

Review Article

*Primary Care***INFECTIONS IN PATIENTS WITH DIABETES MELLITUS**

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CONTRARY to common belief, the association between diabetes mellitus and increased susceptibility to infection in general is not supported by strong evidence.^{1,2} However, many specific infections are more common in diabetic patients, and some occur almost exclusively in them. Other infections occur with increased severity and are associated with an increased risk of complications in patients with diabetes.

Several aspects of immunity are altered in patients with diabetes. Polymorphonuclear leukocyte function is depressed, particularly when acidosis is also present. Leukocyte adherence, chemotaxis, and phagocytosis may be affected.³⁻⁵ Antioxidant systems involved in bactericidal activity may also be impaired.⁶ The clinical data on humoral immunity are limited, but responses to vaccines appear to be normal. Cutaneous responses to antigen challenges and measures of T-cell function may be depressed.

Although these *in vitro* findings have not yet been fully confirmed in clinical studies, there is evidence that improving glycemic control in patients improves immune function. For example, the efficiency of intracellular killing of microorganisms may improve with better glycemic control.⁵ Among diabetic patients undergoing heart surgery, those given insulin infusions have better neutrophil function than those given intermittent insulin therapy.⁷ Blood glucose levels should be closely controlled in diabetic patients with infections.⁸

COMMON INFECTIONS IN PATIENTS WITH DIABETES

Table 1 summarizes the clinical features, diagnosis, and causative organisms of common infections in

patients with diabetes; Table 2 summarizes their treatment, and Table 3 summarizes the various aspects of foot infections.

Respiratory Tract Infections

It remains uncertain whether diabetes is an independent risk factor for an increased incidence or severity of common upper or lower respiratory tract infections.^{9,10} In the largest meta-analysis of community-acquired pneumonia to date, the odds ratio for death associated with diabetes was only 1.3 (95 percent confidence interval, 1.1 to 1.5).¹¹ A retrospective cohort study did not identify diabetes as a significant independent risk factor for death at 30 days in elderly patients with pneumonia.¹² However, two patterns of susceptibility to pneumonia in patients with diabetes have been noted.⁹ Infections caused by certain microorganisms (*Staphylococcus aureus*, gram-negative organisms, and *Mycobacterium tuberculosis*) occur with increased frequency. Infections due to other microorganisms (*Streptococcus pneumoniae* and influenza virus) are associated with increased mortality and morbidity.

Diabetes is a risk factor for bacteremia in patients with pneumococcal pneumonia and is associated with increased mortality.^{13,14} Diabetic patients have a normal response to pneumococcal vaccination, and vaccination is a cost-effective preventive strategy. There is increased mortality and an increased incidence of bacterial pneumonia and ketoacidosis among diabetic patients during epidemics of influenza pneumonia.⁹ Reduced pulmonary ciliary clearance in patients with influenza, combined with the high incidence of nasal carriage of *Staph. aureus* among diabetic patients, leads to an increased incidence of staphylococcal pneumonia. Guidelines recommend influenza and pneumococcal vaccines for all patients with diabetes.¹⁵

Urinary Tract Infections

Several controlled studies have demonstrated a higher incidence of bacteriuria (by a factor of two to four) in diabetic women than in nondiabetic women.¹⁶⁻¹⁸ Whether this increase is due to the increased use of urinary tract catheters in these women or to diabetes itself is debated.¹⁹ Diabetes may also predispose patients to more severe infections of the upper urinary tract; the upper tract is involved in up to 80 percent of urinary tract infections in diabetic patients.²⁰ Complications also occur more frequently in diabetic patients than in nondiabetic patients with established urinary tract infections.¹

The clinical presentation of acute pyelonephritis in diabetic patients is similar to that in nondiabetic

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TABLE 1. CLINICAL FEATURES, DIAGNOSIS, AND CAUSATIVE ORGANISMS OF SELECTED INFECTIONS IN PATIENTS WITH DIABETES.

INFECTION	CLINICAL FEATURES	DIAGNOSTIC PROCEDURE*	ORGANISMS	COMMENTS
Respiratory tract Community-acquired pneumonia	Cough, fever	Chest radiography	<i>Streptococcus pneumoniae</i> , <i>Staphylococcus aureus</i> , <i>Haemophilus influenzae</i> , other gram-negative bacilli, atypical pathogens	Pneumococcal infection carries a higher risk of death in diabetic than in nondiabetic patients
Urinary tract Acute bacterial cystitis	Increased urinary frequency, dysuria, suprapubic pain	Urine culture	<i>Escherichia coli</i> , proteus species	Bacteriuria more common in diabetic than in nondiabetic women
Acute pyelonephritis	Fever, flank pain	Urine culture	<i>E. coli</i> , proteus species	Emphysematous infection should be considered
Emphysematous pyelonephritis	Fever, flank pain, poor response to antibiotics	Radiography or CT scanning	<i>E. coli</i> , other gram-negative bacilli	Emergency nephrectomy often required
Perinephric abscess	Fever, flank pain, poor response to antibiotics	Ultrasonography or CT scanning	<i>E. coli</i> , other gram-negative bacilli	Surgical drainage usually required
Fungal cystitis	Same as for acute bacterial cystitis	Urine culture	Candida species	Difficult to distinguish colonization from infection
Soft tissue† Necrotizing fasciitis	Local pain, redness, crepitus, bullous skin lesions	Radiography or CT scanning	Gram-negative bacilli, anaerobes (type I), or group A streptococci (type II)	High mortality; emergency surgery required
Other Invasive otitis externa	Ear pain, otorrhea, hearing loss, cellulitis	Clinical examination, magnetic resonance imaging	<i>Pseudomonas aeruginosa</i>	Prompt otolaryngologic consultation recommended
Rhinocerebral mucormycosis	Facial or ocular pain, fever, lethargy, black nasal eschar	Clinical examination, magnetic resonance imaging, pathological findings	Mucor and rhizopus species	Strong association with ketoacidosis; emergency surgery required
Abdomen Emphysematous cholecystitis	Fever, right-upper-quadrant abdominal pain, systemic toxicity	Radiography	Gram-negative bacilli, anaerobes	High mortality; gallstones in 50%; emergency cholecystectomy required

*CT denotes computed tomography.

†Foot infections are described in detail in Table 3.

patients, except that bilateral infection is more common in patients with diabetes.²¹ Plain abdominal radiography may document emphysematous infection.²² Treatment includes hydration and parenteral antibiotics (Table 2). A poor response to antibiotic therapy suggests complications, which may include papillary necrosis or perinephric abscess.¹ Symptoms of papillary necrosis include flank and abdominal pain, accompanied by fever.^{23,24} The diagnosis is established by retrograde pyelography.²⁵ In one series of patients with perinephric abscess, 36 percent had diabetes.²⁶ Most cases (80 percent) occur as a complication of ascending urinary tract infection and are therefore caused by *Escherichia coli* or proteus species. Hematogenous infection, most commonly caused by *Staph. aureus*, accounts for the remainder of the cases. Although localizing clinical findings such as a flank or abdominal mass are highly suggestive, they are present in less than 25 percent of cases. Thorley et al.²⁷ noted that fever that persisted for more than four days after the initiation of antibiotic therapy was the most useful factor in differentiating perinephric abscess from uncomplicated pyelonephritis. The diagnosis is established by ultrasonography or computed tomographic (CT) scan.

Surgical drainage and systemic antibiotics are the mainstays of therapy.¹

Diabetes is a common predisposing factor for urinary tract infections caused by fungi, particularly candida species. The extent of involvement ranges from inconsequential lower urinary tract colonization to clinical cystitis, emphysematous cystitis,²⁸ pyelonephritis, and renal or perinephric abscess.^{29,30} Whereas upper urinary tract and disseminated infections require systemic therapy, the appropriate treatment of candida infection confined to the bladder remains controversial.³⁰ Distinguishing such infection from colonization may be difficult. The presence of symptoms or pyuria suggests infection. Spontaneous resolution of funguria occurs in many cases.^{31,32} Removal of an indwelling catheter, if one is present, is recommended as the initial intervention. The treatment options include bladder irrigation with amphotericin B,³³ a single dose of intravenous amphotericin B,³⁴ or oral fluconazole.³⁵ In one study, the rate of eradication seven days after therapy was higher in patients who received oral fluconazole for four days or single-dose intravenous amphotericin B than in those who underwent bladder irrigation with amphotericin B for

TABLE 2. TREATMENT OF SELECTED INFECTIONS IN PATIENTS WITH DIABETES.

INFECTION	EMPIRICAL ANTIMICROBIAL THERAPY		OTHER TREATMENT
	PREFERRED DRUGS*	ALTERNATIVE DRUGS*	
Respiratory tract			
Community-acquired pneumonia (outpatient)	Macrolide (e.g., erythromycin, 500 mg orally every 6 hr, or azithromycin, 500 mg orally on day 1, then 250 mg per day on days 2–5)	Doxycycline, 100 mg orally twice daily	
Community-acquired pneumonia (hospitalized patient)	Cefuroxime, 0.75 g intravenously every 6 hr, or ceftriaxone, 1–2 g intravenously per day; consider adding erythromycin, 0.5–1.0 g intravenously every 6 hr (or azithromycin, 500 mg intravenously per day, or doxycycline, 100 mg intravenously every 12 hr)	Levofloxacin, 500 mg intravenously every 24 hr, or doxycycline, 100 mg intravenously every 12 hr	
Urinary tract			
Acute bacterial cystitis	Trimethoprim–sulfamethoxazole, double strength, 1 pill twice daily	Fluoroquinolones (e.g., ciprofloxacin, 250 mg twice daily, or ofloxacin, 200 mg twice daily)	
Acute pyelonephritis	Fluoroquinolones (e.g., ciprofloxacin, 400 mg intravenously every 12 hr, or ofloxacin, 400 mg intravenously every 12 hr)	Ampicillin, 2 g intravenously every 6 hr, plus gentamicin, 5 mg/kg every 24 hr, or ceftriaxone, 2 g intravenously per day, or piperacillin, 3 g intravenously every 6 hr	Early surgical intervention in emphysematous infection
Perinephric abscess			
Associated with staphylococcal bacteremia	Nafcillin, 2 g intravenously every 4 hr	Cefazolin, 2 g intravenously every 8 hr, or vancomycin, 15 mg/kg intravenously every 6 hr	Surgical drainage
Associated with pyelonephritis	Same as for acute pyelonephritis		
Fungal cystitis	Fluconazole, 200 mg orally on day 1, then 100 mg per day for 4 days	Amphotericin B bladder irrigation (50 mg per liter of sterile water at 40 ml/hr for 24–48 hr), or single dose of intravenous amphotericin B, 0.3 mg/kg	Removal of urinary catheter
Soft tissue†			
Necrotizing fasciitis	Penicillin G, 24 million U intravenously per day, plus clindamycin, 900 mg intravenously every 8 hr, and gentamicin, 5 mg/kg intravenously per day	Ceftriaxone, 2 g intravenously every 24 hr, plus clindamycin, 900 mg intravenously every 8 hr	Prompt surgical débridement
Other			
Invasive otitis externa	Ciprofloxacin, 400 mg intravenously every 12 hr, and topical antipseudomonal or acetic acid drops	Ceftazidime, 2 g intravenously every 8 hr, or imipenem, 500 mg intravenously every 6 hr	Surgical débridement
Rhinocerebral mucormycosis	Amphotericin B, target dose, 1.0–1.5 mg/kg intravenously per day Total dose, 2.5–3.0 g		Surgical débridement; aggressive treatment of ketoacidosis (if present)
Abdomen			
Emphysematous cholecystitis	Ampicillin–sulbactam, 3 g intravenously every 6 hr	Ampicillin, 2 g intravenously every 6 hr, plus gentamicin, 5 mg/kg every 24 hr, plus clindamycin, 900 mg intravenously every 8 hr (or metronidazole, loading dose of 15 mg/kg intravenously, followed by 7.5 mg/kg intravenously every 6 hr), or ceftriaxone, 2 g intravenously every 24 hr plus clindamycin (or metronidazole)	Emergency cholecystectomy required

*All doses are for patients with normal renal and hepatic function. The initial intravenous regimen may be changed to an oral regimen as soon as the patient's clinical condition allows, unless the underlying infection requires prolonged parenteral therapy (e.g., staphylococcal bacteremia).

†Foot infections are described in detail in Table 3.

TABLE 3. FOOT INFECTIONS IN PATIENTS WITH DIABETES.

INFECTION	CLINICAL FEATURES	DIAGNOSTIC PROCEDURE	CAUSATIVE ORGANISMS	INITIAL MANAGEMENT
Mild, non-limb-threatening	Shallow ulcer; less than 2 cm cellulitis; no evidence of fasciitis, abscess, or osteomyelitis; no evidence of ischemia; good metabolic control	Plain radiography, possibly culture*	Primarily aerobic gram-positive cocci (e.g., <i>Staphylococcus aureus</i> , streptococci)	Oral antibiotics†; wound care‡; outpatient management if there is good home support
Limb-threatening	Deep ulcer; more than 2 cm cellulitis; suspected deep infection; ischemia; poor metabolic control	Plain radiography; deep cultures; "probe to bone" test§	Polymicrobial: aerobic gram-positive cocci, strict anaerobes (e.g., <i>Bacteroides fragilis</i>), and gram-negative bacilli (e.g., <i>Escherichia coli</i>)	Immediate hospitalization and surgical consultation; broad-spectrum intravenous antibiotics¶; wound care‡

*Since gram-positive cocci are the anticipated pathogens, cultures are not clearly required in each case.

†Recommended oral antibiotics include cephalexin, clindamycin, and amoxicillin-clavulanate.

‡Wound care includes sharp débridement of devitalized tissue and callus, sterile dressings, and relief of pressure at the ulcer.

§The ability to touch bone when the wound is gently probed with a sterile surgical probe is predictive of underlying osteomyelitis.

¶Recommended intravenous antibiotics include a beta-lactam plus a beta-lactamase inhibitor (e.g., ampicillin-sulbactam) or clindamycin plus a gram-negative drug (e.g., a third-generation cephalosporin, a fluoroquinolone, or aztreonam). Vancomycin plus imipenem-cilastatin is recommended for life-threatening infections.

three days.³⁵ In another study, patients receiving amphotericin B bladder irrigation had higher rates of eradication two days after the beginning of therapy than those receiving oral fluconazole, but the cure rates in the two groups were similar one month after the beginning of therapy.³⁶ Currently, fluconazole is the preferred drug because of its ease of administration and relative absence of toxicity (Table 2).

Soft-Tissue Infections

Foot infections are the most common soft-tissue infections in patients with diabetes (Table 3). Potential complications include osteomyelitis, amputation, and death. Surgical débridement of all devitalized tissue is essential, and a multidisciplinary approach to the treatment of foot infection is recommended.³⁷

Among nonpedal soft-tissue infections, necrotizing fasciitis is the most important.³⁸⁻⁴¹ The associated mortality is approximately 40 percent. The infection starts in the subcutaneous space and spreads along fascial planes. The most common locations are the arms and legs and the abdominal wall. Necrotizing fasciitis has been classified as type I (infection caused by a combination of anaerobic and one or more facultative aerobic organisms) or type II (caused by group A streptococci, with or without staphylococci). It is clinically more useful to classify them as monomicrobial infections caused by streptococci (10 percent of cases) or polymicrobial infections caused by facultative gram-negative bacilli such as *E. coli* and strict anaerobes such as *Bacteroides fragilis* or clostridium species (90 percent of cases).

The degree of pain typically is disproportionate to the severity of the findings on physical examination, such as erythema, swelling, and tenderness.³⁸ Marked systemic toxicity is present. Later, more definitive skin

changes appear in the form of bullous lesions accompanied by localized anesthesia as a result of the occlusion of cutaneous arterioles. A cutaneous wound or eschar is often noted. Crepitus is a useful finding but is noted in only about half of cases. Soft-tissue gas may be detected more frequently by plain radiography than by clinical examination. In one study, gas was identified radiographically in 17 of 21 diabetic patients with necrotizing fasciitis.⁴² Fournier's gangrene is a form of necrotizing fasciitis involving the male genitalia.⁴³ The infection usually involves the scrotum but may extend to the penis, perineum, and abdominal wall, and scrotal gangrene can occur rapidly.

Emergency evaluation and treatment of necrotizing fasciitis are imperative. Broad-spectrum intravenous antibiotics are required (Table 2). Both Stevens et al.⁴⁴ and Eagle⁴⁵ noted a decreased efficacy of penicillin, due to the slower growth rate of the organism at a high inoculum, in laboratory animals with severe streptococcal infection. Clindamycin is more effective than penicillin in vitro.⁴⁴ Because of the possibility of clindamycin resistance and the potentially life-threatening nature of this infection, a combination of penicillin and clindamycin is recommended, with the addition of gentamicin, pending the results of cultures. Prompt, aggressive surgical débridement is crucial in decreasing mortality.

INFECTIONS OCCURRING PRINCIPALLY IN PATIENTS WITH DIABETES

Invasive Otitis Externa

Invasive ("malignant") otitis externa is an uncommon but potentially life-threatening infection of the external auditory canal and skull.^{46,47} *Pseudomonas aeruginosa* is the causative organism in the vast majority of cases. Unrelenting pain, otorrhea, and hearing

loss without fever are the characteristic symptoms. The diagnosis is often delayed for six to eight weeks if these symptoms are mistakenly attributed to typical, noninvasive otitis externa. There is intense cellulitis and edema of the auditory canal with formation of polypoid granulation tissue. Extension of the infection may result in cranial osteomyelitis and intracranial involvement.⁴⁷

Early consultation with an otolaryngologist will facilitate the clinical diagnosis, the débridement of necrotic tissue, and acquisition of deep tissue samples for Gram's staining and culture. Tissue biopsy to rule out epidermal carcinoma is recommended. Magnetic resonance imaging with gadolinium is the most useful method for documenting the initial extent of soft-tissue involvement (including dural inflammation) and bone involvement. Gallium-67 single-photon-emission CT has also been reported to be useful both for early diagnosis and for follow-up during treatment.^{48,49}

Treatment includes repeated débridement of the ear, application of topical antipseudomonal or acetic acid drops, and use of systemic antibiotic therapy against *Pseud. aeruginosa* for four to six weeks (Table 2).

Rhinocerebral Mucormycosis

Approximately 50 percent of cases of rhinocerebral mucormycosis occur in diabetic patients. Ketoacidosis is the most important risk factor; in vitro studies have documented a lack of inhibitory activity of serum from patients with diabetic ketoacidosis against *Rhizopus oryzae* that is restored on correction of acidosis.⁵⁰ Early manifestations include facial or ocular pain and nasal stuffiness, with or without discharge.⁵¹ Later, proptosis, chemosis, and necrotic lesions on the palate or nasal mucosa occur. A black necrotic eschar on the nasal turbinates may be an important clue to the diagnosis.⁵² Generalized headache, fever, and lethargy may be present. Ophthalmoplegia or visual loss from cranial-nerve involvement may accompany cavernous sinus thrombosis. Thrombosis of the carotid artery or jugular vein may cause hemiparesis.

The diagnosis is established by biopsy and culture of necrotic tissue from the nasal passages or the palate. Direct sampling from the sinuses may be necessary. The histologic finding of broad, nonseptate, haphazardly branching hyphae invading tissue confirms the diagnosis; cultures are often negative. Magnetic resonance imaging is preferred to define involvement of the sinuses, orbit, cavernous sinus, and central nervous system.

Surgical débridement of infected tissue and drainage of infected sinuses are key elements in achieving a cure. Control of diabetes and institution of amphotericin B are crucial adjunctive therapies. Imidazole antifungal drugs (fluconazole and itraconazole) cannot be recommended as first-line therapy.⁵³

Emphysematous Infections

Cholecystitis

The intraabdominal infection characteristically associated with diabetes is emphysematous cholecystitis, an uncommon, gas-producing, virulent infection of the gallbladder. Approximately 35 percent of cases occur in patients with diabetes.^{54,55} Emphysematous cholecystitis may be clinically similar to acute cholecystitis, but the proportion of male patients is higher, gangrene of the gallbladder and perforation are more frequent, and the overall mortality is substantially higher (15 percent vs. less than 4 percent) than in patients with acute cholecystitis.⁵⁵ Gallstones are present in only 50 percent of patients with emphysematous cholecystitis. The patients have pain in the right upper quadrant of the abdomen, nausea, vomiting, and fever. Although clinical signs of peritonitis are often absent, crepitus on abdominal palpation may be present and is an ominous sign.²⁵ The diagnosis is established by radiographic demonstration of gas on plain films or by abdominal CT scanning.^{55,56} Polymicrobial infection with gram-negative bacilli and anaerobes is most common. Prompt cholecystectomy, in addition to broad-spectrum antibiotic therapy, is imperative (Table 2).

Pyelonephritis and Cystitis

Emphysematous pyelonephritis is a gas-forming infection of the renal parenchyma, perinephric tissues, and collecting system. Over 90 percent of cases occur in diabetic patients.²⁵ Papillary necrosis complicates 21 percent of cases.²³ Between 50 percent and 75 percent of cases are caused by *E. coli*,^{23,24} and most of the rest are caused by other gram-negative bacilli. Patients with emphysematous pyelonephritis usually present with a fever of rapid onset, chills, flank pain, nausea, and vomiting, occasionally accompanied by an abdominal mass. Failure of fever to resolve after three or four days of treatment of a urinary tract infection in a diabetic patient should arouse concern about the possibility of this uncommon complication.¹

The diagnosis is made by demonstrating gas within the kidney tissue. Abdominal CT scanning is best for this purpose, since plain radiographs show gas in only about one third of patients.²³ Initial treatment consists of vigorous hydration and intravenous antibiotics, in addition to aggressive control of hyperglycemia. Most cases require additional surgical intervention. Obstruction should be sought and treated appropriately. Total nephrectomy is considered for patients whose condition does not improve clinically or in whom gas spreads despite nonsurgical treatment. Radiographically guided percutaneous drainage has been reported to be successful in cases in which infection is localized.⁵⁷ The presence of emphysematous cystitis, an uncommon sequela of lower urinary tract infections, is suggested by pneumaturia. Plain radiographs of the pelvis confirm the diagnosis.

MICROORGANISMS STRONGLY ASSOCIATED WITH INFECTIONS IN PATIENTS WITH DIABETES

Patients with diabetes seem to be at particularly high risk for infection with certain microorganisms. For example, in a group of nonpregnant adults with group B streptococcal bacteremia, the prevalence of diabetes was found to be 27.5 percent.⁵⁸ A disproportionately high incidence (30 to 60 percent) of diabetes has been reported in several series of patients with klebsiella infections, including bacteremia,⁵⁹ liver abscess,⁶⁰ endophthalmitis,⁶¹ and thyroid abscess.⁶² Diabetes has been identified as a risk factor for infection with *Salmonella enteritidis*.⁶³ In several studies in the first half of the 20th century, the incidence of tuberculosis among persons with diabetes was found to be three or four times as high as in the general population.^{64,65} More recently, in an immigrant Asian community in England, lung cavitation was found to be more common among diabetic than nondiabetic persons.⁶⁶

Although *Staph. aureus* infections have been noted to be more common among patients with diabetes, a recent careful review concluded that currently available data do not allow an estimation of the proportional risk of such infection among diabetic patients.⁶⁷ A study of bacteremia caused by *Staph. aureus* found no difference in mortality between diabetic and nondiabetic patients.⁶⁸ Other infections that occur with increased frequency in patients with diabetes include mucocutaneous candida infections such as oropharyngeal candidiasis, candidal vulvovaginitis, and cutaneous candidiasis in the intertriginous areas of obese diabetic patients.⁶⁹

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