fourth, because ICD-9 codes were used to compute the analyses, true prevalence estimates may be underestimated. Despite these limitations, however, the information provided is important to understanding the relationship between diabetes and infections.

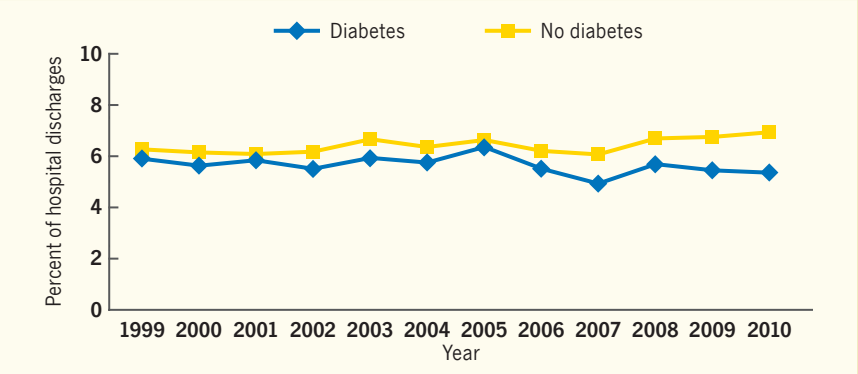
GENERAL INFECTIONS IN INDIVIDUALS WITH DIABETES

RESPIRATORY TRACT INFECTIONS

Influenza and Pneumonia

Epidemiologic studies suggest that individuals with diabetes are at high risk for complications, hospitalization, and death from influenza and pneumococcal disease (8). However, there are few data on whether individuals with diabetes are more likely to contract influenza compared to those without diabetes (Figure 30.9). Non-age-adjusted death rates among individuals with diabetes increase by 5%–15% during influenza epidemics (9). Data show that respiratory infections are common in diabetes and that influenza is the most common respiratory infection diagnosis (Appendix 30.2).

FIGURE 30.9. Age-Standardized Percent of Hospital Discharges Listing Influenza, by Diabetes Status, U.S., 1999–2010



Diabetes is defined using ICD-9 codes: 250, 357.2, 362.0, 366.41, 648.0, and 775.1. ICD-9 codes used to define influenza are 480–488. Data are age-standardized to the overall National Hospital Discharge Survey 2010 using age categories <44, 45–64, and ≥65 years. ICD-9, The International Classification of Diseases, Ninth Revision, is the official system of assigning codes to diagnoses and procedures associated with hospital utilization in the United States.

SOURCE: National Hospital Discharge Surveys 1999–2010

TABLE 30.3. Guidelines for Vaccination for Influenza and Pneumonia

INFECTION	ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES RECOMMENDATIONS
Influenza	▪ Yearly (starting September) for patients with diabetes age ≥6 months. ▪ Intramuscular dosage and vaccine type should be based on the patient's age.
Pneumonia	▪ Pneumococcal polysaccharide vaccine 23 (PPSV23) should be administered to all patients with diabetes age ≥2 years. ▪ Both PPSV23 and pneumococcal conjugate vaccine 13 (PCV13) should be administered in series routinely to all adults age ≥65 years. ▪ Administer PCV13 to adults age ≥65 years if not previously vaccinated or if vaccination status unknown, followed by PPSV23 6–12 months after the initial vaccination with PCV13. ▪ If previously vaccinated with PPSV23, administer PCV13 ≥12 months later as follow-up in adults age ≥65 years.

SOURCE: Reference 8

Rapid influenza diagnostic testing can be used to establish that patients presenting with high fever, myalgias, and cough are infected with this disease. In a new analysis of NVSS data for *Diabetes in America* assessing the percentage of deaths with infections by diabetes status, approximately 1%–1.5% of deaths in individuals with diabetes were associated with a respiratory tract infection, such as influenza, between 1999 and 2010 compared to slightly over 2% in individuals without diabetes during the same time period (Figure 30.1, Appendix 30.1). Contrarily, a new analysis of NHDS 1999–2010 data for *Diabetes in America* demonstrated a higher percentage of hospital discharges listing influenza as a diagnosis in individuals without diabetes (approximately 6%–7%) compared to individuals with diabetes (approximately 5%–6%) (Figure 30.9, Appendix 30.2).

Treatment for influenza is mostly symptomatic, but antiviral agents can be used as well. Major complications are sinusitis, bronchitis, and pneumonia. Although one study found that prophylactic influenza vaccination was associated with only a 12.3% reduction in hospitalization rates for older individuals (age ≥65 years) with diabetes compared to 23% in people without diabetes (p=0.08) (10), most epidemiologic studies suggest that persons with diabetes are at higher risk for complications, hospitalization, and death from influenza (8,11,12). Accordingly, the Advisory Committee on Immunization Practices recommends vaccinating individuals with diabetes before the influenza season as the most effective way to reduce the impact of influenza (Table 30.3) (8).

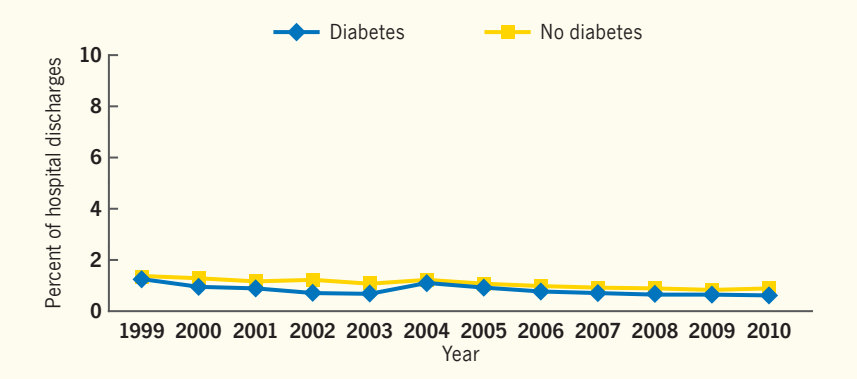
Controlled data comparing the incidence of pneumonia in individuals with and without diabetes are scarce. The question remains whether diabetes is an individual risk factor for developing pneumonia; however, data support the notion that diabetes increases the risk for pneumonia-related hospitalizations (13), increased length of hospital stay (14), and pneumonia-related mortality (15). In one 12-month prospective study, individuals with type 1 or type 2 diabetes were shown to have a greater risk of lower respiratory tract infection (type 1 diabetes: adjusted odds ratio [AOR] 1.42, 95% confidence interval [CI] 0.96–2.08; type 2 diabetes: AOR 1.32, 95% CI 1.13–1.53) (16), but results from other studies have yielded conflicting results (16).

Diabetes is one of the conditions associated with recurrent pneumonia (17), and microorganisms responsible for pneumonia in individuals with diabetes differ from those in individuals without diabetes. Individuals with diabetes are more likely to develop pneumonia from *Staphylococcus aureus*, *Klebsiella pneumonia,* and other gram-negative rods (18,19). Pneumonia from *Streptococcus pneumonia* is associated with increased mortality and bacteremia among individuals with diabetes (8,18). In one population-based case-control study, the odds ratio (OR) for community-acquired pneumococcal bacteremia, adjusted for comorbidities, was 1.5 (95% CI 1.1–2.0) in those with diabetes compared with persons without diabetes (19). Accordingly, the Advisory Committee on Immunization Practices recommends pneumococcal vaccination in individuals with diabetes as a strategy to reduce invasive disease from pneumococcus (Table 30.3) (8).

Sinusitis and Bronchitis

No direct comparison data are available to determine whether individuals with diabetes are more likely to develop acute sinusitis and bronchitis than those without diabetes. Based on NHDS 1999–2010 data analyzed for *Diabetes in America,* similar estimates for the rates of hospital discharges for both conditions are observed (Figure 30.10, Appendix 30.2).

FIGURE 30.10. Age-Standardized Percent of Hospital Discharges Listing Sinusitis and Bronchitis, by Diabetes Status, U.S., 1999–2010



Diabetes is defined using ICD-9 codes: 250, 357.2, 362.0, 366.41, 648.0, and 775.1. ICD-9 codes used to define sinusitis and bronchitis are 461 and 466. Data are age-standardized to the overall National Hospital Discharge Survey 2010 using age categories <44, 45–64, and ≥65 years. ICD-9, The International Classification of Diseases, Ninth Revision, is the official system of assigning codes to diagnoses and procedures associated with hospital utilization in the United States.

SOURCE: National Hospital Discharge Surveys 1999–2010

URINARY TRACT INFECTIONS

UTIs are described in Chapter 28 *Urologic Diseases and Sexual Dysfunction in Diabetes*. UTIs among individuals with diabetes occur at a higher frequency than in those without diabetes, especially among those with type 1 diabetes (16). However, there are few high-quality observational studies on the relationship between diabetes and UTI (Figure 30.5, Appendix 30.2) (20,21,22), with most of the available studies subject to patient selection bias due to patient and physician referrals and hospital-based sampling.

Several pathogenic mechanisms have been investigated to better understand the causal mechanism of UTI in persons with diabetes, and neither the presence of glucosuria (23) nor level of hyperglycemia (24) explains the higher incidence of UTIs in individuals with diabetes. UroEDIC is a urologic complications ancillary study of the Epidemiology of Diabetes Interventions and Complications Study that followed Diabetes Control and Complications Trial participants after the conclusion of the clinical trial. Among women with type 1 diabetes, sexual activity—a risk factor common to all young, sexually active women with and without diabetes—but not diabetes duration, measures of diabetes control, or complications, was the main risk factor associated with increased cystitis risk (AOR 8.28, 95% CI 1.45–158.32, p=0.01) (25). Others have suggested that impaired renal function secondary to glomerulosclerosis and micturition abnormalities causing increased residual urine could account for an increased susceptibility to infection (26). Studies have also shown that patients with poorly controlled diabetes have higher adherence of *Escherichia coli* with type 1 fimbriae to uroepithelial cells (23). Predominant organisms include *Escherichia coli* (the most common pathogen) and *Klebsiella pneumonia*, *Proteus*, group B streptococci, *Candida albicans,* and multimicrobial-resistant pathogens in patients with complicated infection (e.g., polynephritis, indwelling catheters, recent antibiotic therapy) (5).

Asymptomatic Bacteriuria

Asymptomatic bacteriuria is the presence of a pathogen in the urine of an asymptomatic patient. In 2005, the Infectious Diseases Society of America published guidelines for the diagnosis and treatment of asymptomatic bacteriuria in adults (27). For asymptomatic women, bacteriuria is defined as two consecutive clean catch voided urine samples with the same bacterial strain in counts ≥10^5 cfu/mL (26) or a single catheterized urine specimen with one bacterial species isolated in counts ≥10^5 cfu/mL; the latter also defines bacteriuria in asymptomatic men (27,28).

The true incidence and prevalence of asymptomatic bacteriuria is unknown (especially in men) (27). Multiple studies show that asymptomatic bacteriuria is more common in women with diabetes (2,5,29). In one study, the prevalence of asymptomatic bacteriuria was 26% in women with diabetes compared with 6% in those without diabetes (23). In another, the prevalence was 29% in women with diabetes, which was about three times greater than that in women without diabetes (30). Hypothesized reasons for this greater prevalence include urethral reflex and residual volume due to morphologic and functional changes in the bladder that results from diabetes (31). In men with diabetes, the overall prevalence of asymptomatic bacteriuria is 1%–11% and is similar to that in men without diabetes (2).

As mentioned, female sex is an independent risk factor for developing asymptomatic bacteriuria (32). In women with diabetes, diabetes duration of ≥10 years (relative risk [RR] 2.6, 95% CI 1.3–5.1) and use of insulin (RR 3.7, 95% CI 1.8–7.3), but not the level of glycemic control, increase the risk for developing the condition compared with age-matched women without diabetes (20). Diabetic neuropathy and nephropathy have been associated with asymptomatic bacteriuria in women with type 1 diabetes, but not type 2 diabetes (2).

Escherichia coli remains the organism most commonly isolated in urine specimens, but other gram-negative organisms, such as *Staphylococcus saprophyticus* and enterococci, are also common. Individuals with diabetes have an increased risk of developing symptomatic cystitis, pyelonephritis, and perinephric abscess (see the sections *Cystitis and Pyelonephritis*, *Emphysematous Pyelonephritis*, and *Renal and Perinephric Abscess*). Though a few small studies suggest that asymptomatic bacteriuria can increase the risk for developing symptomatic UTI in women with diabetes, large-scale studies are needed to support this link (33,34). Furthermore, studies evaluating the effect of antibiotic therapy on asymptomatic bacteriuria failed to show a change in long-term outcomes. In one study evaluating the effect of antibiotic therapy in adult women with diabetes and asymptomatic bacteriuria, during a mean follow-up of 27 months, 40% of women in the placebo group and 42% of women in the antimicrobial therapy group had at least one episode of symptomatic UTI (35). The time to a first symptomatic episode was similar in the placebo group and the antimicrobial therapy group (p=0.67 by the log-rank test), as were the incidence rates (±standard deviation) per 1,000 days of follow-up of any symptomatic UTI (i.e., bacteriuria) (1.10±0.17 and 0.93±0.14, respectively; RR 1.19, 95% CI 0.28–1.81), pyelonephritis (0.28±0.08 and 0.13±0.05, respectively; RR 2.13, 95% CI 0.81–5.62), and hospitalization for UTI (0.10±0.36 and 0.06±0.22, respectively; RR 1.93, 95% CI 0.47–7.89) (33). In a systematic review of published literature from 1967–2003, antimicrobial therapy did not show a reduction in symptomatic UTIs, pyelonephritis, or hospitalization for UTI (36). Therefore, based on present evidence, the Infectious Diseases Society of America does not recommend screening and treating individuals with diabetes for asymptomatic bacteriuria in their guidelines (19,27).

Cystitis and Pyelonephritis

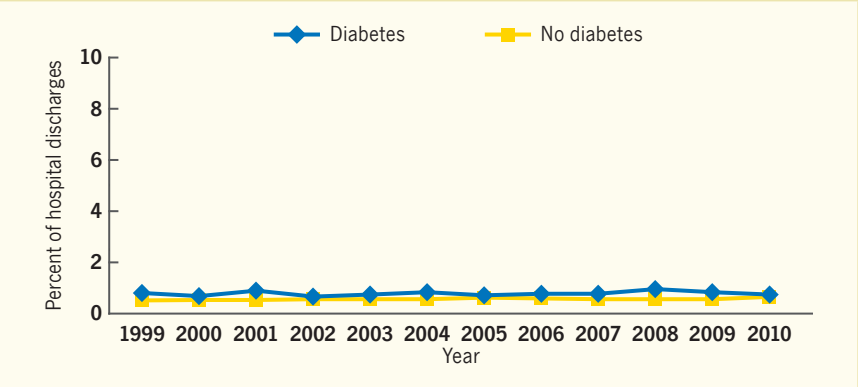
Patients with cystitis present with complaints of increased frequency of urination, dysuria, and suprapubic tenderness. Fever is uncommon in uncomplicated cystitis. Patients with pyelonephritis present more dramatically

with high fever, chills, and back pain. Diagnosis is confirmed with urine analysis and urine culture.

Diabetes is a predisposing factor for developing pyelonephritis in both sexes (2). In a case-control study conducted at the Group Health Cooperative of Puget Sound in Washington State among postmenopausal women with symptomatic UTIs, 13.1% had diabetes compared to controls, of whom 6.8% had diabetes (21). In this population, adjustment for frequency of sexual intercourse and history of UTIs had little effect on the estimate of association, and neither duration of diabetes nor the glycosylated hemoglobin (A1c) level was associated with higher odds ratios for UTIs (21). A retrospective cohort study using administrative data in Ontario found that the risk ratio for cystitis among individuals with diabetes compared to those without diabetes was 1.43 (99% CI 1.39–1.46) in 1996 and 1.39 (99% CI 1.36–1.42) in 1999 (37). In the same population-based study, the risk ratio for pyelonephritis was 1.86 (99% CI 1.69–2.05) in 1996 and 1.95 (99% CI 1.78–2.13) in 1999 (37). In another study describing the diagnosis and treatment of renal, perinephric, and mixed abscesses of patients treated at an academic center, acute pyelonephritis was shown to be four to five times more common in individuals with diabetes (38). In the UroEDIC study, among women with type 1 diabetes, the prevalences of cystitis and pyelonephritis in the preceding 12 months were 15% and 3%, respectively (25). The adjusted prevalence of cystitis (19.1%) was similar to that found in women without diabetes (23.1%) in the National Health and Nutrition Examination Survey III (AOR 0.78, 95% CI 0.51–1.22, p=0.28) (25).

Diabetes is also one of the most important risk factors for hospitalization from acute pyelonephritis. Among individuals with diabetes, the mean hospitalization rate for women was 128–144 per 10,000 and 24–34 per 10,000 for men (26). A new analysis of NHDS 1999–2010 data for *Diabetes in America* showed that, in the United States,

FIGURE 30.11. Age-Standardized Percent of Hospital Discharges Listing Pyelonephritis, by Diabetes Status, U.S., 1999–2010



Diabetes is defined using ICD-9 codes: 250, 357.2, 362.0, 366.41, 648.0, and 775.1. ICD-9 codes used to define pyelonephritis are 590.1 and 590.8. Data are age-standardized to the overall National Hospital Discharge Survey 2010 using age categories <44, 45–64, and ≥65 years. ICD-9, The International Classification of Diseases, Ninth Revision, is the official system of assigning codes to diagnoses and procedures associated with hospital utilization in the United States.

SOURCE: National Hospital Discharge Surveys 1999–2010

the average percentage of hospital discharges listing pyelonephritis among individuals with diabetes was 0.78% compared with 0.56% in those without diabetes (Figure 30.11, Appendix 30.2). Also, individuals with diabetes with acute pyelonephritis were more likely to develop complications (2). Bacteremia is about four times more likely and acute renal failure is nearly twice as likely to occur in individuals with diabetes (5,39).

Emphysematous Pyelonephritis

Emphysematous pyelonephritis is an uncommon (200 cases reported by 2013) necrotizing, gas-producing infection of the renal parenchyma (40). Diabetes is present in 70%–90% of patients presenting with this infection (19). Among persons with diabetes, urinary tract obstruction is shown to be a risk factor (present in 5 out of 10 patients in one case series) (41). The transport of metabolic endproducts is impaired due to decreased tissue perfusion in individuals with diabetes, and there is an increase in carbon dioxide produced by microorganisms from glucose (5,40), with the most common causative organisms being *Escherichia coli* and *Klebsiella* (19). The clinical course can be difficult to distinguish from acute pyelonephritis, as most patients present with fever, flank pain, and nausea. Severe symptoms and failure to respond to antibiotic therapy should be warning signs prompting further investigation. Diagnosis is confirmed by identifying the gas in renal tissues. Computed tomography (CT) is the most sensitive diagnostic method (19). Despite pharmacological and surgical therapy, mortality remains high (60%–80%), but nephrectomy, if appropriate, has a potential to reduce it to 20% (19).

Renal and Perinephric Abscess

Renal and perinephric abscess is a complicated UTI characterized by tissue necrosis forming either a walled off cavity (renal abscess) or a more diffuse liquefaction (perinephric abscess). Major risk factors are diabetes and kidney stones. In one study, each of these risk factors was present in 28% of patients (38). In a study conducted in Taiwan, among more than one-half million adults with diabetes and sex- and age-matched controls, the hazard ratio of hospitalization for renal abscess in individuals with diabetes was 3.81 (95% CI 3.44–4.23) (42). Renal ultrasound and CT are the most sensitive tests.

SKIN AND SOFT TISSUE INFECTIONS

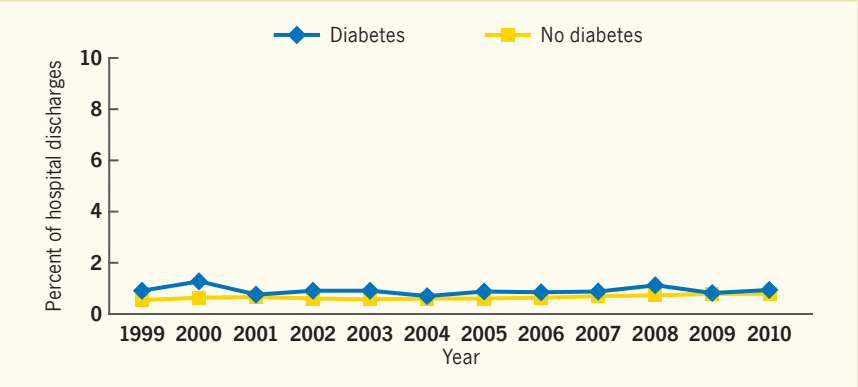
Skin and soft tissue infections are common complications in individuals with diabetes, with skin infections occurring in 20%–50% of patients annually. These infections are more common among individuals with undiagnosed and diagnosed type 2 diabetes and poor metabolic control (43). In a 12-month prospective

cohort study, comparing adults with type 1 and type 2 diabetes to adults with hypertension and without diabetes, patients with type 1 and type 2 diabetes had an increased risk for bacterial skin and mucous membrane infections (type 1 diabetes: AOR 1.59, 95% CI 1.12–2.24; type 2 diabetes: AOR 1.33, 95% CI 1.15–1.54) (16). A new analysis for *Diabetes in America* of NHDS 1999–2010 data found that the average percentage of hospital discharges listing skin and connective tissue infections among individuals with diabetes was 9.1%, which was the highest among all infections (Figure 30.6, Appendix 30.2). In individuals without diabetes, the average percentage of hospital discharges listing skin and connective tissue infections was 3.6% (Figure 30.6, Appendix 30.2). The proposed etiologies include: decreased immune function due to decreased neutrophil and T cell function (18,44), as well as "local" factors, such as diabetic neuropathy, poor circulation due to peripheral vascular disease, and small vessel angiopathy.

Fungal Skin and Soft Tissue Infections

Though the true prevalence of fungal infections in individuals with diabetes has not been well established, diabetes has been identified as a risk factor for developing onychomycosis (45) and oral and vulvovaginal candidiasis (Figure 30.12, Appendix 30.2) (46). *Candida* is present in the gastrointestinal and genitourinary tracts of humans, but it can become a pathogen if there is a change in the environment of the ecologic niches where the organisms are typically found. *Candida albicans* infections, including moniliasis, are common among individuals with diabetes, and such infections can be an initial presentation or sign of undiagnosed diabetes. In a 12-month prospective cohort study, comparing adults with type 1 and type 2 diabetes to adults with hypertension and without diabetes, patients with type 1 and type 2 diabetes had an increased relative risk for mycotic skin and mucous membrane infections (type 1 diabetes: AOR 1.34, 95% CI 0.97–1.84; type 2 diabetes: AOR 1.44, 95% CI 1.27–1.63) (16).

FIGURE 30.12. Age-Standardized Percent of Hospital Discharges Listing Oral and Vaginal Candidiasis, by Diabetes Status, U.S., 1999–2010



Diabetes is defined using ICD-9 codes: 250, 357.2, 362.0, 366.41, 648.0, and 775.1. ICD-9 codes used to define oral and vaginal candidiasis are 112.0–112.3. Data are age-standardized to the overall National Hospital Discharge Survey 2010 using age categories <44, 45–64, and ≥65 years. ICD-9, The International Classification of Diseases, Ninth Revision, is the official system of assigning codes to diagnoses and procedures associated with hospital utilization in the United States.

SOURCE: National Hospital Discharge Surveys 1999–2010

Candida infections may take many forms. A classic manifestation of childhood diabetes is candida angular stomatitis, which is also common in older adults. Oropharyngeal candidiasis, or thrush, is diagnosed by the presence of white plaques on the oral mucosa. It is difficult to distinguish moniliasis from other forms of fungal infections, but it usually occurs in moist areas, such as between skin folds. Vulvovaginal candidiasis presents with increasing soreness and itching in the vulvar area with a vaginal discharge that looks like thick cottage cheese, and it can be recurrent and chronic. Men with diabetes can suffer from balanitis manifested as itching, pain, and scaly white plaques. This disease is more common among uncircumcised and older men with diabetes (47,48). Findings from the U.K. General Practice Research Database of 125,237 female patients and 146,603 males showed that among patients with type 2 diabetes, the incidence of vaginitis was 21.0 per 1,000 patient years (95% CI 19.8–22.1) with the risk being 1.81 (95% CI 1.64–2.00) times greater than among patients without diabetes; the incidence of balanitis was 8.4 per 1,000 patient years (95% CI 7.8–9.1) with a relative risk of 2.85 (95% CI 2.39–3.39) compared to patients without diabetes (49). Diagnosis is made by identifying budding yeasts in potassium hydroxide-prepared slides of suspected lesion scrapings. In some cases, a culture can be used. The most important factors for prevention are good glycemic control and local hygiene (48).

Onychomycosis is present in nearly one-third of individuals with diabetes and was diagnosed in 57% of abnormal toenails in individuals with diabetes (50). As with subjects without diabetes, onychomycosis is predominantly caused by either *Trichophyton rubrum* or *Trichophyton mentagrophytes.*

Bacterial Skin and Soft Tissue Infections

Poor glycemic control has been linked to an increased risk of bacterial skin and soft tissue infections (47). Superficial infections, such as impetigo, cellulitis, erysipelas, folliculitis, furunculosis, and carbunculosis, can present in more severe forms and have a higher risk for complications among poorly controlled and older individuals with diabetes (43,51). In one study, examining 2,227,401 episodes of skin and soft tissue infections among individuals age 0–64 years enrolled in U.S. health plans between 2005 and 2010, 10% of infections occurred in individuals with diabetes (52). In this study, abscess/cellulitis was the most common infection in both individuals with and without diabetes (66% and 59%, respectively, p<0.01); complication rates of skin and soft tissue infections were over five times higher in people with diabetes

than in people without diabetes (4.9% vs. 0.8%, p<0.01) in ambulatory settings; and hospitalization rates due to these infections were 4.9% and 1.1% in patients with and without diabetes, respectively (52). In the same study, 75.6% of all skin and soft tissue infections in patients with diabetes occurred in the 45–64 years age group versus 31.1% in individuals without diabetes in the same age group (p<0.01) (52).

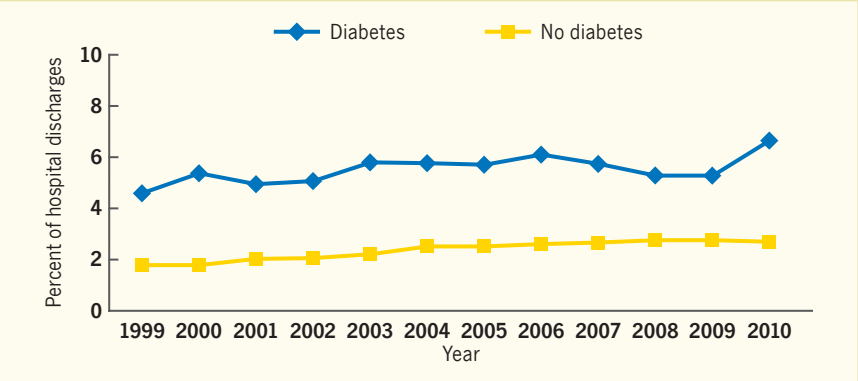
Of all skin and connective tissue infections, cellulitis and impetigo were the most frequent hospital discharge diagnoses among individuals with diabetes in the United States in 1999–2010 (Figure 30.13, Appendix 30.2), as seen in a new analysis of NHDS data for *Diabetes in America*. Most superficial bacterial soft tissue infections in individuals with and without diabetes are caused by either *Staphylococcus aureus* or β-hemolytic streptococci, though soft tissue infections caused by group B streptococci occur in higher frequency among individuals with diabetes (53) (see the section *Group B Streptococcus Infections* for more details).

Erythrasma, presenting as shiny, hyperpigmented patches in areas of increased maceration and friction, is caused by *Corynebacterium* and occurs more frequently in obese individuals with diabetes (43). Prompt diagnosis, proper glycemic control, antibiotic therapy, and in some cases, timely surgical debridement are all factors needed to improve outcomes for superficial skin and soft tissue infections.

Foot Ulcers and Osteomyelitis

The relationship between diabetes and foot ulcers is detailed in Chapter 20 *Peripheral Arterial Disease, Foot Ulcers, Lower Extremity Amputations, and Diabetes*. Infections of the foot are the most common soft tissue complaints in individuals with diabetes, with foot ulcer being the most common lower extremity microvascular complication with the lifetime risk of a foot ulcer as high as 25% (54,55,56). According to new analysis of NHDS data for *Diabetes in America* demonstrating age-standardized hospital discharges between 1999 and 2010, approximately 3% of patients

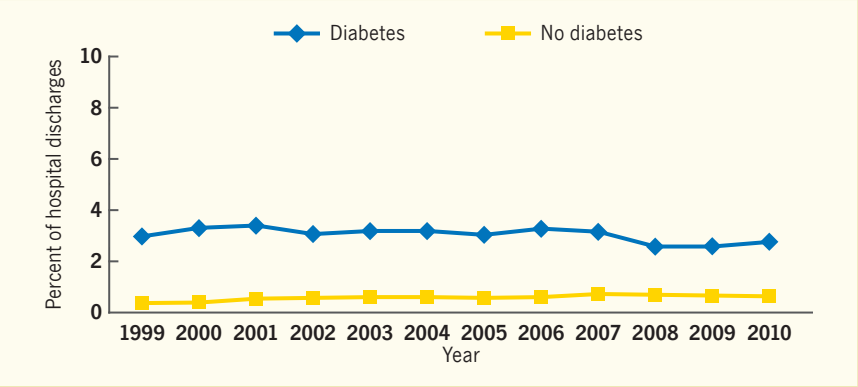
FIGURE 30.13. Age-Standardized Percent of Hospital Discharges Listing Cellulitis and Impetigo, by Diabetes Status, U.S., 1999–2010



Diabetes is defined using ICD-9 codes: 250, 357.2, 362.0, 366.41, 648.0, and 775.1. ICD-9 codes used to define cellulitis and impetigo are 682 and 684. Data are age-standardized to the overall National Hospital Discharge Survey 2010 using age categories <44, 45–64, and ≥65 years. ICD-9, The International Classification of Diseases, Ninth Revision, is the official system of assigning codes to diagnoses and procedures associated with hospital utilization in the United States.

SOURCE: National Hospital Discharge Surveys 1999–2010

FIGURE 30.14. Age-Standardized Percent of Hospital Discharges Listing Foot Ulcers, by Diabetes Status, U.S., 1999–2010



Diabetes is defined using ICD-9 codes: 250, 357.2, 362.0, 366.41, 648.0, and 775.1. The ICD-9 code used to define foot ulcers is 707.1. Data are age-standardized to the overall National Hospital Discharge Survey 2010 using age categories <44, 45–64, and ≥65 years. ICD-9, The International Classification of Diseases, Ninth Revision, is the official system of assigning codes to diagnoses and procedures associated with hospital utilization in the United States.

SOURCE: National Hospital Discharge Surveys 1999–2010

with diabetes had foot ulcers listed on their discharge summaries compared to <1% of patients without diabetes (Figure 30.14, Appendix 30.2). In a study of 1,033 patients with diabetes treated in 56 U.S. hospitals from June 2008 to December 2009 for complicated skin and soft tissue infections, infections occurred most commonly in the foot (28.5%) and lower leg (23.7%), and 27% of patients had diabetic foot infection (57). Diabetic foot infections account for nearly 80% of all nontraumatic amputations of the lower limb (56,58).

Factors increasing the risk of developing foot infection in individuals with diabetes are hyperglycemia, foot deformity, neuropathy, occlusive peripheral arterial disease (most likely to affect smaller, below-knee tibial arteries), nonocclusive microvascular dysfunction, undetected trauma, and recurrent fungal nail and skin infections (59). Neuropathy, inadequate patient education, vision impairment, and obesity are risk factors for delayed recognition and diagnosis of foot infections. Due to late diagnosis, inadequate management, and impeded healing, foot infections are more likely to lead to complications, such as more severe infections, deep ulcers, necrosis, and osteomyelitis, with 30%–50% of patients requiring amputation (59). The diagnosis of foot infections is made based on clinical presentation

TABLE 30.4. Classification of Diabetic Foot Infections

WAGNER CLASSIFICATION, 1983	INFECTIOUS DISEASES SOCIETY OF AMERICA (IDSA) CLASSIFICATION, 2012	PEDIS GRADE*
Grade 0: No ulcer in high risk foot Grade 1: Superficial ulcer involving the full skin thickness but no underlying tissue Grade 2: Deep ulcer penetrating down to ligaments and muscle, but no bone involvement or abscess formation Grade 3: Deep ulcer with cellulitis or abscess formation, often with osteomyelitis Grade 4: Localized gangrene Grade 5: Extensive gangrene involving the whole foot	Uninfected: Wound lacking purulence or any manifestations of inflammation. Mild: Presence of ≥2 manifestations of inflammation (purulence, erythema, pain, tenderness, warmth, induration), but any cellulitis/erythema extends ≤2 cm around the ulcer, and infection is limited to the skin and subcutaneous tissues; no other complications or systemic illness. Moderate: Presence of ≥1 of these characteristics: cellulitis extending >2 cm, lymphangitis streaking, spread beneath the superficial fascia, deep tissue abscess, gangrene, and involvement of muscle, tendon, joint, or bone. Patient is systemically well and metabolically stable. Severe: Infection in patients with systemic toxicity or metabolic instability.	1 (uninfected) 2 (mild) 3 (moderate) 4 (severe)

* PEDIS (perfusion, extent/size, depth/tissue loss, infection, sensation), based on IDSA classification.

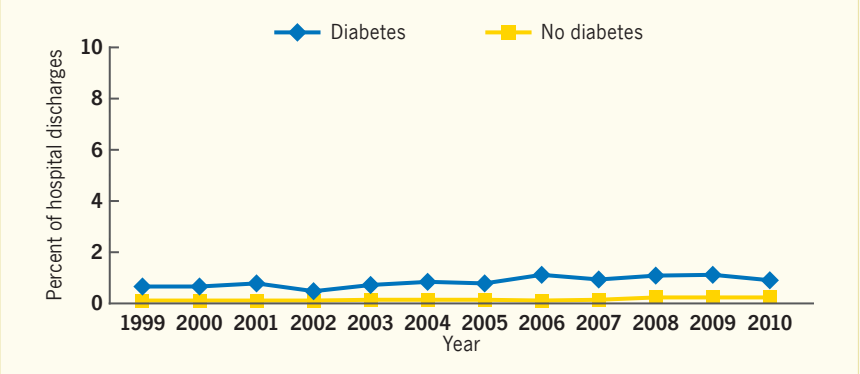
SOURCE: Reference 54

and examination, noting the presence of inflammation, size and extent of ulceration, and purulence. The severity of diabetic foot ulcers can be categorized according to ulcer depth, signs of infection, and the degree of systemic toxicity (Table 30.4).

Superficial ulcers are most commonly caused by gram-positive cocci, such as *Staphylococcus aureus* and β-hemolytic streptococci (54). Hospitalized patients with diabetes presenting with deep ulcers and chronic infection while under antibiotic therapy are more likely to be infected by polymicrobial or antibiotic-resistant flora, such as gram-positive cocci, enterococci, *Pseudomonas aeruginosa,* and *Enterobacteriaceae* (54). If extensive inflammation is observed or ischemia and necrosis are present, the infection may be caused by anaerobic streptococci, *Clostridium,* or *Bacteroides* species.

Superficial wound swab cultures are not reliable in establishing a pathogenic diagnosis and should not be used. Deep tissue cultures and bone biopsy can be obtained during debridement if deep tissue infection or osteomyelitis is suspected. Blood cultures can be performed if sepsis is suspected in the presence of severe systemic toxicity. In new analyses of NHDS 1999–2010 data for *Diabetes in America*, the percentage of hospital discharges listing osteomyelitis in patients diagnosed with diabetes was 0.7% in 1999, peaked at 1.1% in 2006, and dropped to 0.9% in 2010 compared to 0.1% in both 1999 and 2006 for patients without diabetes, with a slight increase to 0.2% in 2010 (Figure 30.15, Appendix 30.2). Osteomyelitis should be suspected in patients with deep, chronic, nonhealing ulcers, exposed bone, or positive probe-to-bone tests (54). Increased erythrocyte sedimentation rate can be suggestive of this complication as well. Serial plain radiograms, radioisotope scans, and magnetic resonance imaging (MRI) are radiological techniques that can be used to establish a diagnosis. MRI is the most sensitive diagnostic test, while a positive culture from a bone biopsy remains the gold standard for diagnosis (54). A multi-specialty team, comprised of an infectious disease specialist, vascular/general surgeon, and an endocrinologist are necessary for optimal treatment of foot ulcers in individuals with diabetes. Initial empiric treatment with pathogen-specific antibiotic therapy (when culture results are available) and surgical debridement are acceptable treatment options depending on the severity of the disease. In severe cases (unsalvageable foot, untreatable infection, critically ischemic limb that cannot be adequately revascularized), amputation may need to be done.

FIGURE 30.15. Age-Standardized Percent of Hospital Discharges Listing Osteomyelitis, by Diabetes Status, U.S., 1999–2010



Diabetes is defined using ICD-9 codes: 250, 357.2, 362.0, 366.41, 648.0, and 775.1. The ICD-9 code used to define osteomyelitis is 730.2. Data are age-standardized to the overall National Hospital Discharge Survey 2010 using age categories <44, 45–64, and ≥65 years. ICD-9, The International Classification of Diseases, Ninth Revision, is the official system of assigning codes to diagnoses and procedures associated with hospital utilization in the United States.

SOURCE: National Hospital Discharge Surveys 1999–2010

Deep Subcutaneous Tissue Infections

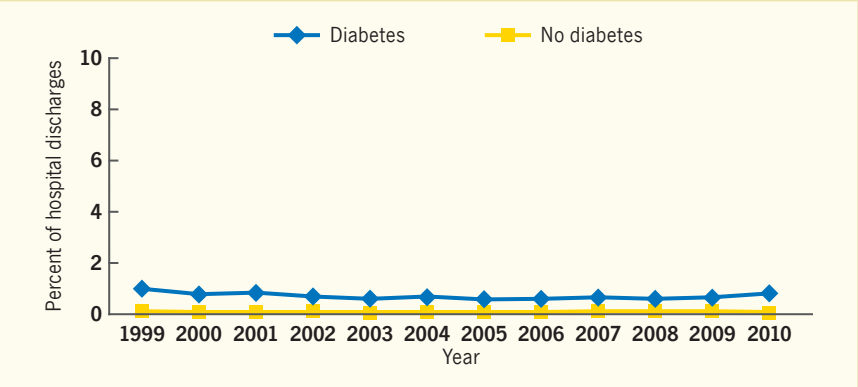
The incidence of necrotizing soft-tissue infections in the United States is estimated to be 500–1,500 cases per year (60). Among complicated skin and soft tissue infections, necrotizing fasciitis and Fournier's gangrene are more prevalent in individuals with diabetes, and as many as 75% of those diagnosed with necrotizing fasciitis have diabetes (51). As seen in a new analysis of NHDS 1999–2010 data for *Diabetes in America*,

approximately 1% of patients with diabetes were discharged with Fournier's gangrene as a diagnosis (Figure 30.16, Appendix 30.2). This was not the case for those without diabetes, where <1% of the patients had Fournier's gangrene listed as a diagnosis at hospital discharge (Figure 30.16, Appendix 30.2). Among the patients included in the National Surgical Quality Improvement database in 2005–2008 with necrotizing soft tissue infections, 45% had diabetes (61). Necrotizing fasciitis is usually associated with moderate to severe systemic toxicity presenting with swelling, pain, and redness of the affected area. Monomicrobial necrotizing fasciitis is caused by one of the following: *Staphylococcus pyogenes*, *Staphylococcus aureus*, *Vibrio vulnificus,* and anaerobic streptococci. Polymicrobial necrotizing fasciitis can be caused by various anaerobic and aerobic organisms and is usually associated with abdominal trauma, abdominal surgery, decubitus ulcers, or vulvovaginal/perineal infections (62).

Progression of necrotizing fasciitis is fast, and it may present as bullae, wound, or eschar. Though crepitus on physical examination and gas detected by radiography are very useful signs, depending on the causative organisms, they are not always present. The absence of crepitus and gas should not delay surgical intervention. Mortality remains high, especially in patients with hypotension and shock, and is between 12% and 70% (25,60,61). Data from the National Surgical Quality Improvement Program database between 2005 and 2008 did not show diabetes as being a risk factor for mortality (61).

Fournier's gangrene is one of the most common forms of necrotizing fasciitis in individuals with diabetes and involves mainly the male genitalia. Twenty to seventy percent of patients with this disease have diabetes, and the disease can be an initial presentation of diabetes, but it is still debatable whether diabetes is associated with increased mortality (51,63). Necrotizing infections involving muscles, such as Clostridial myonecrosis and non-Clostridial myonecrosis, have also been described in individuals with diabetes; however, it is not clear whether these infections occur more frequently in individuals with diabetes compared with the general population.

FIGURE 30.16. Age-Standardized Percent of Hospital Discharges Listing Fournier's Gangrene, by Diabetes Status, U.S., 1999–2010



Diabetes is defined using ICD-9 codes: 250, 357.2, 362.0, 366.41, 648.0, and 775.1. The ICD-9 code used to define Fournier's gangrene is 785.4. Data are age-standardized to the overall National Hospital Discharge Survey 2010 using age categories <44, 45–64, and ≥65 years. ICD-9, The International Classification of Diseases, Ninth Revision, is the official system of assigning codes to diagnoses and procedures associated with hospital utilization in the United States.

SOURCE: National Hospital Discharge Surveys 1999–2010

HOSPITAL-ACQUIRED INFECTIONS

Hyperglycemia, a manifestation of diabetes, results in immunosuppression, a state in which glycosylation endproducts are associated with inactivation of the immune response and contribute to an increased risk of infection (64), especially in hospitalized individuals.

Among individuals with diabetes, acute illness is associated with worsening of glycemic control. Many studies have attempted to evaluate the relationship between diabetes status, the level of hyperglycemia, and clinical outcomes, but results are variable and not consistent. This is likely due to differences in patient selection and methodology. New analyses of national data (NHDS) are shown in Figure 30.7 and Appendices 30.2, 30.4, and 30.5. Figure 30.7 compares age-standardized percentages of hospital discharges listing hospital-acquired infections by diabetes status. In individuals with diabetes, approximately 3.2% of discharge summaries listed hospital-acquired infection as a diagnosis compared to 2.4% in individuals without diabetes in 1999. By 2010, the percentage of individuals with diabetes who had a hospital-acquired infection listed as a discharge diagnosis decreased to 2.8%, and the discharge diagnosis of hospital-acquired infections in individuals without diabetes nearly doubled to 4.1%. Summarily, in 1999, for a greater percentage of individuals with diabetes, hospital-acquired infections were listed at hospital discharge, but this percentage trended down by 2010 to ultimately be less than the percentage of hospital-acquired infections listed at discharge for individuals without diabetes (Appendix 30.2). Similarly, this trend was observed in individuals with sepsis listed at hospital discharge (Appendix 30.4). Hospital discharges listing postoperative wound infections in individuals with and without diabetes between 1999 and 2010 were similar (<1%) with a slight peak to 0.8% in individuals with diabetes in 2003 compared to individuals without (Appendix 30.5).

In the study of patients with type 2 diabetes admitted into acute medical wards, diabetes was associated with the development of hospital-acquired *Clostridium difficile* infection (65). The patients were younger (mean 53.8 years, p=0.02) and had diarrhea and abdominal pain (p=0.001), but lacked fever (65). Developing *Clostridium difficile* was significantly associated with sepsis (p=0.02) and use of a proton pump inhibitor medication (p=0.01) (65). Additionally, antibiotic therapy with carbapenem (28.6% vs. 4.1%, p=0.01) and metronidazole

(42.9% vs. 19.3%, p=0.04) was significantly associated with hospital-acquired *Clostridium difficile* infection (65). In a study to assess the impact of A1c and diabetes on wound-healing complications and infection after foot and ankle surgery, A1c level was significantly associated with postoperative infections, with each increment of 1% increasing the odds of developing an infection 1.59-fold (95% CI 1.28–1.99) (66). A1c, the marker used to assess glycemic control over a 3-month period, was significantly associated with postoperative complications following foot and ankle surgery in patients with diabetes.

Studies investigating patients after coronary artery bypass grafting surgery show that patients experiencing postoperative hyperglycemia had a higher risk of developing surgical site infections (67). In this study, high preoperative mean glucose levels were the main risk factor for the development of postoperative infection (p=0.012 and p=0.028 for the mean glucose levels 1 and 2 days before operation, respectively). For those with diabetes, 5% were diagnosed with postoperative infection (superficial sternal wound in 0.75%, vein donor site infection in 1%, mediastinitis in 1.25%, UTI in 1.5%, and lung infection in 0.5% of patients). They also had significantly higher prevalences compared to persons without diabetes of mediastinitis, vein donor site infection, UTI, and total infections (p<0.05). Another study showed that patients with diabetes who have sinus surgery for chronic rhinosinusitis are more prone to infections. Compared to patients without diabetes, patients with diabetes were significantly more likely to development infections due to *Pseudomonas aeruginosa* (26.32% vs. 7.56%, p=0.004) and gram negative rods (26.32% vs. 8.96%, p=0.013) (68). Among diabetes patients who underwent elective lumbar fusion surgery, another study determined the effect of non-insulin-dependent diabetes and insulin-dependent diabetes on postoperative complications (69). Having a diagnosis of type 1 diabetes (formerly known as insulin-dependent diabetes mellitus or IDDM) was significantly associated with postoperative complications, including sepsis (RR 2.2, p=0.002), septic shock (RR 3.3, p=0.032), wound-related infection (RR 1.9, p=0.001), UTI (RR 1.6, p=0.011), and pneumonia (RR 3.1, p<0.001), compared to a diagnosis of type 2 diabetes (formerly known as non-insulin-dependent diabetes mellitus or NIDDM) (69). Similarly, in a study to examine the differential impact of no diabetes, type 2 diabetes (NIDDM), and type 1 diabetes (IDDM) on breast reconstruction outcomes, the rates of medical (such as UTI and sepsis/septic shock), surgical (such as superficial, deep, and organ-space surgical site infections), and overall complications (medical plus surgical) were significantly higher in individuals having a diagnosis of diabetes (regardless of being diagnosed with type 1 or type 2 diabetes). Having type 2 diabetes (NIDDM) was significantly associated with surgical complications (OR 1.51, 95% CI 1.05–2.17, p=0.026) compared to type 1 diabetes (IDDM) and not having diabetes, while type 1 diabetes was significantly associated with medical (OR 1.82, 95% CI 1.00–3.29, p=0.049) and overall (OR 1.85, 95% CI 1.12–3.06, p=0.016) complications compared to having type 2 diabetes or no diabetes (70).

Multiple studies have tested whether interventions to normalize glucose level in hospitalized patients improve outcomes, but results from data collected over the past few decades conflict. In 1999, Furnary *et al*. demonstrated that intensive treatment with an intravenous insulin infusion decreased the incidence of deep sternal wound infection in patients after coronary bypass graft surgery to 0.8% compared to 2% among the conventionally treated group (p=0.01) (71). Consequently, more studies are needed to investigate whether glycemic control is beneficial in prevention or control of infections and at what glycemic levels benefits are maximized, especially for individuals with diabetes.

PERIODONTAL DISEASE

Studies have not established that periodontal disease is more prevalent among individuals with diabetes, but disease severity and complication rates are greater (72,73). In 2006, a meta-analysis of 23 studies showed that individuals with diabetes had worse oral hygiene measured by the average of plaque index, higher severity of gingival disease, and higher severity of periodontal disease (measured by the average probing pocket depth and clinical attachment loss) (72). The studies included in the meta-analysis differed by sample characteristics (i.e., age, type of diabetes, etc.) and study design (i.e., proposed outcome variables and other matching and adjusted covariates) (72). Diabetic microvascular disease, increased salivary glucose levels, and decreased salivary pH, as well as impaired collagen metabolism, have been studied as potential risk factors (2). The impact of periodontal disease treatment on glycemic control has not been clearly established (73). Additional discussion of periodontal disease in diabetes is provided in Chapter 31 *Oral Health and Diabetes*.

INFECTIONS ASSOCIATED WITH DIABETES

MALIGNANT OTITIS EXTERNA

Malignant or invasive otitis externa (MOE) is an infection of the external auditory canal and skull base. It is an uncommon, though potentially life-threatening, disease. The true incidence of MOE is unknown, as only case reports have been published. MOE most likely affects older patients with diabetes and other immune system-compromising diseases. Studies have found that 65%–100% of patients with MOE have diabetes (74). Interestingly, MOE is rarely reported to affect children with diabetes, prompting the thought that the prolonged course and complications of diabetes are the most important predisposing factors. In individuals with diabetes, small vessel angiopathy, the decreased function of polymorphonuclear cells, such as impaired chemotaxis and phagocytosis, and the higher pH of cerumen have been reported to be pathogenic factors (74,75). *Pseudomonas aeruginosa* is the most common causative organism, though other bacteria, such as *Staphylococcus aureus*, *Staphylococcus epidermidis*, and other gram-negative bacteria, and fungi have been reported as well.

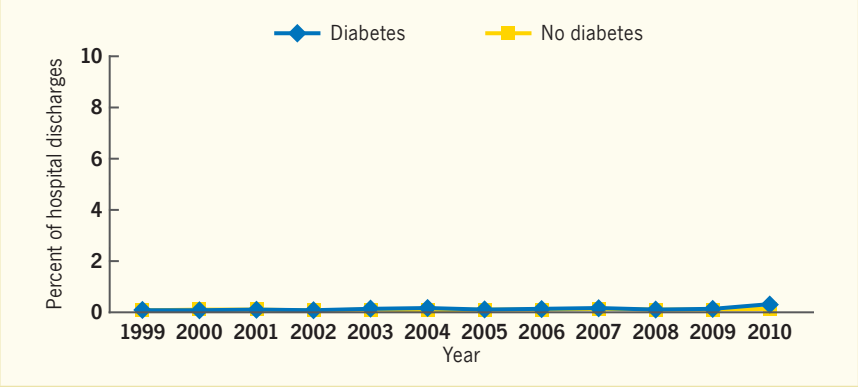
MOE presents with severe pain, otorrhea, and hearing loss. Diagnosis is made by recognition of clinical symptoms and signs, obtaining laboratory data supporting the presence of infection, and obtaining imaging studies showing the involvement of bony structures. Though CT scanning and MRI are used, nuclear imaging has proven to be superior in the diagnosis and follow-up of patients with MOE (53). Timely diagnosis, aggressive hyperglycemia treatment, and the appropriate selection of antibiotic therapy are required to achieve a positive outcome, as the mortality rate is as high as 50% (74).

RHINOCEREBRAL MUCORMYCOSIS

Mucormycosis is a collection of angioinvasive infections caused by fungi of the *Mucoraceae* family. Though true estimation of prevalence is clouded by the lack of well-collected data, mucormycosis appears to represent only 8.3%–13% of all fungal infections, including candidiasis and aspergillosis, remaining rare and uncommon, even in high-risk individuals (76). The largest registry of mucormycosis cases found that 9% of 230 cases from 2005–2007 were among patients with diabetes, though a majority (>50%) were attributed to those with hematologic malignancies (44%) and trauma (15%). Uncontrolled diabetes and especially ketoacidosis are predisposing factors for this infection. Though mucormycosis is an uncommon disease, mortality rates among individuals with diabetes are as high as 44% (77).

Among all clinical forms of mucormycosis (pulmonary, cutaneous, gastrointestinal, etc.), the rhinocerebral form is most common in patients with diabetes (76). As many as 36% of patients presenting with rhinocerebral mucormycosis have diabetes (77). Early on, the disease presents with facial and ocular pain, nasal congestion, and occasionally, nasal discharge and may be difficult to differentiate from sinusitis. The disease progresses to cause severe facial pain, proptosis, cranial nerve palsies, headache, and vision loss. A black necrotic eschar may be present, but it need not be present for diagnosis. Due to the rapid progression and increased mortality rate associated with this infection, early diagnosis is of paramount importance. CT imaging and MRI are used to determine the extent of bony, soft tissue, and cerebral invasion. Direct tissue sampling may also be necessary for diagnosis. The control of hyperglycemia and acidosis, aggressive surgical debridement, and intravenous amphotericin B are the most important factors in reducing mortality rates.

FIGURE 30.17. Age-Standardized Percent of Hospital Discharges Listing Emphysematous Cholecystitis, by Diabetes Status, U.S., 1999–2010



Diabetes is defined using ICD-9 codes: 250, 357.2, 362.0, 366.41, 648.0, and 775.1. The ICD-9 code used to define emphysematous cholecystitis is 575.0. Data are age-standardized to the overall National Hospital Discharge Survey 2010 using age categories <44, 45–64, and ≥65 years. ICD-9, The International Classification of Diseases, Ninth Revision, is the official system of assigning codes to diagnoses and procedures associated with hospital utilization in the United States.

SOURCE: National Hospital Discharge Surveys 1999–2010

EMPHYSEMATOUS CHOLECYSTITIS

Emphysematous cholecystitis (EC) is a life-threatening form of acute cholecystitis caused by gas-producing bacteria, most commonly those of the *Clostridium* species, though other bacteria, such as *Escherichia coli*, *Pseudomonas,* and *Klebsiella,* have been reported as well (78,79). New analyses of hospital discharge listings from NHDS 1999–2010 data for those with and without diabetes demonstrated a slightly higher percentage of individuals with diabetes listing EC (Figure 30.17, Appendix 30.2). The percentage of hospital discharges listing EC in individuals with diabetes ranged from 0.1% in 1999 to 0.3% in 2010 compared to 0.1% in both 1999 and 2010 for individuals without diabetes. Approximately 25%–35% of patients with EC have diabetes (18,78). The risk of complications, such as gangrene and perforation, is higher in patients with EC compared with non-emphysematous cholecystitis, which results in correspondingly higher mortality (15% compared to 4% in patients with acute, non-emphysematous cholecystitis) (79). Clinical presentation is not different from the

presentation of acute, non-emphysematous cholecystitis. Crepitus on abdominal palpation can be present in some patients and is a pathognomonic sign. Diagnosis is based on radiographic findings of gas in the gallbladder wall or lumen. Plain radiography, CT scanning, and abdominal ultrasound can be used for diagnosis. Treatment includes urgent cholecystectomy and the administration of broad spectrum antibiotics.

GROUP B STREPTOCOCCUS INFECTIONS

Group B *Streptococcus* (GBS) is a gram-positive coccus that normally resides in the human genital and gastrointestinal tracts and can also be present in the upper respiratory tract of young infants. In the past, GBS infections were the leading cause of meningitis and sepsis in the first week of life, but since 1990, there has been an increase in the rate of this infection among nonpregnant adults (80,81). A study of GBS-infected nonpregnant adults from 1990–2007 observed that the incidence among this demographic group increased from 3.6 cases per 100,000 to 7.3 cases per 100,000 during the study period (81).

Adults with this infection are more likely to have underlying diseases, including: cancer, heart failure, cirrhosis, peripheral vascular disease, neurogenic bladder, HIV, and diabetes (81,82). Depending on the population studied, diabetes is the most common comorbidity, being present in 13.3%–44.4% of patients (81,82,83). Prevalence of diabetes among patients with GBS infections in the United States increased from 36.5% in 1998 to 44.4% in 2007 (81). In the United States, serotypes Ia, Ib/c, Ia/c, II, III, and V are the most common (62), with serotypes Ia, II, III, and V accounting for 78.5% of isolates in 2005–2006 (81).

Invasive GBS infection can have variable clinical manifestations. Bacteremia without a source is responsible for about 24%–39.3% of cases, skin and soft tissue infections for 20.1%–25.5%, respiratory infections for 12%, genitourinary infections for 10%, and joint and bone infections account for 8% of cases. Infections such as endocarditis, meningitis, intravascular device infections, necrotizing fasciitis, and endophthalmitis occur less frequently (81,82,83). Individuals with diabetes are more likely to present with skin and soft tissue infections, osteomyelitis, and necrotizing fasciitis (81). New analyses of NHDS data demonstrate that a range of 8%–10% of individuals with diabetes had hospital discharges listing skin and soft tissue connective tissue infections between 1999 and 2010 compared to 3%–4% in individuals without diabetes during that same time period (Figure 30.6, Appendix 30.2). New analyses of NHDS data also show that a greater percentage of individuals with diabetes had osteomyelitis listed as a hospital discharge diagnosis between 1999 and 2010 compared to those without diabetes (Figure 30.15, Appendix 30.2).

Patients with diabetes have a higher risk for alterations in the skin and mucosal tissues, likely due to lymphatic and vascular insufficiency, and impaired immune response with chronic hyperglycemia and, thus, are at higher risk for invasive disease from GBS (82). Immunologic factors among individuals with diabetes, such as a decreased production of superoxidase during stimulation with GBS serotype III and poor opsonophagocytosis to serotype II, may explain the increase in GBS infection rates.

DIABETES AND TUBERCULOSIS

The association between diabetes and tuberculosis (TB) is well recognized, and TB continues to be among the most common causes of death in low- or middle-income countries (84). The rise in incidence of type 2 diabetes in the world and the continuous presence of TB as a serious health threat make the association between these diseases an important problem to study and address. In 2011, there were 366 million people affected by diabetes and 12 million TB cases in the world (85). Ninety-five percent of TB patients live in developing countries, and 79% of diabetic patients also reside in low- to middle-income countries (85).

Most evidence regarding diabetes as a risk factor for TB comes from case-control studies conducted worldwide. The overall relative risk of having active TB in patients with diabetes is in the range of 1.16 to 7.83 compared to those without diabetes (84,85,86). In a review of 30 studies, TB was prevalent in 1.7%–36% of persons with diabetes (85,87). A systemic review of studies, conducted according to the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines, and a subsequent random effects meta-analysis of 13 cohort studies showed that diabetes was associated with an increased risk of TB (RR 3.11, 95% CI 2.27–4.26). The relative risk was lower (1.46) in individuals with diabetes in North America than those of other countries ($RR_{CentralAm}$ 6.00, RR_{Europe} 4.40, RR_{Asia} 3.11 compared to North America, meta-regression $p_{CentralAm}$=0.006, p_{Europe}=0.004, p_{Asia}=0.03) (88).

Patients with diabetes are more likely to present with the infection affecting the lower lung (84), while also being more likely to have multilobar disease and pleural effusion (2). Studies suggest that individuals with diabetes respond to TB treatment, and they are not more likely to develop multidrug resistance (2,84); however, the relapse rate is four times greater than in individuals without diabetes (86). Treatment for TB can cause additional morbidity in individuals with diabetes: hyperglycemia can worsen during acute infection, isoniazid can worsen peripheral neuropathy, and rifampicin can reduce the efficacy of sulfonylurea drugs. Death is also more common among individuals with diabetes and TB. Data from Maryland showed that among people infected with TB, individuals with diabetes were 6.5–6.7 times more likely to die compared to controls without diabetes (84).

Many studies in animal models, as well as human subjects, have investigated potential biologic mechanisms for the causal association between diabetes and

the increased risk for TB. Available data show that the bacterial load is higher in subjects with diabetes, and they have decreased T helper 1 adaptive immunity due to lower production of interferon-γ, interleukin-12, and nitric oxide (84,88). Also, monocytes from individuals with diabetes have impaired chemotaxis, and alveolar macrophages have decreased hydrogen peroxidase production that result in less oxidative killing potential and decreased phagocytosis (84,88). Vitamin D deficiency has been shown to affect immunity against *Mycobacterium tuberculosis* in mice (89) and was shown to be prevalent in human patients with TB (90). The above data suggest that there is a causal relationship between diabetes and TB and that hyperglycemia and its effect on physical barriers and immune function play a major role (85).

There is also the question whether TB can lead to hyperglycemia and diabetes. Patients with TB have higher rates of impaired glucose tolerance than community controls (84). Metabolic decompensation due to infection and infection-induced insulin resistance can cause transient hyperglycemia (85). At this point, it is still not clear whether persistent impaired glucose tolerance and even diabetes are truly caused by TB or if these diseases are newly diagnosed due to receiving medical care for TB (84).

CONCLUSION

This chapter presents a broad overview of infections associated with diabetes by examining the link between diabetes and the risk of infection in persons with and without this metabolic disease. Evidence has shown several infections and causative organisms to be more prevalent in individuals diagnosed with diabetes; however, no infection appears to occur exclusively in individuals with diabetes. Additional scientific evidence is needed to examine the association between diabetes and infectious processes.

LIST OF ABBREVIATIONS

A1c. . . . . glycosylated hemoglobin
AOR . . . . . adjusted odds ratio
CI. . . . . confidence interval
CT . . . . . computed tomography
EC . . . . . emphysematous cholecystitis
GBS . . . . . group B *Streptococcus* infections
HIV. . . . . human immunodeficiency virus
IDDM . . . . . insulin-dependent diabetes mellitus
MOE. . . . . malignant otitis externa
MRI . . . . . magnetic resonance imaging
NAMCS . . . National Ambulatory Medical Care Survey
NCHS. . . . . National Center for Health Statistics
NHDS . . . . National Hospital Discharge Survey
NIDDM. . . . non-insulin-dependent diabetes mellitus
NNHS . . . . National Nursing Home Survey
NVSS . . . . . National Vital Statistics System
OR . . . . . odds ratio
RR . . . . . relative risk
TB . . . . . tuberculosis
UroEDIC . . a urologic complications ancillary study of the Epidemiology of Diabetes Interventions and Complications Study
UTI. . . . . urinary tract infection

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DUALITY OF INTEREST

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APPENDICES

APPENDIX 30.1. Percent of Deaths With Infections, by Diabetes Status, U.S., 1999–2010

	PERCENT											
	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
Among persons with diabetes mentioned anywhere on the death certificate												
Any infection (among those below)	3.08	3.14	3.23	3.35	3.30	3.20	3.31	3.12	3.06	2.81	2.75	2.66
Respiratory tract infections	1.27	1.35	1.36	1.43	1.35	1.26	1.31	1.19	1.14	1.14	1.09	1.00
Urinary tract infections	0.67	0.65	0.66	0.64	0.65	0.66	0.68	0.67	0.65	0.42	0.42	0.41
Skin and connective tissue infections	0.13	0.14	0.15	0.17	0.20	0.22	0.21	0.21	0.22	0.22	0.22	0.21
Hospital-acquired infections	0.93	0.92	0.98	1.02	1.00	0.97	1.02	0.96	0.96	0.95	0.93	0.95
Infections associated with diabetes	0.03	0.03	0.04	0.05	0.04	0.04	0.04	0.04	0.04	0.04	0.05	0.04
HIV	0.04	0.04	0.05	0.05	0.06	0.05	0.05	0.06	0.05	0.04	0.04	0.04
Among persons without diabetes mentioned anywhere on the death certificate												
Any infection (among those below)	4.49	4.51	4.48	4.62	4.58	4.49	4.54	4.33	4.29	4.19	4.06	4.09
Respiratory tract infections	2.39	2.41	2.33	2.43	2.37	2.24	2.29	2.09	2.03	2.07	1.94	1.98
Urinary tract infections	0.59	0.58	0.58	0.57	0.57	0.58	0.62	0.60	0.60	0.46	0.45	0.50
Skin and connective tissue infections	0.05	0.05	0.06	0.06	0.08	0.09	0.08	0.08	0.08	0.08	0.09	0.09
Hospital-acquired infections	1.17	1.19	1.23	1.28	1.30	1.31	1.30	1.32	1.35	1.37	1.38	1.34
Infections associated with diabetes	0.03	0.03	0.03	0.03	0.03	0.04	0.04	0.03	0.04	0.04	0.04	0.04
HIV	0.27	0.26	0.25	0.25	0.23	0.23	0.21	0.20	0.18	0.17	0.16	0.14

Diabetes was defined using ICD-10 codes: E10–E14, O24.0–O24.3, and P70.2. ICD-10 codes were used to define infections as follows: respiratory tract infections, including influenza (J10.1, J18.9), and sinusitis and bronchitis (J32.9, J40); urinary tract infections, including asymptomatic bacteriuria (N39.0), cystitis (N30.9), pyelonephritis (N10), and perinephric abscess (N15.1); skin and connective tissue infections, including oral and vaginal candidiasis (B37.0, B37.3), onychomycosis (B35.1), intertrigo (L30.4), cellulitis and impetigo (L3.9, L1.0), foot ulcers (L97), necrotizing fasciitis (M72.6), and osteomyelitis (M86.9); hospital-acquired infections, including sepsis (A41.9); infections associated with diabetes, including malignant otitis externa (H60.2), mucormycosis (B46.5), and emphysematous cholecystitis (K81.0); and HIV (B20). Tuberculosis (A15.9) and Fournier's gangrene (N49.3) were not in the data set. HIV, human immunodeficiency virus; ICD-10, The International Classification of Diseases, Tenth Revision, is the standard diagnostic tool for epidemiologic, health management, and clinical purposes, including the analysis of the general health situation of population groups. It is used to monitor the incidence and prevalence of diseases and other health problems, providing a picture of the general health situation of countries and populations.

SOURCE: National Vital Statistics System 1999–2010

APPENDIX 30.2. Age-Standardized Percent of Hospital Discharges Listing Infection, by Diabetes Status, U.S., 1999–2010

	ICD-9 CODES	PERCENT (STANDARD ERROR)											
		1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
Among people with diabetes													
Any infection (among those below)		18.41 (0.46)	18.82 (0.51)	18.19 (0.45)	16.91 (0.40)	18.62 (0.44)	18.58 (0.42)	18.85 (0.40)	18.16 (0.41)	17.39 (0.43)	17.73 (0.56)	16.75 (0.52)	18.47 (0.57)
Respiratory tract infections		7.00 (0.31)	6.53 (0.27)	6.66 (0.31)	6.18 (0.25)	6.51 (0.25)	6.73 (0.25)	7.21 (0.26)	6.21 (0.25)	5.60 (0.22)	6.20 (0.31)	5.97 (0.30)	5.91 (0.29)
Influenza	480–488	5.89 (0.28)	5.64 (0.24)	5.83 (0.29)	5.51 (0.23)	5.92 (0.24)	5.76 (0.22)	6.36 (0.25)	5.51 (0.24)	4.93 (0.20)	5.68 (0.30)	5.44 (0.29)	5.37 (0.27)
Sinusitis and bronchitis	461, 466	1.24 (0.18)	0.95 (0.12)	0.90 (0.12)	0.72 (0.10)	0.68 (0.09)	1.09 (0.14)	0.92 (0.08)	0.77 (0.08)	0.71 (0.09)	0.66 (0.13)	0.65 (0.12)	0.60 (0.10)
Urinary tract infections		0.89 (0.14)	0.84 (0.10)	0.95 (0.14)	0.74 (0.09)	0.84 (0.11)	0.96 (0.17)	0.84 (0.09)	0.85 (0.10)	0.88 (0.12)	1.22 (0.19)	1.02 (0.16)	0.88 (0.13)
Asymptomatic bacteriuria	791.9	0.03 (0.01)[1]	0.07 (0.02)	0.03 (0.01)[1]	0.03 (0.01)[1]	0.02 (0.01)[2]	0.01 (0.00)	0.06 (0.03)[2]	0.02 (0.01)[2]	0.05 (0.02)[1]	0.03 (0.01)[1]	[3]	0.01 (0.00)
Cystitis	595.0	0.06 (0.03)[2]	0.07 (0.03)[2]	0.02 (0.01)[2]	0.04 (0.01)	0.07 (0.03)[2]	0.09 (0.03)[1]	0.05 (0.01)	0.05 (0.02)[1]	0.03 (0.01)[1]	[3]	0.07 (0.03)[2]	0.13 (0.05)[1]
Pyelonephritis	590.1, 590.8	0.80 (0.13)	0.68 (0.09)	0.90 (0.14)	0.66 (0.09)	0.74 (0.11)	0.84 (0.17)	0.72 (0.09)	0.77 (0.10)	0.78 (0.12)	0.95 (0.13)	0.84 (0.14)	0.73 (0.12)
Perinephric abscess	590.2	0.02 (0.01)[2]	0.02 (0.01)[2]	[3]	[3]	[3]	0.01 (0.00)	0.02 (0.01)[2]	[3]	0.03 (0.01)[1]	0.08 (0.04)[2]	[3]	[3]

Appendix 30.2 continues on the next page.

APPENDIX 30.2. (continued)

	ICD-9 CODES	PERCENT (STANDARD ERROR)											
		1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
Skin and connective tissue infections		8.32 (0.31)	9.53 (0.43)	8.89 (0.32)	8.53 (0.30)	9.51 (0.35)	9.37 (0.31)	9.18 (0.30)	9.59 (0.33)	9.25 (0.34)	8.86 (0.45)	8.50 (0.42)	9.76 (0.45)
Oral and vaginal candidiasis	112.0–112.3	0.92 (0.13)	1.26 (0.16)	0.75 (0.09)	0.92 (0.12)	0.92 (0.10)	0.70 (0.07)	0.87 (0.09)	0.85 (0.10)	0.88 (0.10)	1.11 (0.22)	0.83 (0.13)	0.95 (0.12)
Onychomycosis	110.1	0.13 (0.03)	0.18 (0.07)[1]	0.14 (0.02)	0.12 (0.02)	0.16 (0.04)	0.16 (0.04)	0.13 (0.03)	0.14 (0.03)	0.11 (0.02)	0.10 (0.03)	0.08 (0.04)[2]	0.13 (0.05)[1]
Intertrigo	695.89	[3]	0.02 (0.01)[2]	0.02 (0.01)[2]	0.01 (0.00)	0.06 (0.03)[2]	[3]	0.02 (0.01)[2]	0.02 (0.01)[2]	0.03 (0.01)[1]	0.01 (0.00)	[3]	0.02 (0.01)[2]
Cellulitis and impetigo	682, 684	4.59 (0.24)	5.36 (0.31)	4.94 (0.24)	5.07 (0.24)	5.80 (0.30)	5.76 (0.27)	5.72 (0.25)	6.10 (0.28)	5.74 (0.28)	5.29 (0.35)	5.29 (0.36)	6.66 (0.42)
Foot ulcers	707.1	2.96 (0.18)	3.31 (0.29)	3.41 (0.20)	3.07 (0.17)	3.19 (0.18)	3.19 (0.16)	3.05 (0.15)	3.28 (0.18)	3.16 (0.20)	2.57 (0.22)	2.58 (0.19)	2.76 (0.22)
Necrotizing fasciitis	728.86	0.05 (0.02)[1]	0.09 (0.03)[1]	0.04 (0.01)	0.24 (0.08)[1]	0.10 (0.03)	0.09 (0.03)[1]	0.14 (0.05)[1]	0.07 (0.02)	0.12 (0.05)[2]	[3]	0.03 (0.01)[1]	[3]
Fournier's gangrene	785.4	1.00 (0.10)	0.80 (0.08)	0.84 (0.09)	0.68 (0.07)	0.60 (0.06)	0.68 (0.07)	0.58 (0.05)	0.61 (0.07)	0.67 (0.08)	0.60 (0.09)	0.65 (0.10)	0.82 (0.14)
Osteomyelitis	730.2	0.67 (0.10)	0.66 (0.16)	0.77 (0.10)	0.48 (0.05)	0.71 (0.09)	0.86 (0.10)	0.77 (0.08)	1.12 (0.15)	0.93 (0.13)	1.08 (0.15)	1.11 (0.15)	0.91 (0.11)
Hospital-acquired infections		3.21 (0.21)	3.12 (0.24)	2.74 (0.16)	2.77 (0.18)	2.72 (0.16)	2.55 (0.14)	2.51 (0.15)	2.47 (0.18)	2.37 (0.16)	2.62 (0.24)	2.44 (0.21)	2.76 (0.26)
Sepsis	038	2.69 (0.20)	2.45 (0.20)	2.15 (0.13)	2.14 (0.15)	1.90 (0.12)	2.04 (0.13)	1.96 (0.13)	1.98 (0.17)	1.85 (0.15)	1.99 (0.20)	1.97 (0.19)	2.22 (0.21)
Postoperative wound infections	998.59	0.54 (0.07)	0.67 (0.14)	0.63 (0.09)	0.64 (0.09)	0.83 (0.11)	0.53 (0.06)	0.60 (0.07)	0.52 (0.06)	0.54 (0.08)	0.63 (0.14)	0.48 (0.08)	0.56 (0.15)
Infections associated with diabetes		0.08 (0.02)	0.08 (0.02)	0.12 (0.04)[1]	0.09 (0.02)	0.15 (0.05)[1]	0.17 (0.05)	0.12 (0.04)[1]	0.15 (0.05)[1]	0.18 (0.06)[1]	0.15 (0.04)	0.13 (0.05)[1]	0.33 (0.11)[1]
Malignant otitis externa	380.14	[3]	[3]	[3]	[3]	[3]	[3]	[3]	0.01 (0.00)	0.01 (0.00)	[3]	[3]	[3]
Mucormycosis	117.7	[3]	[3]	[3]	[3]	[3]	[3]	0.02 (0.01)[2]	[3]	[3]	[3]	[3]	[3]
Emphysematous cholecystitis	575.0	0.08 (0.02)	0.08 (0.02)	0.11 (0.04)[1]	0.08 (0.02)	0.15 (0.05)[1]	0.16 (0.05)[1]	0.09 (0.03)[1]	0.14 (0.05)[1]	0.18 (0.06)[1]	0.12 (0.03)	0.13 (0.05)[1]	0.31 (0.11)[1]
Tuberculosis	010–018	[3]	0.12 (0.04)[1]	[3]	0.02 (0.01)[2]	0.02 (0.01)[2]	0.04 (0.01)	0.02 (0.01)[2]	0.03 (0.01)[1]	0.06 (0.03)[2]	[3]	0.02 (0.01)[2]	[3]
HIV	042–044	0.48 (0.09)	0.41 (0.09)	0.32 (0.07)	0.32 (0.07)	0.33 (0.07)	0.19 (0.03)	0.33 (0.08)	0.45 (0.09)	0.36 (0.08)	0.30 (0.07)	0.26 (0.06)	0.44 (0.16)[1]
Among people without diabetes													
Any infection (among those below)		12.62 (0.12)	12.54 (0.12)	12.53 (0.12)	12.79 (0.12)	13.38 (0.12)	13.58 (0.12)	13.88 (0.12)	13.55 (0.11)	13.68 (0.12)	14.39 (0.15)	14.71 (0.16)	14.91 (0.16)
Respiratory tract infections		7.49 (0.09)	7.27 (0.10)	7.09 (0.09)	7.25 (0.09)	7.57 (0.10)	7.40 (0.09)	7.53 (0.09)	7.07 (0.09)	6.84 (0.09)	7.43 (0.12)	7.46 (0.12)	7.68 (0.12)
Influenza	480–488	6.26 (0.09)	6.15 (0.09)	6.10 (0.09)	6.19 (0.09)	6.65 (0.09)	6.36 (0.09)	6.64 (0.09)	6.22 (0.08)	6.07 (0.09)	6.69 (0.11)	6.77 (0.11)	6.95 (0.12)
Sinusitis and bronchitis	461, 466	1.39 (0.04)	1.29 (0.04)	1.15 (0.04)	1.22 (0.04)	1.07 (0.03)	1.21 (0.03)	1.06 (0.03)	0.98 (0.03)	0.91 (0.03)	0.88 (0.04)	0.83 (0.04)	0.89 (0.04)
Urinary tract infections		0.59 (0.03)	0.61 (0.03)	0.60 (0.03)	0.63 (0.03)	0.62 (0.03)	0.65 (0.03)	0.69 (0.03)	0.65 (0.03)	0.65 (0.03)	0.68 (0.04)	0.68 (0.04)	0.79 (0.04)
Asymptomatic bacteriuria	791.9	0.03 (0.01)[1]	0.04 (0.01)	0.02 (0.00)	0.02 (0.00)	0.03 (0.01)[1]	0.03 (0.01)[1]	0.03 (0.01)[1]	0.02 (0.00)	0.05 (0.01)	0.05 (0.01)	0.05 (0.01)	0.06 (0.01)
Cystitis	595.0	0.05 (0.01)	0.03 (0.00)	0.04 (0.01)	0.04 (0.01)	0.04 (0.01)	0.04 (0.01)	0.04 (0.01)	0.04 (0.01)	0.04 (0.01)	0.05 (0.01)	0.07 (0.02)	0.07 (0.02)
Pyelonephritis	590.1, 590.8	0.51 (0.03)	0.53 (0.03)	0.53 (0.03)	0.57 (0.03)	0.55 (0.02)	0.57 (0.02)	0.61 (0.03)	0.59 (0.02)	0.55 (0.03)	0.57 (0.03)	0.55 (0.03)	0.65 (0.04)
Perinephric abscess	590.2	[3]	0.01 (0.00)	0.01 (0.00)	0.01 (0.00)	[3]	0.01 (0.00)	0.01 (0.00)	0.02 (0.00)	0.02 (0.00)	0.01 (0.00)	0.01 (0.00)	0.01 (0.00)

Appendix 30.2 continues on the next page.

APPENDIX 30.2. (continued)

	ICD-9 CODES	PERCENT (STANDARD ERROR)											
		1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
Skin and connective tissue infections		2.80 (0.06)	2.95 (0.06)	3.26 (0.06)	3.25 (0.06)	3.36 (0.06)	3.74 (0.07)	3.70 (0.06)	3.75 (0.06)	4.01 (0.07)	4.17 (0.09)	4.20 (0.09)	4.15 (0.09)
Oral and vaginal candidiasis	112.0–112.3	0.54 (0.03)	0.65 (0.03)	0.67 (0.03)	0.61 (0.03)	0.56 (0.03)	0.62 (0.03)	0.61 (0.03)	0.63 (0.03)	0.69 (0.03)	0.74 (0.04)	0.79 (0.04)	0.79 (0.04)
Onychomycosis	110.1	0.08 (0.01)	0.09 (0.01)	0.08 (0.01)	0.07 (0.01)	0.08 (0.01)	0.07 (0.01)	0.08 (0.01)	0.05 (0.01)	0.06 (0.01)	0.05 (0.01)	0.06 (0.01)	0.06 (0.01)
Intertrigo	695.89	0.01 (0.00)	0.02 (0.01)[2]	0.01 (0.00)	0.02 (0.01)[2]	0.01 (0.00)	0.02 (0.00)	0.02 (0.01)[2]	0.01 (0.00)	0.02 (0.00)	0.02 (0.01)[2]	0.01 (0.00)	0.02 (0.01)[2]
Cellulitis and impetigo	682, 684	1.78 (0.05)	1.80 (0.05)	2.03 (0.05)	2.07 (0.05)	2.20 (0.05)	2.51 (0.05)	2.50 (0.05)	2.60 (0.05)	2.66 (0.05)	2.75 (0.07)	2.75 (0.07)	2.69 (0.07)
Foot ulcers	707.1	0.37 (0.02)	0.40 (0.02)	0.55 (0.02)	0.57 (0.03)	0.59 (0.03)	0.60 (0.03)	0.56 (0.03)	0.60 (0.02)	0.73 (0.03)	0.68 (0.04)	0.65 (0.04)	0.63 (0.04)
Necrotizing fasciitis	728.86	0.02 (0.00)	0.02 (0.00)	0.03 (0.01)[1]	0.02 (0.00)	0.03 (0.01)[1]	0.03 (0.01)[1]	0.02 (0.00)	0.02 (0.00)	0.03 (0.01)[1]	0.03 (0.01)[1]	0.02 (0.01)[2]	0.04 (0.01)
Fournier's gangrene	785.4	0.12 (0.01)	0.10 (0.01)	0.08 (0.01)	0.10 (0.01)	0.08 (0.01)	0.09 (0.01)	0.08 (0.01)	0.08 (0.01)	0.13 (0.01)	0.12 (0.02)	0.13 (0.02)	0.10 (0.02)
Osteomyelitis	730.2	0.11 (0.01)	0.13 (0.01)	0.13 (0.01)	0.13 (0.01)	0.15 (0.01)	0.15 (0.01)	0.16 (0.01)	0.13 (0.01)	0.16 (0.01)	0.23 (0.02)	0.25 (0.02)	0.23 (0.02)
Hospital-acquired infections		2.42 (0.05)	2.33 (0.05)	2.39 (0.05)	2.52 (0.06)	2.65 (0.06)	2.80 (0.06)	2.99 (0.06)	3.11 (0.06)	3.37 (0.06)	3.59 (0.08)	3.83 (0.09)	4.11 (0.09)
Sepsis	038	1.95 (0.05)	1.86 (0.05)	1.87 (0.05)	1.99 (0.05)	2.13 (0.05)	2.24 (0.05)	2.43 (0.05)	2.62 (0.05)	2.81 (0.06)	3.10 (0.08)	3.26 (0.08)	3.55 (0.09)
Postoperative wound infections	998.59	0.51 (0.03)	0.51 (0.02)	0.56 (0.03)	0.57 (0.03)	0.57 (0.03)	0.63 (0.03)	0.61 (0.03)	0.54 (0.02)	0.61 (0.03)	0.55 (0.03)	0.63 (0.04)	0.62 (0.04)
Infections associated with diabetes		0.08 (0.01)	0.09 (0.01)	0.09 (0.01)	0.08 (0.01)	0.09 (0.01)	0.08 (0.01)	0.10 (0.01)	0.11 (0.01)	0.13 (0.01)	0.13 (0.02)	0.12 (0.02)	0.13 (0.02)
Malignant otitis externa	380.14	[3]	[3]	[3]	[3]	[3]	0.01 (0.00)	[3]	[3]	[3]	[3]	[3]	[3]
Mucormycosis	117.7	[3]	[3]	[3]	[3]	[3]	[3]	[3]	[3]	[3]	[3]	[3]	[3]
Emphysematous cholecystitis	575.0	0.08 (0.01)	0.09 (0.01)	0.09 (0.01)	0.08 (0.01)	0.09 (0.01)	0.07 (0.01)	0.10 (0.01)	0.11 (0.01)	0.13 (0.01)	0.12 (0.02)	0.12 (0.02)	0.13 (0.02)
Tuberculosis	010–018	0.05 (0.01)	0.05 (0.01)	0.05 (0.01)	0.04 (0.01)	0.04 (0.01)	0.05 (0.01)	0.06 (0.01)	0.04 (0.01)	0.05 (0.01)	0.05 (0.01)	0.04 (0.01)	0.03 (0.01)[1]
HIV	042–044	0.38 (0.02)	0.39 (0.02)	0.39 (0.02)	0.39 (0.02)	0.44 (0.02)	0.39 (0.02)	0.34 (0.02)	0.44 (0.02)	0.43 (0.02)	0.39 (0.02)	0.27 (0.02)	0.32 (0.02)

Diabetes was defined using ICD-9 codes: 250, 357.2, 362.0, 366.41, 648.0, and 775.1. Data are age-standardized to the overall National Hospital Discharge Survey 2010 using age categories <44, 45–64, and ≥65 years. Standard errors were most likely underestimated because the National Hospital Discharge Survey sampling variables were not available, and consequently, it was not possible to take into account the complex sampling design. HIV, human immunodeficiency virus; ICD-9, The International Classification of Diseases, Ninth Revision, is the official system of assigning codes to diagnoses and procedures associated with hospital utilization in the United States.

[1] Relative standard error >30%–40%

[2] Relative standard error >40%–50%

[3] Relative standard error >50%; estimate is too unreliable to present.

SOURCE: National Hospital Discharge Surveys 1999–2010

APPENDIX 30.3. Age-Standardized Percent of Outpatient Visits to a Physician Pertaining to Infections Among Persons With and Without Diabetes, U.S., 1999–2010

	PERCENT (STANDARD ERROR)											
	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
Diabetes	4.3 (1.19)	2.7 (0.56)	2.9 (1.09)[1]	2.7 (1.03)[1]	5.1 (1.49)	5.1 (1.62)[1]	4.9 (2.05)[2]	3.8 (1.48)[1]	3.5 (0.95)	2.8 (1.10)[1]	1.6 (0.54)[1]	2.6 (0.74)
No diabetes	3.4 (0.35)	3.1 (0.29)	2.6 (0.25)	2.9 (0.22)	3.1 (0.34)	3.0 (0.24)	3.1 (0.22)	3.1 (0.22)	2.6 (0.19)	3.3 (0.29)	3.5 (0.25)	3.6 (0.28)

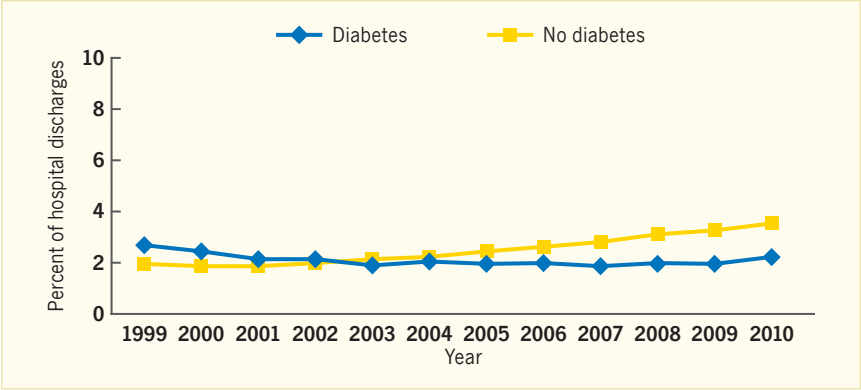
Diabetes is defined using ICD-9 codes: 250, 357.2, 362.0, 366.41, 648.0, and 775.1. ICD-9 codes used to define infections are as follows: influenza (480–488), sinusitis and bronchitis (461, 466), asymptomatic bacteriuria (791.9), cystitis (595.0), pyelonephritis (590.1, 590.8), perinephric abscess (590.2), oral and vaginal candidiasis (112.0–112.3), onychomycosis (110.1), intertrigo (695.89), cellulitis and impetigo (682, 684), foot ulcers (707.1), necrotizing fasciitis (728.86), Fournier's gangrene (785.4), osteomyelitis (730.2), sepsis (038), postoperative wound infections (998.59), malignant otitis externa (380.14), mucormycosis (117.7), emphysematous cholecystitis (575.0), HIV (human immunodeficiency virus) (042–044), tuberculosis (010–018). Data are age-standardized to the overall National Ambulatory Medical Care Survey 2010 using age categories <45, 45–64, and ≥65 years. ICD-9, The International Classification of Diseases, Ninth Revision, is the official system of assigning codes to diagnoses and procedures associated with hospital utilization in the United States.

[1] Relative standard error >30%–40%

[2] Relative standard error >40%–50%

SOURCE: National Ambulatory Medical Care Surveys 1999–2010

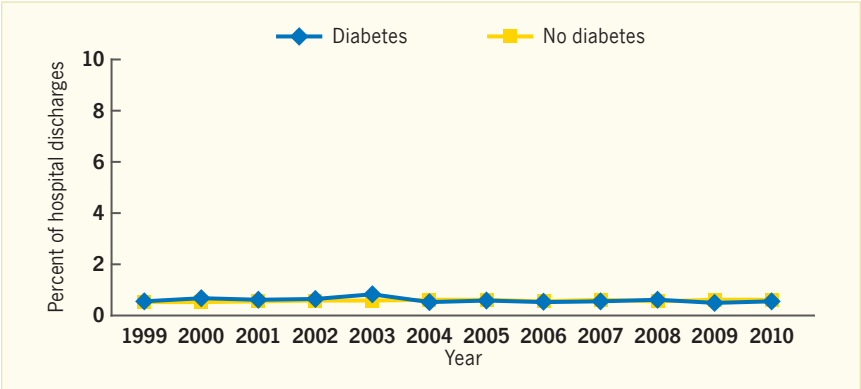
APPENDIX 30.4. Age-Standardized Percent of Hospital Discharges Listing Hospital-Acquired Sepsis, by Diabetes Status, U.S., 1999–2010



Diabetes is defined using ICD-9 codes: 250, 357.2, 362.0, 366.41, 648.0, and 775.1. The ICD-9 code used to define sepsis is 038. Data are age-standardized to the overall National Hospital Discharge Survey 2010 using age categories <44, 45–64, and ≥65 years. ICD-9, The International Classification of Diseases, Ninth Revision, is the official system of assigning codes to diagnoses and procedures associated with hospital utilization in the United States.

SOURCE: National Hospital Discharge Surveys 1999–2010

APPENDIX 30.5. Age-Standardized Percent of Hospital Discharges Listing Postoperative Wound Infections, by Diabetes Status, U.S., 1999–2010



Diabetes is defined using ICD-9 codes: 250, 357.2, 362.0, 366.41, 648.0, and 775.1. The ICD-9 code used to define postoperative wound infection is 998.59. Data are age-standardized to the overall National Hospital Discharge Survey 2010 using age categories <44, 45–64, and ≥65 years. ICD-9, The International Classification of Diseases, Ninth Revision, is the official system of assigning codes to diagnoses and procedures associated with hospital utilization in the United States.

SOURCE: National Hospital Discharge Surveys 1999–2010