

# Infections in Patients With Diabetes Mellitus: Importance of Early Recognition, Treatment, and Prevention

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## ABSTRACT

**PURPOSE:** To review the spectrum of infectious complications in patients with diabetes, common presentations and warning signs, therapeutic options, and strategies for prevention.

**EPIDEMIOLOGY:** There is evidence that patients with diabetes are more susceptible to infection than are nondiabetic patients. Moreover, patients with diabetes have about double the risk of infection-related mortality.

**REVIEW SUMMARY:** The risk of microvascular and macrovascular complications increases with older age in patients with diabetes; these complications presumably increase the risk of infection. Several defects in cell-mediated immunity also have been noted in patients with diabetes. Common infections that can cause serious complications in patients with diabetes include community-acquired pneumonia, urinary tract infections, necrotizing fasciitis, and foot ulcers. Certain rare infectious diseases occur predominantly in patients with diabetes, including malignant otitis externa, rhinocerebral mucormycosis, emphysematous cholecystitis, and emphysematous pyelonephritis. Because these conditions can have serious complications, progress rapidly, and/or be life-threatening, prompt recognition and treatment is imperative. Glycemic control, screening for foot ulcers and educating patients about foot care, and vaccination against pneumococcus and influenza are critically important strategies for preventing infection.

**TYPE OF AVAILABLE EVIDENCE:** Nationally recognized treatment guidelines, randomized controlled trials, prospective and retrospective cohort studies, case-control studies, meta-analyses, nonsystematic reviews.

**GRADE OF AVAILABLE EVIDENCE:** Fair to good.

**CONCLUSION:** Anticipating serious complications of common infections in patients with diabetes is as important as appreciating rare disease entities that affect these patients disproportionately. Primary care clinicians should be aware of how infections present in patients with diabetes in order to provide early diagnosis and aggressive treatment. (*Adv Stud Med.* 2006;6(2):71-81)

**D**iabetes mellitus affects 7% to 8% of adults in the United States, including 18% of individuals between the ages of 65 and 75 years and up to 40% of those older than 80 years.<sup>1</sup> Infectious diseases are a significant source of morbidity and mortality in people with diabetes. Confirming the longstand-

ing belief among clinicians that patients with diabetes are especially susceptible to infection, a large retrospective cohort study conducted in Canada documented that nearly half of all people with diabetes had at least one physician visit or hospitalization for an infectious disease per year in each of 2 cohorts studied.<sup>2</sup> The risk ratio for such an event was 1.21 (95% confidence

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**Off-Label Product Discussion:** The author of this article discusses the use of posaconazole for mucormycosis.

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interval [CI], 1.20-1.22) compared with individuals without diabetes. Furthermore, patients with diabetes have about twice the risk of infection-related mortality compared with those without diabetes, according to results from the same study<sup>2</sup> and from a similar investigation conducted in the United States.<sup>3</sup> A subsidiary analysis in the latter study suggested that this increased risk is mediated by concurrent cardiovascular disease.

Whether patients with diabetes have increased susceptibility to all infections has not been conclusively proven.<sup>3,4</sup> However, investigators from The Netherlands analyzed data from the Second Dutch National Survey of General Practice and showed that patients with diabetes had an increased risk for several types of infections. They compared 705 patients with type 1 diabetes mellitus (DM1) and 6712 patients with type 2 diabetes mellitus (DM2) with 18 911 control patients who had hypertension.<sup>5</sup> Individuals with DM1 and DM2 had a higher adjusted risk of acquiring lower respiratory tract infection (DM1: odds ratio [OR] 1.42, 95% CI 0.96-2.08; DM2: OR 1.32, 95% CI 1.13-1.53), urinary tract infection (DM1: OR 1.96, 95% CI 1.49-2.58; DM2: OR 1.24, 95% CI 1.10-1.39), bacterial skin and mucous membrane infections (DM1: OR 1.59, 95% CI 1.12-2.24; DM2: OR 1.33, 95% CI 1.15-1.54), and fungal skin and mucous membrane infection (DM1: OR 1.34, 95% CI 0.97-1.84; DM2: OR 1.44, 95% CI 1.27-1.63) compared with controls. Using polytomous logistic regression analyses, the authors also demonstrated that the risk of recurrent infections was higher in patients with diabetes compared with controls.<sup>5</sup> As individuals with diabetes age, the risk of microvascular and macrovascular complications increase severalfold; these complications presumably increase the risk of infection further.<sup>13</sup>

Defects in the function of lymphocytes, neutrophils, and monocytes contribute to the impact of infectious diseases on individuals with diabetes. Polymorphonuclear neutrophils (PMNs) in these patients show alterations in chemotaxis, adherence, phagocytosis, intracellular killing, and bactericidal activity,<sup>6,7</sup> accompanied by decreased levels of leukotriene B<sub>4</sub>, prostaglandin E, and thromboxane B<sub>2</sub>.<sup>8,9</sup> Although spontaneous activation of PMNs with increased free-radical activation has been observed, neutrophil response after stimulation of free radicals was lower in patients with diabetes than in controls.<sup>7</sup> Some experts believe that hyperglycemia leads to low-level persistent activation of PMNs, resulting in a tolerant state with a less exuberant response to infection.<sup>1</sup> Monocytes in patients with diabetes have decreased levels of phagocytosis<sup>10</sup>; decreased lymphocyte function in these patients also has been described.<sup>11</sup> Conversely, there is evidence that improving glycemic control improves cellular immunity.<sup>4</sup> There is less information on humoral immuni-

ty, but patients with diabetes appear to have a normal response to vaccines.<sup>12</sup>

Some rare infectious diseases occur almost exclusively in patients with diabetes, such as malignant otitis externa, mucormycosis, emphysematous cystitis, and emphysematous pyelonephritis. Other more common infectious diseases (eg, soft-tissue infections) can occur with severe complications in this population. Many patients with diabetes who have infections first present to primary care clinicians, because the initial symptoms of infection can be subtle. This review aims to help primary care clinicians understand the spectrum of infectious complications in patients with diabetes, recognize common presentations and warning signs, and appreciate strategies for preventing infections in these individuals. Treatment options, while covered, will not be emphasized. Table 1 lists some relevant clinical pearls.<sup>13</sup>

## SPECTRUM OF DISEASE

### HEAD AND NECK

*Malignant Otitis Externa.* Malignant (necrotizing) otitis externa is an invasive infection of the external auditory canal and adjacent bony structures. Although it is still an uncommon illness and its incidence has been difficult to document, malignant otitis externa has been diagnosed earlier and more frequently during the past decade, probably because of increased suspicion by generalists.<sup>14</sup> Most cases (86% to 90%) affect older adult patients who have diabetes.<sup>14</sup> Patients typically present with intractable ear pain and discharge or with persistent headache, without fever. The tympanic membrane is almost always intact; however, the pain is usually more severe than that associated with simple external otitis or chronic otitis media with tympanic membrane perforation. The pain often extends to the temporomandibular joint, and patients may report that pain is aggravated by chewing.

More than 98% of cases of malignant otitis externa are caused by *Pseudomonas aeruginosa*.<sup>14</sup> Ear irrigation with nonsterile tap water appears to be a risk factor for this infection<sup>15</sup>; two other possible predisposing factors are the increased pH of diabetic cerumen and aging-related microangiopathy in the ear.<sup>14</sup> Altered mental status and cranial nerve palsies are poor prognostic signs, generally reflecting advanced disease that has resulted in osteomyelitis of the skull base and temporomandibular joint.

The diagnosis of malignant otitis externa may be confirmed by magnetic resonance imaging (MRI) with gadolinium, which shows the extent of bony involvement.<sup>16</sup> The erythrocyte sedimentation rate is usually markedly elevated and can be used to monitor disease activity.<sup>15</sup> The treatment of choice is an antibiotic that has antipseudomonal activity, such as oral

ciprofloxacin, used for a prolonged period of 6 to 8 weeks until there is radiographic evidence of improvement.<sup>17</sup> If a fungus is the causative microorganism, >12 weeks of treatment with amphotericin B (followed by oral itraconazole) or a newer triazole, such as voriconazole, may be recommended.<sup>18,19</sup> Topical antibiotics are not recommended because they may prevent the isolation of causative organisms from the ear canal.

Many patients with mild disease can be treated on an outpatient basis. However, quinolone-resistant *Pseudomonas* is increasingly prevalent.<sup>20</sup> If symptoms persist or worsen after a short course of a quinolone, the patient should be referred to an otolaryngologist. Hospitalization for a biopsy to rule out invasive carcinoma and for debridement and administration of parenteral antibiotics may be necessary.

Patients with diabetes should be instructed about proper ear hygiene. Patients should be reminded that the use of cotton swabs for ear cleaning should be avoided.

Swimmers, particularly those with a history of malignant otitis externa, should be advised to wear ear plugs while in the water and to dry the ear completely after swimming.

**Rhinocerebral Mucormycosis.** Rhinocerebral mucormycosis is a rare invasive fungal infection caused by the Zygomycetes fungal class (eg, *Rhizopus*, *Absidia*, and *Mucor* species). These moulds are highly angioinvasive, and rapid dissemination and death can occur if infection is not recognized in a timely fashion.

Zygomycetes can cause invasive disease at other sites, but rhinocerebral disease is the most common,<sup>21</sup> and diabetes is the major risk factor.<sup>22</sup> An estimated 50% to 75% of all cases of rhinocerebral mucormycosis occur in patients with diabetes, and diabetic ketoacidosis is the most important predisposing factor in these patients.<sup>1</sup> Rhinocerebral mucormycosis is almost universally fatal if left untreated,<sup>21</sup> but mortality in patients with diabetes may be as low as 20% if the disease is recognized early and managed aggressively.<sup>23</sup>

**Table 1. Clinical Pearls: Infections in Patients With Diabetes**

Condition	“Pearls”
Malignant otitis externa	<ul style="list-style-type: none"> <li>Consider in patients with diabetes who have persistent external otitis and unremitting ear pain and/or cranial nerve findings.</li> <li>Have a low threshold to refer the patient to an otolaryngologist; surgical debridement may be necessary.</li> </ul>
Mucormycosis	<ul style="list-style-type: none"> <li>A visible black eschar in the nasal turbinates or the hard palate may be the first clue to diagnosis (present in 40% of affected patients).<sup>13</sup> In the office, the physician can scrape the eschar onto a slide and use a potassium hydroxide preparation to demonstrate fungal forms.</li> <li>Diabetic ketoacidosis is an important risk factor, but 50% of patients with diabetes who develop mucormycosis do not have diabetic ketoacidosis.</li> </ul>
Emphysematous cholecystitis	<ul style="list-style-type: none"> <li>Gallstones are present only 50% of the time.</li> <li>One early clue is the presence of right upper lobe crepitus on abdominal palpation—an ominous sign.</li> </ul>
Bacteriuria in women	<ul style="list-style-type: none"> <li>The decision to treat is based on the presence of symptoms in the patient who is able to give an accurate report.</li> </ul>
Acute pyelonephritis	<ul style="list-style-type: none"> <li>Persistent fever &gt;4 days in a patient with diabetes who has acute pyelonephritis and is receiving appropriate antimicrobial therapy should increase suspicion for complications such as perinephric abscess or emphysematous pyelonephritis.</li> </ul>
Emphysematous cystitis	<ul style="list-style-type: none"> <li>Pneumaturia seems to be more characteristic of emphysematous cystitis than of emphysematous pyelonephritis.</li> </ul>
The diabetic foot	<ul style="list-style-type: none"> <li>Minimize the threat of loss of limb by involving a surgical team early and taking a multidisciplinary approach. Consider involving a vascular surgeon, orthopedic foot specialist, endocrinologist or diabetologist, and infectious disease consultant.</li> </ul>
Necrotizing fasciitis	<ul style="list-style-type: none"> <li>Consider in the patient with diabetes whose pain is disproportionate with clinical findings.</li> <li>Consider in the patient with diabetes who has cellulitis along with systemic signs of infection, such as an elevated white blood cell count, elevated heart rate, or very high blood glucose or acidosis.</li> <li>Do not delay surgical intervention if necrotizing fasciitis is suspected.</li> </ul>

Patients with diabetes are at increased risk for mucormycosis because of several possible factors. The enzyme ketone reductase in *Rhizopus* permits the organism to thrive in high-glucose and acidic environments. Serum from healthy individuals was shown to inhibit growth of *Rhizopus*, in contrast to serum from individuals with diabetic ketoacidosis, in whom an absence of serum inhibitory activity against *Rhizopus* has been observed.<sup>24</sup> Patients with diabetes have elevated serum iron levels because of decreased transferrin binding, and increased iron uptake by *Rhizopus* stimulates fungal growth.<sup>25</sup>

Affected patients are febrile and complain of sinus, facial, or ocular pain and swelling, and they may appear to have acute sinusitis. The progression of disease is usually rapid; infection soon progresses beyond the sinuses to involve contiguous structures, such as the palate, orbit, and brain parenchyma. Signs of extrasinus spread may include destruction of the nasal turbinates, protrusion of the globe, edema of the mucous membranes of the globe and eyelid lining, and presence of black eschars in the nasal turbinates or the hard palate caused by tissue necrosis. Frontal lobe involvement from an ethmoid sinus source may manifest as obtundation, and infection may spread from the sphenoid sinus to cause cavernous sinus and carotid artery thrombosis.

The diagnosis of rhinocerebral mucormycosis is confirmed by biopsy, which reveals tissue-invasive, broad, nonseptate hyphae with right-angle branching (Figure 1). MRI can be used to define the extent of invasive disease.<sup>26</sup> The treatments of choice are wide surgical debridement, control of hyperglycemia and/or ketoacidosis, and administration of systemic amphotericin B or a lipid formulation of amphotericin B.<sup>21</sup> Other antifungal agents (such as fluconazole, itracona-

zole, voriconazole, and caspofungin) are not effective. Posaconazole is an investigational triazole in phase 3 trials that has activity against Zygomycetes.<sup>22,27</sup>

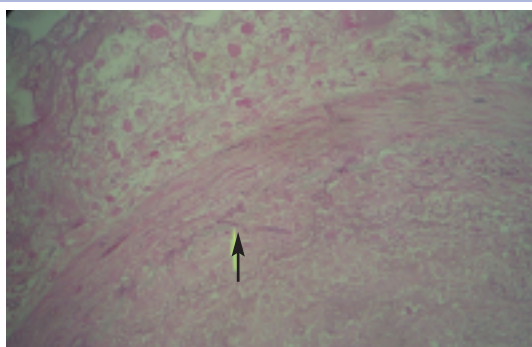
#### PULMONARY

**Community-Acquired Pneumonia.** Diabetes is probably not a significant risk factor for higher incidence of or mortality from uncomplicated community-acquired pneumonia. In a meta-analysis of more than 33 000 patients, diabetes mellitus was independently associated with mortality, but the effect was small (OR 1.3; 95% CI, 1.1-1.5).<sup>28</sup> Similar risk estimates for lower respiratory tract infection in patients with diabetes compared with those without diabetes were shown in a prospective cohort study from The Netherlands.<sup>5</sup> However, patients with diabetes who have pneumonia are more likely to have pneumococcal bacteremia, which may be associated with higher mortality. A Danish population-based case-control study showed that the 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.<sup>29</sup>

Patients with diabetes are more likely than those without diabetes to be infected with *Staphylococcus aureus* and gram-negative rods.<sup>30</sup> Although these are not typical community-acquired pneumonia pathogens, diabetes is a risk factor for the development of both *S aureus* and gram-negative rod pneumonia. Other common etiologic organisms are *Streptococcus pneumoniae* and *Haemophilus influenzae*. Because individuals with diabetes have a normal response to pneumococcal vaccination,<sup>30</sup> it should be routinely offered.<sup>31</sup> Patients with diabetes who have influenza are more likely to develop superinfection with bacterial pneumonias and ketoacidosis; influenza vaccination is therefore also indicated in this population.<sup>30</sup> Although guidelines from the American Diabetes Association have established pneumococcal and influenza vaccinations as a key public health strategy in patients with diabetes,<sup>31</sup> population-level coverage is suboptimal. According to a report issued by the US Centers for Disease Control and Prevention, in 2003 the median pneumococcal vaccination rate in US patients with diabetes was 37%, and the median influenza vaccination rate was 49%.<sup>32</sup>

The first step in managing community-acquired pneumonia in patients with diabetes is to triage patients to inpatient or outpatient care. Following guidelines from the Infectious Diseases Society of America, physicians can prescribe a macrolide, such as azithromycin, to outpatients who have comorbidities (eg, cardiopulmonary disease or diabetes) if they have not received antibiotic therapy within the past 3 months (Table 2).<sup>32-37</sup> If the patient has a history of

Figure 1. Mucormycosis in a Patient With Diabetes



Arrow points to tissue-invasive, broad, nonseptate hyphae with right-angle branching on pathologic examination.

recent antibiotic therapy, a fluoroquinolone is recommended. Inpatients can receive regimens such as ceftriaxone and a macrolide or doxycycline, or fluoroquinolone monotherapy.

#### GASTROINTESTINAL

**Emphysematous Cholecystitis.** Emphysematous cholecystitis is an uncommon, gas-producing, virulent infection of the gallbladder; 35% of cases occur in patients with diabetes.<sup>4</sup> Patients initially present with typical symptoms of uncomplicated cholecystitis: right upper quadrant pain, fever, nausea, and vomiting. What defines this entity is the presence of gas in the gallbladder lumen, gallbladder wall, or surrounding tissue on plain films or

computed tomography (CT) images.<sup>38</sup> Gas-producing anaerobic organisms, such as *Clostridium* species, have been implicated. However, polymicrobial organisms (streptococci, anaerobes, gram-negative bacilli) are most often isolated on surgical exploration.

The treatment of choice for emphysematous cholecystitis is emergency surgical removal of the gallbladder.<sup>39</sup> Broad-spectrum antibiotics (which target anaerobes and other possible causative organisms), such as ampicillin-sulbactam, are also administered. Outcomes are affected by gallbladder gangrene or perforation, resulting in a 15% mortality rate compared with 4% in uncomplicated cholecystitis.<sup>4</sup>

**Table 2. Recommendations From Selected Guidelines Addressing Treatment and Prevention of Infections in Patients With Diabetes**

Infection	Treatment Recommendation	Organization
<i>Community-acquired pneumonia</i> Outpatient*		Infectious Diseases Society of America <sup>33</sup>
No recent† antibiotic therapy	Advanced macrolide‡ or fluoroquinolone	
Recent† antibiotic therapy	Advanced macrolide‡ plus $\beta$ -lactam§ or fluoroquinolone	
Inpatient	Advanced macrolide‡ plus $\beta$ -lactam   or fluoroquinolone	
<i>Asymptomatic bacteriuria</i>	Screening and treatment not recommended	Infectious Diseases Society of America <sup>34</sup>
<i>Diabetic foot infections</i>		Infectious Diseases Society of America <sup>35</sup>
Mild, non-limb-threatening	Oral antibiotics¶ as outpatient, debride and probe the wound, wound care, re-evaluate in 3-5 days	
Limb-threatening	Intravenous antibiotics# as inpatient, supportive therapy (eg, fluid resuscitation), surgical consultation, re-evaluate daily	
<b>Prevention</b>		
<i>Pneumococcal vaccine</i> (23-valent, polysaccharide vaccine; PPV23)	Recommended once for patients with diabetes $\geq 2$ years of age Revaccinate once if $>65$ years of age and first vaccine administered $\geq 5$ years earlier	American Diabetes Association <sup>36</sup> US Centers for Disease Control and Prevention <sup>37</sup>
<i>Pneumococcal vaccine</i> (7-valent, conjugated vaccine; PCV)	Recommended (4 doses) for all children aged 2-23 months	US Centers for Disease Control and Prevention <sup>37</sup>
<i>Influenza vaccine</i>	Recommended yearly for patients with diabetes aged $\geq 6$ months	American Diabetes Association <sup>36</sup> US Centers for Disease Control and Prevention <sup>32</sup>

\*Outpatient therapy recommended for patients with medical comorbidities, including diabetes.

†Within the previous 3 months.

‡Azithromycin or clarithromycin.

§High-dose amoxicillin (1 g orally 3 times daily), high-dose amoxicillin-clavulanate (2 g orally 3 times daily), cefpodoxime, cefprozil, or cefuroxime (all orally).

||Cefotaxime, ceftriaxone, ampicillin-sulbactam, or ertapenem (all intravenously).

¶Dicloxacillin, clindamycin, cephalixin, trimethoprim-sulfamethoxazole, amoxicillin-clavulanate, or levofloxacin.

#Piperacillin-tazobactam, levofloxacin, or ciprofloxacin with clindamycin, imipenem-cilastatin, and vancomycin (for patients in whom methicillin-resistant *S aureus* infection is proven or likely) and ceftazidime (with or without metronidazole).

### URINARY TRACT

**Bacteriuria and Cystitis in Women.** Bacteriuria is more common in women with diabetes than in women without diabetes,<sup>40,41</sup> although published reports vary regarding prevalence rates. Because screening for microalbuminuria is recommended in patients with diabetes, an incidental finding of bacteriuria is not uncommon. Cystopathy due to diabetes, with the resulting increase in ureteral reflux and residual volume, may explain the increased prevalence.<sup>42</sup> Risk factors for bacteriuria in patients with diabetes include longer duration of diabetes and the presence of long-term complications of diabetes, but not poor diabetes control.<sup>41</sup> As in patients without diabetes,<sup>41</sup> *Escherichia coli* is the most common organism causing urinary tract infections (UTIs) in individuals with diabetes,<sup>40,41</sup> although it is not as predominant as in a nondiabetic population with UTI.<sup>40</sup> Other common etiologic organisms are *Staphylococcus saprophyticus*, *Proteus*, *Klebsiella*, and enterococci. The prevalence of bacteriuria does not appear to be increased in men with diabetes compared with those without diabetes.<sup>41</sup>

Whether treatment of asymptomatic bacteriuria in patients with diabetes should be offered has been a longstanding question of interest.<sup>40</sup> According to guidelines from the Infectious Diseases Society of America, screening for and treatment of asymptomatic bacteriuria is not recommended in women with diabetes because no evidence has shown that treatment changes long-term outcomes (Table 2).<sup>34</sup> In a prospective trial with a 6-week double-blind period, 105 women with diabetes who had asymptomatic bacteriuria were randomly assigned to receive 14 days of placebo or antimicrobial therapy.<sup>43</sup> Four weeks after the initial course of treatment, bacteriuria was present in 20% of the women in the treatment group versus 78% of the women in the placebo group. After the 6-week period, group assignment was revealed, and patients continued follow-up. Bacteriuria was assessed at 3-month intervals, and patients who were originally assigned to the treatment arm continued to receive antibiotics for asymptomatic bacteriuria. Patients were also assessed for symptomatic UTI, pyelonephritis, and UTI-associated hospitalizations. The investigators reported outcomes after a mean follow-up period of 27 months. No significant differences existed between groups with respect to episodes of symptomatic UTI, hospitalizations for UTI, or pyelonephritis. However, the average number of days of antimicrobial use for UTI was 5 times higher in the treatment group than in the placebo group; the investigators attributed this difference entirely to the use of antibiotics for management of asymptomatic bacteriuria. Moreover, women in the treatment group had significantly

more antimicrobial-related adverse events compared with women in the placebo group.

Patients with UTI may present with dysuria, increased urinary frequency, and suprapubic tenderness. The diagnosis is confirmed with urinalysis and urine culture. Some experts advocate a longer (7- to 14-day) course of antibiotics for symptomatic and uncomplicated UTI in patients with diabetes because of the possibility of upper tract involvement.<sup>42</sup> However, many clinicians treat uncomplicated UTI in individuals with diabetes for the same duration as in other patients. The regimens of choice for all patients include trimethoprim-sulfamethoxazole at double strength or a fluoroquinolone for 3 days, nitrofurantoin for 7 days, or fluconazole if *Candida albicans* cystitis is diagnosed.<sup>44,45</sup>

**Acute Pyelonephritis.** Acute pyelonephritis is 4 to 5 times more common in patients with diabetes than in those without diabetes.<sup>42</sup> Presenting symptoms are similar in both populations, with fever and flank pain predominant, except that bilateral involvement of the kidneys is more likely in those with diabetes.<sup>42</sup> *E coli* is the predominant etiologic organism; others include *S saprophyticus*, *Proteus*, *Klebsiella*, and enterococci. Treatment options include an intravenously administered quinolone, ceftriaxone, or ampicillin and gentamicin. Patients with diabetes are more likely to have complications, such as renal or perinephric abscesses, papillary necrosis, and emphysematous pyelonephritis,<sup>1</sup> which may require surgical or radiologically guided drainage. CT can help distinguish between these possibilities, and interventional radiology or surgery can be life-saving. Consider referral of any case of complicated pyelonephritis to an infectious disease specialist.

**Emphysematous Pyelonephritis.** Emphysematous pyelonephritis is an uncommon, gas-producing, virulent infection of the renal parenchyma or surrounding tissue. Patients with diabetes account for 70% to 90% of cases, with women at twice the risk of men.<sup>42</sup> The diagnosis is suggested by fever, flank pain, and failure to respond to antibiotics for presumptive treatment of acute pyelonephritis. Confirmation of the diagnosis is obtained by the presence of gas in the renal tissue on imaging.<sup>46,47</sup> Abdominal CT is the most sensitive diagnostic method. *E coli*, *Klebsiella*, and other gram-negative bacilli are the organisms that most commonly cause infection.

Emphysematous pyelonephritis should be treated with a combination of pharmacologic and surgical methods.<sup>47</sup> Pharmacologic options include ceftriaxone and metronidazole, or ampicillin, gentamicin, and metronidazole. Mortality in patients receiving pharmacologic therapy alone can be high—60% to 80%<sup>42</sup>—particularly if emphysematous pyelonephritis is not recognized early. Nephrectomy reduces mortality to

20%<sup>42</sup> and may be necessary if there is extensive destruction of the kidney or if patients do not respond clinically to antibiotics. If involvement is localized and patients are clinically stable, radiologically guided percutaneous drainage may be an alternative.<sup>47</sup> Based on retrospective outcome data in 48 patients and by using CT imaging, investigators in one study developed treatment recommendations depending on the location and extension of the gas or abscess and presence of concomitant organ failure (eg, shock, disseminated intravascular coagulopathy, or renal failure).<sup>46</sup> Percutaneous drainage and antibiotics were recommended as sufficient if there was no extension of gas or purulence to the extrarenal space. In the setting of pararenal or perinephric space involvement without organ dysfunction, percutaneous drainage with antibiotics could be tried initially, with nephrectomy recommended if this treatment was unsuccessful.

**Emphysematous Cystitis.** Emphysematous cystitis is a rare complication of acute cystitis that occurs predominantly in patients with diabetes.<sup>48</sup> It is confined to the lower urinary tract and is associated with better prognosis than emphysematous pyelonephritis. The most common etiologic agent is *E coli*, but other causative pathogens, such as *Klebsiella*, other gram-negative organisms, and *Candida*, also have been reported. Patients present with symptoms typical of acute cystitis, such as fever, dysuria, and flank pain, often along with chronic abdominal pain. Findings suggestive of the diagnosis are gross hematuria, pneumaturia, and air seen in the bladder wall or lumen on CT scan (Figure 2). Unlike the case of emphysematous pyelonephritis, directed antimicrobial therapy is usually sufficient for cure.

#### SKIN AND SOFT TISSUE

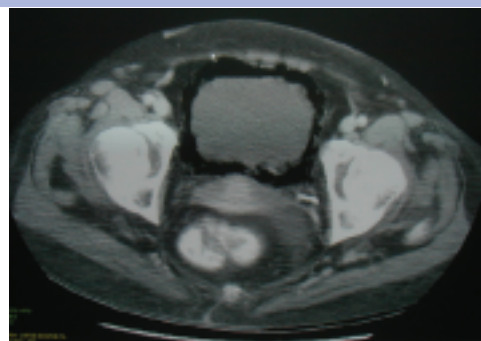
**The Diabetic Foot.** The most common soft-tissue infections in patients with diabetes are foot infections.<sup>49</sup> These patients are particularly prone to foot infections because of several factors. First, paronychia and tinea pedis facilitate the entry of pathogens that cause invasive infection. Second, peripheral neuropathy is present in about 50% of patients with long-standing diabetes<sup>50</sup>; because of undetected injury in these patients, foot ulcers and infections are common after minor trauma and can have severe repercussions (such as osteomyelitis and amputation) if left unchecked. Amputation is eventually necessary for about 10% to 30% of patients with a foot ulcer,<sup>51</sup> and more than half of nontraumatic limb amputations occur in individuals with diabetes.<sup>42</sup> Microvascular and macrovascular peripheral vascular (arterial) disease can result in a reduction of blood supply to infected areas of the diabetic foot; adequate blood supply is important both for wound healing and for the effective deliv-

ery of antibiotics. Finally, hyperglycemia itself results in poor neutrophil function, which can further compromise wound healing.

Foot infections in patients with diabetes can be categorized as mild (non-limb-threatening) or severe (limb-threatening). Mild infections present as shallow ulcers with less than 2 cm of surrounding cellulitis. Patients have no evidence of systemic toxicity. Gram-positive cocci, such as *S aureus* and streptococci, are the main etiologic pathogens, and therapy should not be based on isolation of polymicrobial flora if a superficial swab of the nondebrided wound or its drainage is performed. Obtaining deep-tissue cultures (via curettage or biopsy) to help guide therapy is recommended when possible. However, cultures of infected wounds may not be necessary if the infection is mild and the patient is antibiotic-naïve.<sup>35</sup> Examination of a diabetic foot ulcer with a sterile probe is a fairly specific test for osteomyelitis, with osteomyelitis ruled in if bone can be probed, although this test is not useful for ruling out disease.<sup>52</sup> If abnormality is evident on a plain-film radiograph, further confirmation of osteomyelitis should be pursued with an indium-labeled leukocyte scan and/or 3-phase technetium-99 bone scan, MRI, or percutaneous biopsy.

An oral antibiotic targeting gram-positive organisms (eg, cephalexin, dicloxacillin, or clindamycin) is generally sufficient for mild diabetic foot ulcers (Table 2).<sup>35</sup> Aggressive wound care also must be a priority. Outpatient care is reasonable if there is good home support and close follow-up, starting 48 hours after initiation of therapy and repeated every few days initially. Guidelines endorsed by the Diabetes Committee of the American Orthopaedic Foot and Ankle Society recommend referral to an infectious disease consultant if there

Figure 2. Emphysematous Cystitis in a Patient With Diabetes



Computed tomography scan demonstrating multiple gas pockets surrounding the urinary bladder.  
Courtesy of Benjamin M. Yeh, MD, Department of Radiology, University of California at San Francisco.

is failure of timely response to empiric therapy, confusing or atypical identification of the infectious process, or the need for culture-specific antibiotic therapy with increased potential for renal or hepatic toxicity.<sup>50</sup>

Severe diabetic foot infections present as deep ulcers with more than 2 cm of adjacent cellulitis. There may be evidence of inflammation distant from the skin wound, and appropriate outpatient therapy may have failed.<sup>51</sup> Patients may be sicker, with evidence of systemic toxicity, ischemia, and poor glucose control. These infections are often polymicrobial, and empiric antibiotic therapy should target gram-positive organisms (eg, *S aureus*), anaerobes (eg, *Bacteroides fragilis*), and gram-negative organisms (eg, *E coli*).

Patients with severe diabetic foot ulcers should be hospitalized and receive intravenous broad-spectrum antibiotic therapy, such as ampicillin-sulbactam or piperacillin-tazobactam. Vancomycin generally is added in life-threatening infections or if there is high probability of methicillin-resistant *S aureus* (Table 2).<sup>35</sup> Wound care should be performed in consultation with a surgical specialist. Guidelines from the Infectious Diseases Society of America recommend surgical consultation for infections associated with a deep abscess, significant joint or bone involvement, skin necrosis or gangrene, crepitus, and suspected necrotizing fasciitis.<sup>35</sup> If the patient is taken to the operating room for debridement or amputation, bone or tissue cultures from deep tissue are recommended so that antimicrobial therapy can be more specifically targeted. About 50% to 60% of severe foot infections are complicated by osteomyelitis.<sup>51</sup> Positive bone cultures are diagnostic of osteomyelitis, which necessitates 4 to 6 weeks of antibiotic therapy. In the absence of osteomyelitis, 2 weeks of antibiotics may be sufficient. In patients with localized osteomyelitis, limited amputation (eg, digit amputation) may preserve a weight-bearing surface and allow for a shorter (2-week), less expensive course of antibiotics.

Although their effectiveness is not well proved, certain adjunctive therapies have improved outcomes in patients with diabetic foot infection in at least one randomized controlled trial. These therapies include hyperbaric oxygen, edema control with a pneumatic pedal compression device, and subcutaneous injection of granulocyte colony-stimulating factor. Maggot therapy is being used at several centers but has been less thoroughly studied.<sup>51</sup>

**Necrotizing Fasciitis.** Necrotizing fasciitis is a serious infection characterized by extensive tissue destruction, systemic toxicity, and a mortality rate of about 40%.<sup>53,54</sup> It should be evaluated and treated as an emergency. Different terminology exists, but all variants of necrotizing fasciitis have a common pathophysiology. Infection begins in the subcutaneous tissue and then rapidly extends along fascial planes, most commonly in

the arms, legs, and abdominal wall. The type I variant (90% of cases)<sup>55</sup> is more common in patients with diabetes and is caused by mixed anaerobic (eg, *Peptostreptococcus* species, *Prevotella* and *Porphyromonas* species, *Bacteroides fragilis*, and *Clostridium* species) and aerobic (eg, *S aureus*, *E coli*, and group A streptococci) bacteria. Type II necrotizing fasciitis (10% of cases) is caused predominantly by group A streptococci, sometimes with coinfection with staphylococcal species.

It has not been established whether necrotizing fasciitis occurs more commonly in patients with diabetes than in those without diabetes, but 2 variants are known to have a predilection for patients with diabetes. One of these variants is synergistic necrotizing cellulitis (SNC), a particularly severe form of necrotizing fasciitis characterized by extensive involvement of muscle as well as skin, fat, and fascia. An estimated 75% of patients with SNC have diabetes.<sup>42</sup> Another variant is Fournier's gangrene, which refers to necrotizing fasciitis of the male genitalia. It usually involves the scrotum, where gangrene can develop rapidly, and may advance into the penis, perineum, and abdominal wall. Approximately 40% to 60% of patients with Fournier's gangrene have diabetes, although the diabetes may not be recognized prior to this diagnosis.<sup>42</sup>

Patients with necrotizing fasciitis may present with localized pain, erythema, bullous lesions, and crepitus, commonly in the perineum or lower extremities, especially the feet. Patients with Fournier's gangrene may present with scrotal discomfort for several days before progressing to erythema, edema, and skin necrosis. A definitive diagnosis of necrotizing fasciitis often can be made only after surgical exploration, which should not be delayed.

The treatment of choice is extensive surgical debridement, and patients with Fournier's gangrene may require cystostomy or orchiectomy. Empiric antibiotic therapy should be administered intravenously and should include ampicillin with or without sulbactam, plus metronidazole or clindamycin. If the patient has recently been hospitalized or treated with antibiotics, broader-spectrum therapy with piperacillin-tazobactam plus metronidazole or clindamycin is indicated. Antibiotic therapy should be modified after a review of blood and/or tissue cultures. In type II necrotizing fasciitis caused by group A streptococci, clindamycin has been shown to be superior to beta-lactams. This is thought to be due in part to the ability of clindamycin to suppress toxin production.<sup>56</sup> Despite appropriate intervention, outcomes in patients with necrotizing fasciitis are poor, with 20% to 30% mortality in patients with Fournier's gangrene and up to 60% mortality in patients with SNC.<sup>42</sup>

**Dermatophyte (Tinea) Infections.** Superficial fungal infections of the skin and nails are common problems



that can affect normally healthy individuals. *Trichophyton*, *Epidermophyton*, and *Microsporum* species account for the majority of cases that have location-specific names (eg, tinea capitis [scalp], tinea corporis [body], tinea cruris [groin], tinea pedis [feet], and onychomycosis [nails]). Limited information is available regarding whether these infections are more common in patients with diabetes compared with the general population. One study sampled 550 patients with and 2001 patients without diabetes attending dermatology clinics in Ontario, Canada, and in Boston, Massachusetts, and reported an increased adjusted odds for onychomycosis of 2.77 in patients with diabetes compared with those without diabetes (95% CI, 2.15-3.57).<sup>57</sup>

Lesions may vary by site, organism, and underlying immune status of the host, but the typical lesion is a pruritic, scaly ring of erythema with central clearing. Tinea pedis commonly presents with asymptomatic scaling on the sole and heel, which may extend over the sides of the feet in a moccasin-like distribution. This presentation may progress to scaling or fissuring of the toe webs, which may become secondarily infected with bacteria, commonly causing cellulitis. Onychomycosis may present as white, yellow, or brown discoloration of a distal corner of the nail that may eventually extend toward the cuticle. Nails become hypertrophic and brittle, and multiple nails are commonly infected. Potassium hydroxide examination of scrapings from any suspected dermatophytic infection will confirm the diagnosis and rule out other potential diagnoses, such as eczema.

Several therapeutic options exist for dermatophyte infections. Topical antifungal creams, such as clotrimazole, can be used to treat tinea corporis, tinea cruris, and tinea pedis if disease is limited and uncomplicated.<sup>58</sup> Griseofulvin is a safe and effective oral agent for treating all dermatophytic infections except onychomycosis. Itraconazole and terbinafine are effective systemic treatment options for onychomycosis because they persist in the nail plate for up to 6 months.<sup>59</sup> Fluconazole is less effective compared with itraconazole or terbinafine for the treatment of dermatophytosis.

Regardless of whether superficial fungal infections are more common in patients with diabetes, it is important to screen for and treat these common infections. Tinea pedis is an important risk factor for leg cellulitis in all individuals. Thick and distorted nails resulting from onychomycosis may abrade and puncture adjacent skin, increasing the risk of infected ulcers, particularly given the peripheral neuropathy and vascular insufficiency common in patients with diabetes. Some general measures that can be taken to prevent dermatophytosis include drying skin carefully after bathing or perspiring heavily, with the use of talc and other powders as necessary.

## PREVENTION—GENERAL CONSIDERATIONS

Because many patients with diabetes who develop infections have poor outcomes, strategies to prevent infection are of great importance. Glycemic control, widely appreciated for preventing microvascular and macrovascular sequelae of diabetes, has been demonstrated in a retrospective study<sup>60</sup> and in a prospective cohort study<sup>61</sup> to decrease the incidence of infection in patients with diabetes after cardiac surgery. In one prospective study of 761 patients who underwent coronary artery bypass surgery, a continuous insulin drip protocol was associated with a decline in the incidence of wound infections in patients with diabetes compared with the period before the protocol was introduced.<sup>62</sup> Compared with standard insulin therapy, aggressive insulin therapy during cardiopulmonary bypass surgery also improves postoperative neutrophil function in patients with diabetes.<sup>63</sup>

Prophylactic foot care in patients with diabetes decreases morbidity, use of expensive resources, and risk of amputation and premature death.<sup>50</sup> Screening of patients at risk for diabetic foot complications should include evaluation for peripheral neuropathy, skin integrity, ulcers or wounds, structural deformity, vascular insufficiency, and improper footwear (eg, shoes are tight, have inadequate toe box, or provide no means to adjust the instep with laces or straps). Patients should be educated not to walk barefoot, not to use corn or callus removers, and to care for their feet carefully (bathe the feet daily and dry thoroughly, clean around the nails with a soft brush; use oil, lotion, or lanolin cream to avoid dryness; and wear socks that absorb perspiration).

As discussed above, vaccinations elicit normal humoral responses in patients with diabetes, and pneumococcal and influenza vaccines should be administered in all of these patients.<sup>31,32,64</sup>

## FUTURE RESEARCH

Further studies need to elucidate the specific biological mechanisms underlying the increased susceptibility of patients with diabetes to infectious agents, as well as to understand why these patients have an increased risk of complications such as pneumococcal bacteremia. Large population-based studies of diabetes complications also need to include and assess various infectious diseases as outcomes. The impact of therapy and preventive measures, such as tight glycemic control, on other infectious outcomes (other than postsurgical complications) also needs to be studied.

## CONCLUSION

Longer life expectancy and greater prevalence of obesity in the United States are expected to lead to a growing incidence of diabetes mellitus. Primary care clinicians often will treat patients who have symptoms of dia-

betes-associated infections, some of which are subtle. Anticipating serious complications of common infections in patients with diabetes is as important as appreciating rare disease entities that affect these patients disproportionately. Early diagnosis and aggressive treatment should be rigorously pursued to reduce morbidity and mortality in this vulnerable population.

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