Serious Infections in Elderly Patients with Diabetes Mellitus

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The elevated serum glucose levels associated with diabetes mellitus (DM) alter host immune responses, resulting in a well-documented increase in the predisposition to infectious processes. Furthermore, the cumulative effect of age-related immune senescence, superimposed on this enhanced risk of infections, can lead to serious and life-threatening infections in elderly patients with DM. Because infection associated with aging can frequently present in a subtle and atypical manner, prompt recognition of infection and treatment with appropriate empirical broad-spectrum antimicrobial agents, in conjunction with surgical intervention, is often necessary to eradicate such infections. Common sites of serious infection associated with DM include the head and neck, biliary tract, and urinary tract, as well as the skin, soft tissue, and bony structures of the feet in particular.

Diabetes mellitus (DM) is a common disease that affects 7%–8% of the overall adult population of the United States [1]. DM occurs in 18% of persons between the ages of 65 and 75 years and in as many as 40% of persons >80 years old; in addition, 23% of persons aged 65–70 years have impaired glucose tolerance, and nearly 50% of cases in elderly individuals with DM remain undiagnosed [2, 3]. Some investigators have linked persistently elevated glucose levels in individuals with DM to the subsequent development of infection and/or to the inability to control established infection [4]. Although optimal glycemic control contributes to the prevention of common and life-threatening infections associated with DM, the enhanced susceptibility to infection has also been attributed to defects in both cell-mediated immunity (CMI) and humoral immunity [5]; furthermore, immune senescence, which occurs as a result of aging and which predominantly affects CMI, results in increased risk for intracellular bacterial, mycobacterial, fungal, and viral infections [6, 7]. Clinical experience has clearly demonstrated that elderly individuals with DM are especially susceptible to infection. Although infections in elderly individuals with DM seem to be no different from those encountered by their younger counterparts, the combination of immune system deficits that can potentially result from DM and aging can presumably lead to serious and life-threatening complications of infection. Moreover, because a significant number of infections in elderly individuals are known to present in a subtle and atypical manner, prompt recognition and treatment with appropriate empirical broad-spectrum antimicrobial agents in conjunction with surgical intervention is often essential to eradicate such infections [4]. Minimal data exist regarding the pathophysiologic basis of the enhanced susceptibility to infection in elderly individuals with DM, and these data need to be systematically evaluated. I will briefly highlight immune defects that result in an increased susceptibility to infections and that occur due to DM and aging, and I will focus on the unique aspects of specific serious infections that are predominantly encountered in this particular elderly population (table 1).

AGING, DM, AND IMMUNE FUNCTION

Most studies evaluating the effects of aging on immune function have largely focused on the CMI system. Although the total number of T lymphocytes remains constant with age, functional changes in various subsets have been demonstrated [7–10]. The ability of aging T cells to secrete IL-2 (which stimulates the proliferation and differentiation of other T cell clones) is diminished; this functional effect, however, does not consistently affect all T cell subsets. The proportion of naive T cells (i.e., T cells that respond to new antigens) decreases as thymic involution occurs, with a reduction in the production of thymic hormones. As a result, most T cells in elderly persons have already had prior antigenic exposure (i.e., they are mem-
Table 1. Effects of aging and diabetes mellitus on the immune system.

<table>
<thead>
<tr>
<th>Immune function</th>
<th>Aging</th>
<th>Diabetes mellitus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocyte response</td>
<td>No documented alteration</td>
<td>Polymorphonuclear leukocytes, monocytes, and lymphocytes demonstrate a decrease in adherence, chemotaxis, and intracellular killing</td>
</tr>
<tr>
<td>Cell-mediated immunity</td>
<td>Functional change in T cell subsets, with a decrease in IL-2 secretion</td>
<td>Cell-mediated immune responses are reduced, with a decrease in proliferative response to phytohemagglutinin and <em>Staphylococcus aureus</em></td>
</tr>
<tr>
<td>Delayed-type hypersensitivity responses</td>
<td>Naive T cells have decreased ability to respond to new antigens</td>
<td>Abnormal delayed-type hypersensitivity responses</td>
</tr>
<tr>
<td>Humoral immunity</td>
<td>Humoral immunity mildly affected</td>
<td>Humoral immunity remains relatively intact</td>
</tr>
<tr>
<td>Immunoglobulin levels</td>
<td>Overall immunoglobulin levels remain constant; IgM, IgG, and IgG subsets vary with aging</td>
<td>No documented alteration</td>
</tr>
</tbody>
</table>

**NOTE.** Data are adapted from [5–17].

ory T cells), thus explaining why elderly individuals respond to antigens encountered previously but not to new antigens [8, 9]. This phenomenon may also explain the enhanced propensity for reactivation of infection with intracellular pathogens, such as *Mycobacterium tuberculosis* and varicella-zoster virus [11]. During aging, humoral immunity is relatively unaffected, with the exception of B cell functions that are mediated with the cooperation of T-helper cells. Overall, immunoglobulin levels remain constant with age, but their proportions may change with an increase in IgG or IgM levels and various changes in IgA levels [12, 13]. These changes may explain the lack of vigorous response to certain immunizations (e.g., pneumococcal and influenza vaccinations) [14, 15].

In patients with DM, abnormalities in polymorphonuclear neutrophils (PMNs), monocytes, and lymphocytes related to adherence, chemotaxis, opsonization, ingestion of bacteria, oxidative burst, and intracellular killing have been described [2, 16]. Decreased neutrophil chemotaxis has recently been documented among both individuals with type I DM and those with type II DM, confirming previous studies [17]. Diminished neutrophil bactericidal activity associated with increased levels of glycated hemoglobin has been attributed in part to the degree and duration of hyperglycemia and may be reversed with optimal glycemic control [16]. Hyperglycemia or the presence of advanced glycation end products is believed by some researchers to lead to a state of low-level, persistent activation in PMNs. This observation has been evidenced by an increased concentration of neutrophil elastase, increased activity of neutrophil alkaline phosphatase and luminol-dependent chemiluminescence, and an increased rate of oxygen consumption among unstimulated PMNs in patients with DM [17, 18]. This hyperexcited state leads to spontaneous activation of the oxidative burst and release of myeloperoxidase, elastase, and other neutrophil granule components. This process may, in turn, lead to a “burned-out” or tolerant PMN that responds less vigorously when stimulated by an infectious pathogen, initiating pathologic processes leading to vascular injury. Resting levels of cytokines (e.g., TNF-α, IL-6, and IL-8) are elevated in individuals with DM, but on stimulation, the cells produce less IL-1 and IL-6 than do similar cells in control subjects. In addition, abnormalities in monocyte and macrophage chemotaxis and phagocytosis have been reported [2]. Adaptive cellular immunity does appear to be affected, however, with decreased lymphocyte proliferative response to stimulants (e.g., phytohemagglutinin) and certain pathogens (e.g., *Staphylococcus aureus*) but normal response to others (e.g., *Candida albicans*) [19]. Abnormal delayed-type hypersensitivity responses have also been described in individuals with DM. Humoral immunity appears to be normal, with normal levels of immunoglobulins and normal response to vaccinations [2]. Table 1 compares immune-system defects that commonly occur as a result of aging with those that occur as a result of DM.

**UNIQUE ASPECTS OF INFECTION IN ELDERLY PATIENTS WITH DM**

Although many elderly individuals demonstrate clinical manifestations consistent with infection (e.g., fever, chills, and leukocytosis), a significant number of geriatric patients will present with atypical features that may be nonspecific, blunted, or absent (e.g., weakness, malaise, and/or confusion) and that are often the only manifestation of the illness [20]. Clinicians must consider 3 key factors that can influence presentation of infections in elderly individuals: underreporting of illnesses because of cultural, ethnic, and educational background, depression, cognitive impairment, or denial; changing patterns of illness (e.g., susceptibility to infections caused by microbial pathogens, such as gram-negative rods, mycobacteria, and viruses); and altered clinical responses, as mentioned above. Common infections in elderly individuals with DM are similar to those encountered in younger individuals with DM; a list of such infections is given in table 2. Specific serious and life-threatening DM-related infections of importance to elderly individuals will be reviewed below. Detailed discussions of other
Abdominal Emphysematous cholecystitis, for the pathogen at lower pH levels [23]; lack of serum inhibitory activity against this predilection and include the enhanced availability of iron this infection. Various hypotheses have attempted to explain it is present in only this infection. An estimated 50%–75% of cases of rhino-cerebral mucormycosis occur in patients with DM, including elderly individuals [21, 22]. Although this infection does occur at all ages, there is a tendency for patients with this infection to be >45 years old. To our knowledge, there are no studies that specifically evaluate this infection in elderly individuals with DM. A variety of pathogens may be associated with this condition, the most common being in the family Mucoraceae, including Rhizopus, Absidia, and Mucor species. Ketoacidosis is thought to be the most likely predisposing factor, although it is present in only ∼50% of the patients with DM who have this infection. Various hypotheses have attempted to explain this predilection and include the enhanced availability of iron for the pathogen at lower pH levels [23]; lack of serum inhibitory activity against Rhizopus species at lower pH levels [24]; and pulmonary macrophages of individuals with DM showing diminished ability to prevent germination of Rhizopus species [25]. The pathogenesis of the disease probably starts with inhalation of the fungus into the paranasal sinuses. On germination, the fungus may spread inferiorly to invade the palate, posteriorly to invade the sphenoid sinus and spread into the cavernous sinus, laterally to involve the orbits, or superiorly to invade the brain. Initial symptoms and signs may include fever, headache, facial pain or swelling, ocular pain or periorbital swelling, or nasal stuffiness that may be accompanied by a discharge. Elderly patients may manifest infection with low-grade fever and altered level of consciousness (frequently confused with dementia or delirium attributable to other causes). A black eschar may be visible in the nasal mucosa or the palate of ∼40% of patients, which results from the ischemic necrosis of tissues after vascular invasion of the fungus [26]. The invasion progresses rapidly and may lead to proptosis, ophthalmoplegia, and loss of vision caused by involvement of the orbit. Other cranial nerve palsies caused by involvement of the cavernous sinus or massive stroke caused by occlusion of the carotid artery may also result. Early diagnosis and treatment of this condition in elderly patients with DM is critical to limit invasion of the fungus and the accompanying morbidity and mortality. 

**Rhinocerebral mucormycosis: diagnosis and management.** Radiological studies, such as CT or MRI, may show intracranial extension or nodular thickening of the sinus lining with spotty destruction of its bony walls; air-fluid levels are typically not seen. The definitive diagnosis is established by the demonstration of the characteristic broad, nonseptate hyphae with right-angle branching on a potassium hydroxide preparation. Rapid and wide surgical debridement is an essential therapeutic modality and should be accompanied by high-dose amphotericin B therapy (1–1.5 mg/kg per day); the newer lipid formulations of amphotericin B enable higher doses with lower systemic toxicity [27]. The role for the newer azole antifungal agents (e.g., posaconazole and ravuconazole), echinocandins (e.g., caspofungin and micafungin), or fluconazole in treating this infection needs to be further investigated. An increase in the trends of zygomycoses has been reported among immunocompromised patients who received voriconazole for the treatment of infections due to Aspergillus species [28]. Greenberg et al. [29] studied 23 cases of zygomycosis in patients who were intolerant of or refractory to standard therapies; posaconazole therapy was found to be successful in 70% of cases. However, many patients in this study [29] also underwent surgical ther-

### Table 2. Infections in elderly patients with diabetes mellitus.

<table>
<thead>
<tr>
<th>Site of infection</th>
<th>Common infections</th>
<th>Serious and predominant a infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head and neck</td>
<td>Oral candidiasis, esophageal candidiasis</td>
<td>Rhinocerebral mucormycosis, b malignant otitis externa b</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>Bacteriuria and cystitis (women), pyelonephritis, renal/perinephric abscess</td>
<td>Emphysematous cystitis, b emphysematous pyelitis, emphysematous pyelonephritis b</td>
</tr>
<tr>
<td>Skin, soft tissue, and bone</td>
<td>Surgical wound infection, foot infections, osteomyelitis</td>
<td>Synergistic necrotizing cellulitis, b Fournier gangrene b</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Tuberculosis, Staphylococcus aureus pneumonia, pneumonia due to gram-negative pathogens</td>
<td>...</td>
</tr>
<tr>
<td>Abdominal</td>
<td>Emphysematous cholecystitis, Salmonella enteritidis infection, Campylobacter jejuni infection, Listeria monocytogenes infection</td>
<td>...</td>
</tr>
</tbody>
</table>

**NOTE.** Data are modified from [1].

a Predominant infections were defined as those in which >50% of cases occurred in individuals with diabetes mellitus.

b Specific serious infections discussed in this article.
apy, complicating accurate assessment of the role of posaconazole therapy in the favorable outcome. Another trial evaluating the safety and efficacy of posaconazole treatment in elderly patients with invasive fungal infections [30]. Untreated, the disease is universally fatal, but aggressive surgery and long-term therapy with amphotericin B can lead to a mortality rate as low as 16.7% [31–33]. The usefulness of other therapies, such as hyperbaric oxygen therapy and therapy with granulocyte colony-stimulating factor, remains to be determined [31, 32].

**Malignant otitis externa: predisposition and clinical characteristics.** An invasive virulent form of external otitis known as malignant otitis externa has a particular predilection for elderly patients with DM. This necrotizing vasculitic infection is most commonly associated with *Pseudomonas aeruginosa* and has a mean age of onset of ∼69 years [1]. The vast majority (∼90%) of patients with this condition are diabetic [22]; predisposing factors include poor glucose control, swimming, greater age, hearing aid use, and ear irrigation with nonsterile water [19]. Patients present with persistent external otitis with severe and unrelenting ear pain, presence of extensive granulation tissue in the canal, clinical or radiological evidence of erosion of the canal, and isolation of *P. aeruginosa* from samples of the canal debris [26]. The organism gains entry into the temporal bone by way of the cartilaginous junction of the canal, with involvement of the facial nerve at the stylomastoid foramen ∼30%-40% of the time [14]. The temporomandibular joint, mastoid air cells, the base of the skull (presenting as palsies of cranial nerves IX–XII), sigmoid sinus, or meninges may be involved as a consequence [21]. Extensive intracranial involvement can result in a mortality rate of ∼30%; this highlights the importance of rapid diagnosis and treatment [34].

**Malignant otitis externa: diagnosis and management.** The preferred diagnostic radiological modality is MRI with gadolinium because it allows evaluation of the extent of the soft-tissue and bone involvement [21]. CT scan may also be useful; radionuclide studies, such as technetium or gallium scans, can demonstrate early evidence of temporal bone osteomyelitis [35]. Surgical debridement of necrotic tissue with biopsy and culture of the deep tissue is essential to determine the susceptibility pattern of the organism, because long-term antimicrobial therapy is usually indicated. Empirical antibiotic therapy using an antipseudomonal penicillin, cephalosporin, or fluoroquinolone with or without an aminoglycoside is generally indicated; therapy should be administered for a total of 6–8 weeks. Aminoglycosides must be used with caution in elderly individuals with DM and accompanied by careful monitoring of renal function. Gallium scans and erythrocyte sedimentation rates may be useful to document response and ensure adequate duration of therapy [35]. Oral ciprofloxacin therapy may be appropriate and safe for selected patients with mild cases [36].

**Genitourinary Tract Infection**

The frequency of urinary tract infections in elderly individuals with DM, compared with their frequency in elderly individuals who are not diabetic, has not been clearly documented. Moreover, the prevalence of bacteriuria in the geriatric population is high (often as high as 50%), and it may be difficult to determine whether DM could influence an elderly patient’s risk for this infection [37]. The vast majority of elderly patients with bacteriuria do not have urinary symptoms; when symptoms are present, they are difficult to interpret, because uninfected elderly subjects commonly experience dysuria, urgent urination, frequent urination, and incontinence. Moreover, elderly patients with indwelling bladder catheters generally have no symptoms. In addition, complicated forms of urinary tract infection (e.g., emphysematous cystitis, pyelonephritis, and perinephric abscesses) appear to occur more frequently among older individuals with DM than among those without DM.

**Emphysematous cystitis: predisposition and clinical characteristics.** This is an extremely rare complication of lower urinary tract infection that occurs largely in individuals with DM. This complication results from primary infection of the bladder and most commonly occurs due to *Escherichia coli*, but many other pathogens, including *Enterobacter*, *Proteus*, *Klebsiella*, and *Candida* species, have also been reported [38]. Patients with this complication are not as acutely ill as are patients with emphysematous complications of the upper urinary tract, and they present with symptoms typical of urinary tract infection (e.g., fever, chills, dysuria, and frequent and urgent urination), often accompanied by chronic abdominal pain.

**Emphysematous cystitis: diagnosis and management.** Unusual findings that suggest the diagnosis include gross hematuria and pneumaturia and radiographic findings demonstrating air in the bladder wall or lumen [39]. Unlike other emphysematous complications, this cystitis will often respond to antimicrobial agents alone that are directed toward the most common organisms, pending urine culture and susceptibility testing results.

**Diagnosis and Management**

Although plain radiography may demonstrate gas in the kidney ∼85% of the time, CT is the preferred diagnostic radiological modality to enable the localization of the gas to the renal parenchyma and the perinephric space of the renal collecting system [40–45]. If gas is found only in the renal collecting system, the disease is termed “emphysematous pyelitis,” and medical therapy with relief of obstruction, if present, is usually sufficient. Mortality from emphysematous pyelonephritis treated with medical therapy alone is 60%–80%. Nephrectomy
Emphysematous pyelonephritis is more commonly associated with bacteremia and shock in elderly patients than in younger individuals [40]. In addition, in elderly individuals, complications from pyelonephritis, such as perinephric abscesses, appear to occur more frequently than pyelonephritis alone [41]. The emphysematous form of pyelonephritis, a complication of upper urinary tract infection associated with gas in the renal parenchyma or in the perinephric space, is almost exclusively encountered in individuals with DM, who account for 70%–90% of all cases [38]. Moreover, of the 53 cases reported in one study [42], 23 patients (43%) were >60 years old (mean age, 56 years). This process results from a severe form of acute multifocal bacterial nephritis in which *E. coli* is the most commonly implicated pathogen, followed by other enteric gram-negative bacilli, such as *Enterobacter aerogenes*, *Klebsiella* species, and *Proteus* species [38]. *Streptococcus* and *Candida* species have been infrequently reported as causes [38, 40, 41]. Women are twice as likely as men to develop emphysematous pyelonephritis, and obstruction is a common predisposing factor. In addition to the usual clinical findings seen in pyelonephritis, patients present with a flank mass in ~59% of cases; less frequently, crepitus is demonstrable over the flank.

### Treatment of serious infections in elderly patients with diabetes mellitus

<table>
<thead>
<tr>
<th>Site of infection, infection(s)</th>
<th>Treatment(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Head and neck</strong></td>
<td></td>
</tr>
<tr>
<td>Rhinocerebral mucormycosis</td>
<td>Surgical debridement and amphotericin B therapy (lipid formulations may be used); the efficacy of new antifungal agents, including the triazole posaconazole and the echinocandin caspofungin, needs further evaluation; the efficacy of hyperbaric oxygen and granulocyte colony-stimulating factor needs further evaluation</td>
</tr>
<tr>
<td>Malignant otitis externa</td>
<td>Antipseudomonal penicillin, cephalosporin, or fluoroquinolone with or without an aminoglycoside</td>
</tr>
<tr>
<td>Urinary tract</td>
<td></td>
</tr>
<tr>
<td>Emphysematous cystitis, emphysematous pyelitis, emphysematous pyelonephritis</td>
<td>Antimicrobial therapy with fluoroquinolones, third- or fourth-generation cephalosporins with or without antianaerobic agents (clindamycin or metronidazole or β lactam–β lactamase inhibitor combination agents)</td>
</tr>
<tr>
<td>Skin, soft tissue, and bone</td>
<td></td>
</tr>
<tr>
<td>Synergistic necrotizing cellulitis/fasciitis</td>
<td>Surgical debridement and broad-spectrum antimicrobial therapy to cover mixed infection with gram-positive, gram-negative, and anaerobic pathogens (e.g., therapy with penicillin and clindamycin); the efficacy of hyperbaric oxygen for necrotizing skin and soft-tissue infections needs further evaluation</td>
</tr>
<tr>
<td>Fournier gangrene</td>
<td>Treatment is similar to that for necrotizing cellulitis and fasciitis, with the addition of therapy to cover infection with gram-negative pathogens because of possible infection with fecal coliforms (e.g., therapy with fluoroquinolones or aminoglycosides); the efficacy of hyperbaric oxygen for necrotizing skin and soft-tissue infections needs further evaluation</td>
</tr>
</tbody>
</table>

Several complicated skin and soft-tissue infections occur more frequently in individuals with DM than in the general population. Because of peripheral neuropathy, trauma, and peripheral vascular disease, mixed anerobic-aerobic soft-tissue infections (e.g., synergistic necrotizing cellulitis, necrotizing fasciitis, Fournier gangrene, and foot ulcers) are common in this population. The frequency of these infections is higher among older individuals with DM, compared with their younger counterparts, and the frequency and severity (and associated morbidity and mortality) of these infections are also higher [47].

Synergistic necrotizing cellulitis is actually a misnomer, because it represents a severe form of necrotizing fasciitis in which involvement of the underlying muscles is frequent and extensive. It is estimated that ~75% of patients with this condition have DM [48]. Many patients initially present with a subacute course but eventually experience disease progression and become ill and ketoacidotic. The most commonly affected areas include the perineum and lower extremities, and the classic clinical presentation is severe pain in the affected soft tissues in which the skin has limited areas of necrosis with small ulcers draining a discolored, foul-smelling fluid; intervening areas of skin may appear normal.
isolation being gram-negative bacilli, anaerobic streptococci, and Bacteroides species. Therefore, despite the absence of gas in the soft tissues, emergent surgical intervention is essential once such severe necrotizing infection is clinically recognized [49, 50]. The infection is life threatening, and immediate extensive and wide surgical debridement is necessary, with accompanying broad-spectrum antibiotic therapy. Despite appropriate therapy, however, there is still a mortality rate of ~60% [49, 50]. It has not been clearly elucidated whether individuals with DM experience necrotizing fasciitis more often than do individuals without DM, but the microvascular complications of DM lead to chronic open wounds that can predispose to type II—or mixed type—necrotizing fasciitis. One area of involvement with necrotizing fasciitis that does seem to have a specific predilection for individuals with DM is the male genitalia, and the infection referred to as Fournier gangrene. An estimated 40%–60% of patients with Fournier gangrene have DM, but some of these individuals may not have been recognized as having DM before receiving a diagnosis of Fournier gangrene [49, 50]. Predisposing genitourinary or colorectal pathologies are found in most cases, especially in debilitated elderly patients; these pathologies include urethral strictures with leaking of urine, urinary tract trauma caused by instrumentation, incontinence, perianal fissure or abscess, and chronic disease or trauma of the perineal skin [51]. Patients generally present with scrotal discomfort of several days duration, which progresses to erythema and edema and, eventually, to necrosis of the skin. Depending on the initiating source, the infection may extend up the abdominal wall or to the buttocks or thighs. Extensive debridement is indicated, but orchectomy and penile amputation can generally be avoided because of the alternative blood supplies of the testes and corpora [51]. The infection is usually polymicrobial and includes pathogens such as gram-negative bacilli, Clostridium species, aerobic and anaerobic streptococci, and Bacteroides species. In spite of appropriate therapy, mortality is 20%–35%, and there has been no improvement in the mortality rates during the past 10 years [51]. Table 3 outlines serious infections in elderly patients with DM and lists various recommended therapeutic modalities.

Because infections in elderly patients with DM can be severe and life threatening, clinicians must be cognizant of atypical manifestations of illness and maintain a high index of suspicion for various infectious processes common to this population. Prompt recognition and treatment of such infections with broad-spectrum antimicrobial agents are critical to lower morbidity and mortality in this vulnerable population.

Acknowledgments

Potential conflicts of interest. S.R.: No conflicts.


