50 Diabetes and Infections

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Keypoints

- Diabetes is associated with an increased overall risk of infections.
- The presence of diabetes also modifies the course of many infections and increases morbidity and mortality.
- Multiple disturbances in innate immunity have a role in the pathogenesis of the increased prevalence of infections in people with diabetes.
- Impaired phagocytosis by neutrophils, macrophages and monocytes, impaired neutrophil chemotaxis and bactericidal activity, and impaired innate cell-mediated immunity appear to be the most important disturbances of the immune system.
- Humoral immunity appears relatively unaffected, hence plasma levels of antibodies and responsiveness to vaccination are relatively unaffected.
- In general, better regulation of the diabetes leads to an improvement in cellular immunity and function.
- Increased skin and mucosal carriage of *Staphylcoccus aureus* and *Candida* species may increase risk of infection with these organisms.
- Some microorganisms become more virulent in a high glucose environment; examples include certain *Klebsiella* serotypes and *Burkholderia pseudomallei*.
- Viral infections such as hepatitis C are associated with a higher prevalence of diabetes.
- Highly active antiretroviral therapy therapy for HIV/AIDS may also precipitate diabetes.
- Vascular disease such as microangiopathy can further impair the expression of the immune response as well as affecting the overall function of the microcirculation. It is commonly a factor in severe infections such as malignant otitis externa, emphysematous pyelonephritis and necrotizing fasciitis.
- Urinary tract infections and asymptomatic bacteriuria are more common in people with diabetes. Autonomic neuropathy is a common and important underlying factor.
- Skin and soft tissue infections are more common, with the infected diabetic foot as a prime example. Vascular disease and diabetic neuropathy are important underlying factors in the vulnerability of the foot to infection. Skin infection or infections of the external genitalia are common presenting features of diabetes. Necrotizing fasciitis is also associated with diabetes.
- Some uncommon but life-threatening infections occur almost exclusively in people with diabetes. Examples include the rhinocerebral form of mucormycosis, malignant otitis externa, Fournier gangrene and emphysematous forms of cystitis, pyelonephritis and cholecystitis.
- Diabetes increases the risk of tuberculosis and also increases the risk of treatment failure. Unusual or extrapulmonary sites of infection may be important and cavitatory disease more common.
- Other underlying factors that can predispose to infection include renal failure, obesity, need for hospitalization, indwelling catheters and delayed wound healing.

Introduction

People with diabetes develop infections more often than those without diabetes and the course of the infections is also more complicated. Historically, infections have been well recognized as an important cause of death in diabetes and remain a very important cause of morbidity and mortality in people with diabetes. This is particularly true in less well-developed countries and areas, where infections are commonly the first presenting feature of previously unknown diabetes. The infected diabetic foot remains a prime example of this phenomenon despite its potential preventability.

While the association between diabetes and infections is well recognized, the relationships are complex, not always clear-cut and often controversial. Data on the true incidence of certain infections are lacking and a number of factors complicate efforts to assess risk of infections and outcomes. Studies are often retrospective and uncontrolled in nature.

Some infections, which occur predominantly in people with diabetes, are uncommon and inevitably have limited data. Examples include malignant otitis externa, mucormycosis, emphysematous forms of cholecystitis, cystitis and pyelonephritis, and Fournier gangrene.

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In the case of more common infections that, while not limited to people with diabetes, have diabetes as a complicating factor, many potential variables make for considerable heterogeneity in the clinical course. Examples of such factors include duration of disease, presence of diabetic complications, glycemic control (both recent and longer term), access to and provision of medical services, and presence or absence of other concurrent illnesses.

A recent carefully controlled study from Utrecht, the Netherlands, has confirmed that, in general terms, patients with type 1 (T1DM) and type 2 diabetes mellitus (T2DM) are at increased risk of lower (but not upper) respiratory tract infection, urinary tract infection and skin and mucous membrane infections [1]. In this study, the well-documented increased risk of urinary infection was extended to include both risk of recurrence in both sexes and risks in males (perhaps explained by prostatitis).

Another recent study, conducted in Ontario, Canada, compared people with diabetes with matched control subjects without diabetes [2]. The investigators calculated the risk ratios, both for contracting an infection and for death from infection. Forty-six percent of all people with diabetes had at least one hospitalization or outpatient visit for infections compared with 38% of those without diabetes, the relative risk ratio being 1.21. The risk ratios for infectious disease-related hospitalization or death were noticeably higher at 2.17 and 1.92, respectively. This may be attributable to increased severity and presence of complications. In the case of hospitalization, it could also reflect a lower threshold on the part of physicians to admit people with diabetes to hospital when they have intercurrent illnesses. A separate study also from Canada, in this case from the Calgary Health Region, has conducted a population-based assessment of severe bloodstream infections requiring intensive care admission. Demographic and chronic conditions that were significant risk factors for acquiring severe bloodstream infection included diabetes, with a relative risk ratio of 5.9. The most common organisms were *Staphylococcus aureus*, *Escherichia coli* and *Streptococcus pneumoniae* [3].

Data from a study by Bertoni *et al.* [4] suggest that adults with diabetes are at greater risk for infection-related mortality, and that the excess mortality risk may be mediated by cardiovascular disease (CVD). When diabetes was combined with CVD, the relative mortality risk was 3.0 (1.8–5.0), whereas individuals with diabetes without CVD had a risk of 1.0 (0.5–2.2).

Evidence that the presence of diabetes can worsen the outcome or prognosis of infections comes from a number of sources. There is evidence that the presence of T2DM is associated with an increased mortality from community-acquired pneumonia. While much of this may be explained by factors such as age and coexisting comorbid illnesses, admission hyperglycemia has been shown to be a particularly important predictor of death. Also, even in patients without previously diagnosed diabetes, glucose levels in general assume importance [5]. During the outbreaks of severe acute respiratory syndrome (SARS) in 2003 in Toronto, the presence of diabetes was an independent risk factor for poor outcomes (intensive care unit admission, mechanical ventilation and death) with a threefold increase in relative risk [6].

Both host- and organism-specific factors appear to be implicated in the increased susceptibility to particular infections. From the host perspective, defects in innate immunity are important, notably decreased functions (chemotaxis, phagocytosis and killing) of neutrophils, monocytes and macrophages. Other factors include effects of diabetic complications, poor wound healing and the presence of chronic renal failure. Frequent hospitalizations, with the attendant risk of nosocomial infection, can also be contributory.

Infections, as well as leading to considerable morbidity and mortality in people with diabetes, may also precipitate metabolic derangements, producing a bidirectional relationship between hyperglycemic states and infection. Some infections may also be implicated more directly in the etiology of diabetes.

Physicians working in primary care need to have high levels of awareness of the relationships between diabetes and infection, and of the important infections that may be involved. Infections involving the foot, soft tissues, skin and nails, as well as the urinary tract, are of particular importance in the setting of primary care. These infections are commonly encountered in people with diabetes, may be present at diagnosis and may be the presenting feature that leads to the diagnosis of diabetes being suspected. Infections of the foot and skin will receive additional attention elsewhere in this textbook so, in order to avoid duplication, coverage in this chapter is curtailed. This should not be taken as an indication of lack of relative importance, the opposite is the case. The other chapters concerned should be taken as forming part of the overall coverage of the topic of diabetes and infections (see Chapters 44 and 47).

Diabetes, the immune system and host factors

Host immune response

Although the increased susceptibility of people with diabetes to bacterial (and other) infections is well established, the mechanisms remain incompletely understood. Deficiencies in the host innate immune response are apparent and appear more important than changes in adaptive immunity.

The presence of diabetes has multiple effects upon innate immune responses, including effects upon neutrophils, monocytes and other components of innate immunity. These disturbances have important roles in the increased prevalence and enhanced severity of infections in people with diabetes. The effects include reduced chemotaxis, phagocytosis and impaired bactericidal activity.

Some disturbances in the complement system and in cytokine responses have been described in people with diabetes (e.g. low complement factor 4 and decreased cytokine responses after stimulation), but their role in the increased susceptibility to infection is less clear [7]. Consistent defects have not been demonstrated. No clear disturbances in adaptive immunity have been

described. Humeral adaptive immunity, in particular, appears relatively unaffected as exemplified by the relatively normal antibody responses to most vaccinations and the fact that serum antibody concentrations and responses in patients with diabetes are generally normal. For example, people with diabetes respond to pneumococcal vaccine equally as well as controls without diabetes [8,9].

The complexity of the component systems involved in the immune system makes comparison between studies difficult and it is obviously simplistic to study individual components of the immune system in isolation given the interdependency of these components. Many studies have relied upon *in vitro* or animal model methodology.

Investigations to identify the mechanisms of immune impairment in animal models of diabetes and *in vitro* experiments have been numerous. A full review of these animal and *in vitro* studies is beyond the scope of this chapter; however, the observations that follow may serve as examples from within the range of abnormalities that have been found, although many questions remain as to the nature of the defects produced by diabetes and their effects upon infection risk.

Neutrophil chemotaxis, neutrophil adherence to vascular endothelium, phagocytosis, intracellular bactericidal activity, opsonization and other aspects of innate immunity are all depressed in hyperglycemic patients with diabetes, although adaptive immunity appears relatively unaffected [10–12]. These changes lead to reduced host defense in response to infection with extracellular bacteria. Both impaired chemotaxis and phagocytosis have been described in monocytes of people with diabetes [13]. Defects in innate immunity have also been shown to predispose *db/db* mice to *S. aureus* infections. Interestingly, these mice show a heightened inflammatory response which occurs in association with an impaired neutrophil respiratory burst, and the recruited neutrophils fail to resolve the infection [14]. A possible role for advanced glycosylation end-products (AGEs) is postulated as a component in the pathogenesis of the impaired neutrophil function.

While release of tumor necrosis factor α and interleukin 1β (IL-1β) from lipopolysaccharide-stimulated macrophages has been shown to be reduced in diabetic mice compared with control mice [15], study of monocytes from patients with diabetes indicates upregulation of the secretion of the same inflammatory mediators [16]. This further illustrates the difficulty in comparing studies conducted in different settings and species. Some innate (e.g. cytokines, complement) immune functions are decreased while others remain the same in patients with diabetes as those without diabetes. For example, while unstimulated cytokine concentrations may be higher, cytokine responses to stimuli are often reduced [17]. Interpretation of the complexity of the underlying mechanisms may also need to take into account potential underlying proinflammatory effects associated with diabetes itself.

The level of macrophage inflammatory protein 2, a mediator of lung neutrophil recruitment, is significantly decreased in diabetic mice compared to control mice [18]. The deficiency causes a delay in neutrophil recruitment in the lungs. This may be an important factor influencing the susceptibility of people with diabetes to infections of the lower respiratory tract.

Hyperglycemia impairs opsonophagocytosis by diverting nicotinic acid adenine dinucleotide phosphate (NADPH) from superoxide production into the aldose reductase-dependent polyol pathway [19], providing one further example of a mechanism by which hyperglycemia directly impairs phagocytosis.

Diabetic mice show greater than twofold induction of genes that directly or indirectly induce apoptosis [20]. By contrast, it is known that blocking of apoptosis allows for a significant improvement in wound healing and bone growth. This may influence many aspects of responses to infection, including impaired wound healing, which are important in the setting of diabetes.

These examples, while somewhat piecemeal, serve to demonstrate the range of abnormalities in the innate immune system that result from hyperglycemia. Of particular importance are those spanning macrophage, monocyte and neutrophil function, and which impair adherence to endothelium, chemotaxis, phagocytosis and bacteriocidal activity. They also point to other abnormalities (e.g. involving apoptosis), wound healing and cytokine responses to infection. The antioxidant systems involved in bacteriocidal activity may be compromised. These impairments, which are exacerbated by hyperglycemia and acidemia, may be reversed substantially, if not entirely, by normalization of pH and blood glucose levels. It needs to be emphasized, however, that the severity of effects correlates somewhat unpredictably with direct contemporaneous measures of glycemic control such as HbA_{1c}, perhaps reflecting longer term or persistent changes such as accumulation of AGEs [21]. In general, a better regulation of the diabetes leads to an improvement of the cellular aspects of immune function.

Other host-related factors

Other host-specific factors, over and above direct diabetes-related impairment of immune defenses, can further the predisposition to infection. These include vascular insufficiency (microangiopathies and macroangiopathies), sensory peripheral neuropathy, autonomic neuropathy, and skin and mucosal colonization with pathogens such as *S. aureus* and *Candida* species. Abnormalities of the structure and function of the microcirculation can also have additional indirect adverse effects on the immune responses themselves. Thus, immunologic responses may be further compromised by microangiopathy, and additional factors related to diabetes complications specifically increase the risks of certain infections, especially those involving the foot and the urinary tract.

While beyond the direct scope of this chapter, obesity, which is commonly associated with diabetes, also increases the risk of certain infections. These include nosocomial infections, wound and surgical site infections, respiratory infections and infections involving the gastrointestinal tract. The presence of obesity also correlates with infected diabetic foot ulcers in people with diabetes [22].

Diabetic complications

Vascular disease is an important component in the etiology of the diabetic foot and the attendant complications of infection, ulceration and gangrene. Vascular disease is very common in diabetes and macrovascular disease may be premature, extensive, severe and present in unusual sites. Vascular insufficiency results in local tissue ischemia that can, in turn, enhance the growth of microaerophilic and anaerobic organisms, while simultaneously depressing the oxygen-dependent bactericidal functions of leukocytes. The antioxidant systems involved in bacteriocidal activity may be compromised by the combination of microvascular disease and the diabetic metabolic derangement itself. Hyperglycemia and acidemia are important predisposing factors to this latter effect and are reversed substantially by normalization of pH and blood glucose levels. Vascular disease related to diabetes may also further impair the local inflammatory response and may also impair the tissue penetration of antibiotics.

Neuropathy, both peripheral and autonomic, also contributes to the risk of foot infections and ulceration, as well as to certain other infections. Sensory peripheral neuropathy masks the recognition of trauma. Minor local trauma in patients with diabetes-associated peripheral neuropathy may result in skin ulcers, which, in turn, lead to diabetic foot infections. Skin lesions are often either unnoticed or ignored until infection occurs. Autonomic neuropathy contributes to the etiology of diabetic foot infections by mechanisms such as decreased sweating, which predisposes to drying and fissuring of the skin, and by further exacerbating abnormalities in the control of the microcirculation. Both sensory and motor neuropathy can lead to deformity and alter the dynamics of the function of the foot. Fuller discussion of the etiologic factors related to sepsis and the diabetic foot is provided in Chapter 44.

Patients with diabetes-associated autonomic neuropathy may develop urinary retention and stasis in association with loss of innervation to the bladder. This predisposes them to urinary tract infections. This risk is particularly high in females. Autonomic neuropathy can also impair the function of the gastrointestinal tract, predispose to certain gastrointestinal tract infections and contribute to risk of aspiration pneumonia in the context of gastroparesis. Renal papillary necrosis can also contribute to the risk of renal failure as well as to infection within the urinary tract.

Thus, a number of factors contribute to the vulnerability of people with diabetes to infections. In addition to the abnormalities of the immune response, vascular disease and neuropathy can greatly enhance susceptibility (e.g. in the lower limb and urinary tract). Hyperglycemia per se may specifically heighten susceptibility to certain fungal and bacterial infections.

Organism-specific factors

Certain organisms may show increased adherence to diabetic cells [12] and others may demonstrate increased virulence in hyperglycemic environments. Specific factors that predispose people with diabetes to infection with specific organisms include the following examples.

Candida albicans and fungi

Glucose-inducible proteins produced by *Candida albicans* are homologous to a complement receptor on phagocytes. These proteins may promote adhesion of *C. albicans* to buccal or vaginal epithelium. This adhesion, in turn, impairs phagocytosis, giving the organism an advantage over the host [12].

Ketone reductases produced by *Rhizopus* species allow these species to thrive in high glucose, acidic conditions typically present in patients with diabetic ketoacidosis [23].

Klebsiella spp.

A bacterial genus of note in the context of diabetes is *Klebsiella*. *Klebsiella* infections are the second most common causes of Gram-negative sepsis (after *E. coli*). In a report from Taiwan, diabetes was the most commonly associated underlying condition in patients presenting with community-acquired *K. pneumoniae* bacteremia (whereas neoplastic diseases were more commonly associated with nosocomial infections) [24]. The percentage of patients with underlying diabetes was 49%, which is even higher than in earlier reports [25,26]. Apart from the high proportion with diabetes, associations were also observed with serotype K1 (associated with impaired phagocytosis), liver abscess and other metastatic complications (endophthalmitis, meningitis, brain abscess) [24]. Primary liver abscess in other parts of Asia is also increasing in incidence, with 40% reportedly associated with diabetes [27]. Bacteremia is present in 50%, and 8–10% have metastatic complications (endophthalmitis, meningitis, brain abscess, pneumonia, skin and soft tissue infections, lung abscess, septic arthritis, renal abscess and prostatic abscess).

Melioidosis

A combination of organism-specific factors together with the changes in innate immunity may explain the increased susceptibility of people with diabetes to melioidosis. About 50% of cases of melioidosis occur in people with diabetes. The responsible organism, *Burkholderia pseudomallei*, has been shown to be selectively resistant to phagocytosis compared to *Salmonella typhimurium* and *E. coli* in subjects with diabetes.

In a study from Thailand, a country where melioidosis is relatively common, neutrophil responses to *B. pseudomallei*, in both healthy subjects and people with diabetes showed that *B. pseudomallei* displayed reduced phagocytosis by neutrophils compared to *S. enterica typhimurium* and *E. coli*. In addition, intracellular survival of *B. pseudomallei* was detected throughout a 24-hour period, indicating intrinsic resistance of *B. pseudomallei* to killing by neutrophils. Furthermore, neutrophils from subjects with diabetes displayed reduced migration in response to IL-8 and an inability to delay apoptosis. Thus, *B. pseudomallei* appears to be intrinsically resistant to phagocytosis and killing by neutrophils. When added to the impaired migration and

apoptosis seen in diabetes, the combination seems sufficient to explain the increased susceptibility to melioidosis in people with diabetes [28].

Bidirectionality: the effect of infections on diabetes

Bidirectionality exists in the relationship between diabetes and infections. The effect of infections upon diabetes includes the effects of certain infections on the etiology and pathogenesis of diabetes itself, adverse effects upon hyperglycemia in established diabetes and exacerbation of diabetes complications. The importance of the potential adverse effects upon hyperglycemia in established diabetes needs to be stressed. Infections remain an important predisposing cause of both diabetic ketoacidosis and hyperosmolar hyperglycemia syndrome.

The importance of certain viral infections in the possible etiology of diabetes has received increasing attention in recent years with respect to both T1DM and T2DM.

Viral infections have been implicated in the etiology of T1DM for many years. Although this complicated topic is beyond the general scope of this chapter and is considered in detail in Chapters 3 and 9, it is noteworthy that type 1a (autoimmune) diabetes is increasing in prevalence globally, providing strong evidence that environmental factors are involved in the clinical expression of the disease. Viruses have long been included in the list of putative environmental triggers. Enteroviruses (especially coxsackie B viruses, B4 in particular), rubella, mumps, rotavirus, parvovirus and cytomegalovirus have all been implicated and continue to be reported [29,30]. Although correlations between the presentation of diabetes and the occurrence of a preceding viral infection have been recognized, a direct causal relationship, with fulfillment of Koch postulates, between viral infection and the diabetogenic process, remains difficult to prove, possibly because other inflammatory factors are also required. In this context, it is interesting to note that the process may be associated with a dominant CD4 T-helper type 1 immune response, whereas the dominance of a T-helper type 2 response, as seen in the face of certain infectious and parasitic agents, may protect against T1DM and other autoimmune diseases. Thus, the increasing freedom from such infections, especially in developed areas of the world, may allow the increased expression of an underlying genetic predisposition, and infection by certain viruses, such as the coxsackie B viruses, may then be associated with the appearance of (and persistence of) β-cell antigens, mediated by mechanisms such as molecular mimicry and activation of Toll-like receptors. Lack of exposure to infection and infestation in early childhood appears to dilute the ability of the innate immune system to withstand autoimmune responses and challenges. T1DM is not alone in this respect and the general concept has become known as the "hygiene hypothesis" [31].

The high prevalence of T2DM in association with hepatitis C infection and the progression of certain diabetes complications (e.g. diabetic nephropathy) in association with hepatitis B are other noteworthy examples. The treatment of HIV/AIDS with protease inhibitors predisposes to diabetes, metabolic syndrome and increased cardiovascular risk. The public health implications of these issues are considerable given the concordance of the diabetes epidemic with these other highly prevalent diseases.

All infections, especially if severe, have the potential to exacerbate hyperglycemia by a number of mechanisms (e.g. worsening of insulin resistance by production of "stress" or counter-regulatory hormones and production of cytokines such as IL-1 and tumor necrosis factor) [32]. Infection remains a major factor in the pathogenesis of diabetic ketoacidosis or hyperosmolar hyperglycemia. Infections can also precipitate hypoglycemia if symptoms, such as anorexia, nausea and vomiting, lead to reduced food intake. Malaria and its treatment with quinine can also produce hypoglycemia.

Hepatitis C

A number of reports from North America, Europe and the Middle East consistently demonstrate an increased prevalence of diabetes (ranging from 24% to 62%) among patients with chronic hepatitis C virus (HCV) infection compared both with persons with other forms of liver disease and with other control groups. Among HCV-infected individuals reported prevalence of diabetes (21–50%) is much higher when compared with other forms of chronic liver disease (2–12%) and with control subjects (2–6%) [33–38].

In the USA, T2DM occurs more often in persons with HCV infection who are older than 40 years of age, particularly in the range of 40–49 years where the relative risk ratio is 3.77. Apart from age, the prevalence of diabetes is greatest in subjects who are non-white, have a high body mass index, are below the poverty level and have a family history of diabetes. The prevalence of T1DM appears to be unaffected [39].

The suggestion that HCV infection predisposes to T2DM as a result of the progressive liver damage is supported by the observations that the association is most marked in the older age groups (>40 years), and that there is higher risk among patients with advanced HCV cirrhosis. The presence of diabetes is also associated with worse hepatic fibrosis; however, the higher prevalence of diabetes compared to other forms of liver disease suggests an additional mechanism specific to hepatitis C. Tumor necrosis factor α has been suggested as one possible candidate for this role [40].

HCV infection is also strongly associated with diabetes among intravenous drug users and this is independent of HIV infection or use of highly active antiretroviral therapy (HAART) [41]. Thus, it is important to monitor patients with chronic HCV infection for development of diabetes. Bidirectionality again applies with weight loss and good glycemic control improving hepatitis outcomes.

HIV/AIDS

Although HIV/AIDS has not in itself been reported to increase the risk of diabetes, the treatment of HIV/AIDS with HAART predisposes to T2DM, other metabolic risks and premature cardiovascular disease. This has become a major problem in the

management of this already very complicated disease. The effects occur via disturbances in lipid homeostasis and fat partitioning (lipodystrophy), insulin resistance, insulin secretion and mitochondrial function. The underlying cellular mechanisms are complex and incompletely understood. Combination HAART for HIV-1 infection is frequently complicated by lipodystrophy (peripheral fat loss and relative visceral obesity), dyslipidemia and insulin resistance. HIV-infected adults receiving HAART have an increased incidence of elevated blood pressure and cardiovascular morbidity.

Whether antiretroviral therapy-naive patients have altered risk of subsequent CVD or T2DM is unclear, particularly in light of emerging data indicating that rates of CVD may also be higher in people with HIV who are not treated with antiretriviral therapy.

Exposure to antiretroviral therapy for more than 1 year is associated with increasing risk of diabetes. Although the risk is greatest among individuals treated with a protease inhibitors (PI) (attributed to a direct inhibitory effect on cellular glucose transport by PI medications) [41], an increased prevalence of diabetes among those receiving a PI-sparing regimen has also been found and insulin resistance has been reported among PI-naive persons with HIV infection, in association with fat redistribution. Nucleoside analog-induced mitochondrial toxicity is probably of importance. Cessation of PI appears to have little beneficial effect in reversing lipodystrophy, although it may improve the metabolic control in diabetes. Alteration of thymidine analog nucleosidase reverse transcriptase inhibitors may, however, confer benefit on lipodystrophy [42,43].

In a study of almost 900 HIV-infected patients, initiation of antiretroviral therapy was evaluated for prevalence and incidence of metabolic syndrome (using the National Cholesterol Education Program, Adult Treatment Panel III [NCEP ATP-III] and the International Diabetes Federation [IDF] criteria) and subsequent diagnosis of CVD and T2DM over a 3-year period. The prevalence of baseline metabolic syndrome was 8.5% and 7.8% (ATP-III and IDF criteria, respectively). Substantial progression to metabolic syndrome occurred within 3 years following initiation of antiretroviral therapy. The presence of metabolic syndrome at baseline was significantly associated with an increased risk of T2DM while metabolic syndrome occurring during the 3-year period was associated with an increased risk of both CVD and diabetes [44,45].

In another study [46], 123 of 6513 HIV-infected persons developed diabetes during 27 798 person-years of follow-up, resulting in an incidence of 4.4 cases per 1000 person-years of follow-up. An increased incidence rate ratio was found for male subjects, older age, obesity, Afro-American or Asian ethnicity. A weaker, although still significant, association of the incidence rate was also found with Centers for Disease Control and Prevention (CDC) disease stage C. Strong associations were observed with treatment using nucleoside reverse-transcriptase inhibitors (NRTI), NRTI plus PI and NRTI + PI + non-nucleoside reverse-transcriptase inhibitors (NNRTI), but not with an NRTI + NNRTI regimen.

Lipodystrophy is a crucial aspect of the association of HAART with insulin resistance, leading to relative preponderance of visceral fat, hepatic steatosis and fat deposition at other "ectopic" sites. HIV-infected persons with lipodystrophy, compared with those without lipodystrophy, have a reduction in plasma adiponectin and adipose tissue adiponectin mRNA levels of approximately 50%, correlating with insulin resistance and increased cytokine levels [45].

Because baseline and incident metabolic syndrome identifies individuals at risk for both CVD and T2DM, evaluation in all patients commencing HAART is warranted. A fasting plasma glucose concentration should be checked before initiation of therapy and monitored every 3–6 months, especially in patients receiving changes in treatment or who have significant risk factors for insulin resistance. An oral glucose tolerance test may be required, particularly in the presence of risk factors or equivocal glucose concentrations. Dietary guidelines established for the general population remain relevant for the management of glucose disorders in the context of HIV infection. Weight loss through increased activity and caloric restriction should be recommended for overweight HIV-infected patients.

Metformin improves insulin sensitivity in patients with HIV lipodystrophy and is an effective antidiabetic medication; however, it should be used with caution in patients receiving an NRTI, and in persons with impaired renal function because of the possibility of lactic acidosis. Thiazolidinediones also improve insulin sensitivity in patients with HIV lipoatrophy, although rosiglitazone treatment may worsen hyperlipidemia. Insulin therapy should be used according to standard recommendations. Substitution of an NNRTI for a PI has been observed to improve insulin resistance but this needs to be balanced against any risk to virus control. Careful discussion with the HIV physician is therefore essential and it may be deemed safer to increase the antihypoglycemic treatment rather than changing the components of the HAART regime [47–49].

Hepatitis B

Although, in contrast to hepatitis C, hepatitis B virus (HBV) has been less consistently associated with an increased prevalence of diabetes, the presence of hepatitis B markers may nevertheless influence the natural history of diabetes and its complications and the relationship may be bidirectional as the presence of diabetes is associated with more severe fibrosis and cirrhosis. However, there is uncertainty as to cause and effect given the general association of diabetes with liver cirrhosis [50].

Chinese HBV-infected patients with T2DM have been shown to be more likely to develop end-stage renal disease than non-HBV infected patients with T2DM (8.7 vs 6.4%) with a hazard ratio of 4.5. The association of chronic HBV infection with increased risk of end-stage renal disease was independent of other potential confounding factors. HBV-infected patients also reported earlier onset of diabetes and had a higher frequency of diabetic retinopathy than non-HBV-infected patients (28%

compared to 22%). Cardiovascular complications appeared unaffected [51].

Specific infections either strongly associated with diabetes or in which the presence of diabetes is important

Infections involving the head and neck

Two head and neck infections that are associated with high rates of morbidity and mortality, malignant otitis externa and rhinocerebral mucormycosis, are particularly noteworthy in people with diabetes.

Malignant otitis externa

Malignant otitis externa is an invasive infection of the external auditory canal and skull base that typically arises in elderly people with diabetes. An early series of patients was described in 1968 [52]. Most cases (86–90%) have been reported in patients with diabetes. *Pseudomonas aeruginosa* is nearly always the causal organism (>98% of cases) although *Aspergillus* species are occasionally responsible. Microangiopathy in the ear canal has been suggested as a predisposing factor.

Presenting features include severe intractable headache and otalgia, otorrhea and deafness. Patients often report a duration of weeks to months of these symptoms. Intense cellulitis is combined with edema of the ear canal. Focal neurologic signs and cranial nerve palsies may occur. The pain may involve the temporomandibular joint and be aggravated by chewing. Osteomyelitis of the skull base and temporomandibular joint is a potentially life-threatening complication and the mortality in the pre-antibiotic era exceeded 50%. On otoscopy, granulation tissue may be seen in the floor of the ear canal, often in association with edema and intense cellulitis. The tympanic membrane is usually intact. Computed tomography (CT) and magnetic resonance imaging (MRI) studies are essential for defining the extent of bone and soft tissue involvement, together with the bony destruction of the skull base that may be seen in advanced cases.

Systemic antipseudomonal antibiotics are the primary therapy. Early referral to an otorhinolaryngologist is essential and allows diagnostic confirmation by surgical biopsy. Débridement of necrotic tissue can also be carried out if necessary, although the introduction of effective antibiotic therapy has reduced the requirement for surgery. With the introduction of quinolones, the cure rate has increased to 90%, with few adverse effects reported and oral therapy rendered possible. Prolonged treatment for 6–8 weeks is recommended, as for osteomyelitis [53]. Thus, treatment consists of prolonged administration (6–8 weeks) of an antipseudomonal agent (typically, an orally administered quinolone). The emergence of ciprofloxacin resistance is a potential problem. It is recommended that systemic quiniolone use be reserved for treatment of invasive ear infections. An example of invasive aspergillosis involving the skull base is shown in Figure 50.1.

Mucormycosis (zygomycosis)

The term mucormycosis is used to describe a variety of infections caused by fungi of the *Rhizopus* and *Mucor* species which belong to the order Mucorales (class Zygomycetes). These fungi are ubiquitous saprophytes and infections produced by them are essentially confined to immunocompromised individuals. The fungi have a predilection to invade blood vessels. Ketone reductases produced by *Rhizopus* spp. allow them to thrive in high glucose, acidic conditions as are typically present in patients with diabetic ketoacidosis [23]. Rhinocerebral, pulmonary, gastrointestinal, cutaneous and disseminated forms of the infection are described. The rhinocerebral manifestation (and with sinus involvement) has the highest frequency and is potentially the most lethal in the context of people with diabetes (Figure 50.2).

The close connection with diabetes is becoming increasingly diluted as other causes of an immunocompromised state become increasingly common or survivable (notably hematologic cancer and bone marrow transplant recipients). Nevertheless, diabetes remains the most common underlying factor in most reports. In a review of 49 cases of pulmonary mucormycosis, diabetes was the underlying cause of the immunocompromised state in 9 (25%) [54]. In another study, the prevalence and mortality in people with diabetes were 36% and 44%, respectively [55]. It typically, although not exclusively, occurs in association with ketoacidosis, severe hyperglycemia and/or a debilitated state.

Rhinocerebral mucormycosis is a life-threatening fungal infection. Untreated it is universally fatal; if recognized early there is a 20% survival rate. Presenting features include facial or ocular pain and nasal stuffiness. Generalized malaise and fever may also be present. Intranasal black eschars or necrotic turbinates may be found and, if present, provide sites that can be biopsied. Treatment consists of surgical débridement of the involved sinuses and prolonged intravenous therapy with amphotericin B or alternative antifungal agents such as some newer azoles.

Acute invasive fungal sinusitis can also result from aspergillosis, as can malignant otitis externa. Biopsy confirmation of the microbiologic diagnosis is therefore useful [56].

Endophthalmitis

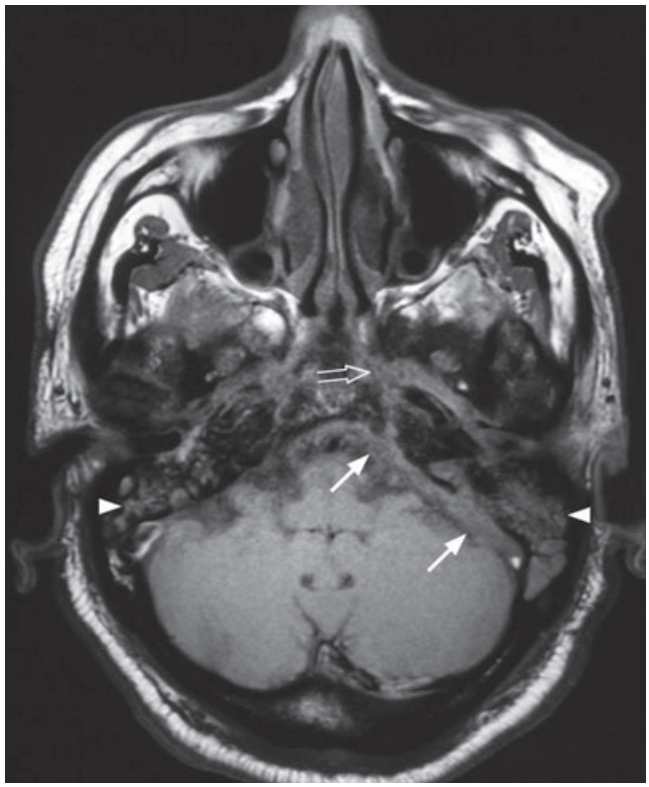
Secondary endophthalmitis may occur as a rare but devastating metastatic complication of septicemia and in this setting is almost entirely confined to people with diabetes. *E. coli* and *Klebsiella* are the more likely pathogens and urinary tract infection is reported as the most common underlying source of infection [57].

People with diabetes are also more prone to postoperative infections following eye surgery or infections secondary to eye trauma. Overall, the most common cause of endophthalmitis is as a postoperative complication of cataract surgery [58], a procedure commonly carried out in patients with diabetes.

Periodontal disease

People with diabetes are very prone to periodontal disease compared to the non-diabetic population, with a two- to fourfold

(a)



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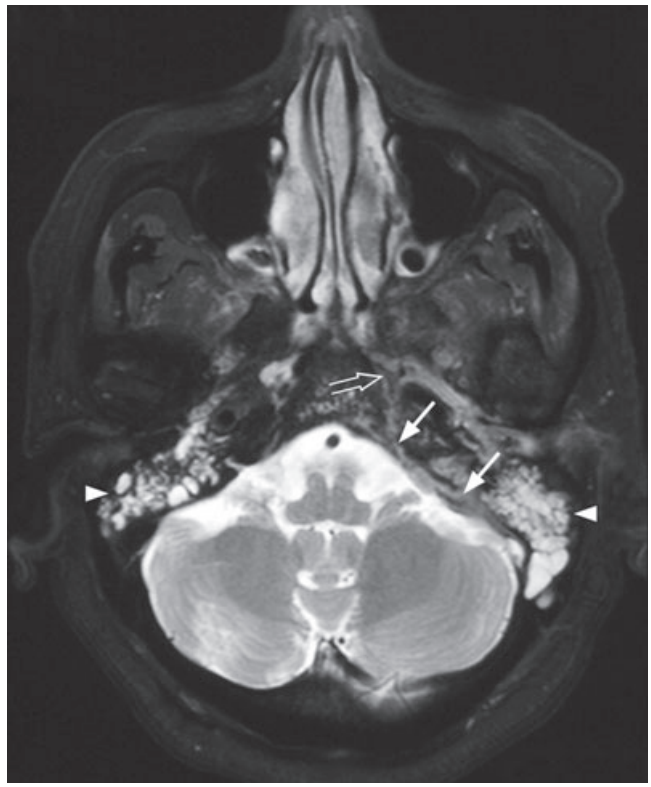


Figure 50.1 Magnetic resonance imaging (MRI) scan of skull base in a 59-year-old male with a 20-year history of diabetes (with nephropathy), treated with insulin who developed severe extensive invasive aspergillosis. He presented with headache and vertigo followed by left sixth and seventh nerve palsies. He subsequently developed bilateral sensorineural hearing impairment and blindness secondary to extensive skull base infiltration by the invasive aspergillosis. MRI demonstrated enhancing soft tissue closely related to the left posterolateral wall of the nasopharynx with parapharyngeal, skull base, perineural and dural infiltration. Biopsy showed inflamed fibrous tissue with degenerated fungal filaments. Culture confirmed *Aspergillus flavus*. He is receiving lifelong therapy with voriconazole. He remains blind. MRI of skull base in the axial plane with: (a) T1-weighted; (b) fat-saturated T2-weighted; and (c) post-gadolinium T1-weighted sequences. These show marked dural thickening (arrows) with enhancement in the left posterior cranial fossa. An abnormal signal with enhancement is also noted in the adjacent left petrous apex (open arrow). Note also the presence of inflammatory fluid within both mastoid air cells (arrowheads). Acknowledgements to Dr. K.T. Wong, Consultant Radiologist, for preparation and reporting of the figures, and to Professor A. Ahuja for permission to use the figures. Both are placed at the Department of Diagnostic Radiology and Organ Imaging, Prince of Wales Hospital, Chinese University of Hong Kong, Hong Kong.

relative increase in prevalence and a particular predilection for those whose diabetes is poorly controlled.

The associated periodontitis, if left untreated, can result in loss of attachment of ligament fibers and supporting alveolar bone, which in turn can increase the mobility of teeth and necessitate extraction. Tooth abscesses and episodes of bacteremia also become more likely. Diabetes may complicate the pathogenesis of periodontitis by causing abnormalities in the vasculature of the gingival tissues, in addition to the effects upon immune responses described earlier. Aggressive and difficult to treat forms of periodontitis are also more common in adults with diabetes. Periodontal health is influenced by glycemic control to the extent that the prevalence of periodontal diseases among people with well-controlled diabetes is not increased [59].

A bidirectional relationship has also been suggested whereby the presence of periodontal disease adds to the overall burden of chronic inflammation, thereby adversely affecting glycemic control as well as overall risk of CVD and diabetic nephropathy.

Respiratory tract infections and tuberculosis

The increased risk of mortality and morbidity from community-acquired pneumonia has been alluded to earlier and includes pneumonia either directly resulting from, or secondary to, common infections such as influenza and *S. pneumoniae* and also includes *Legionella* infections [60]. The risk of bacteremia following pneumococcal infection is increased [61]. Viral shedding may be more prolonged following influenza infections in subjects with co-morbidities including diabetes, which may influence decisions regarding initiation and duration of antiviral therapy [62].

Lower respiratory tract infections, resulting from *S. aureus* and Gram-negative organisms such as *K. pneumoniae*, are more

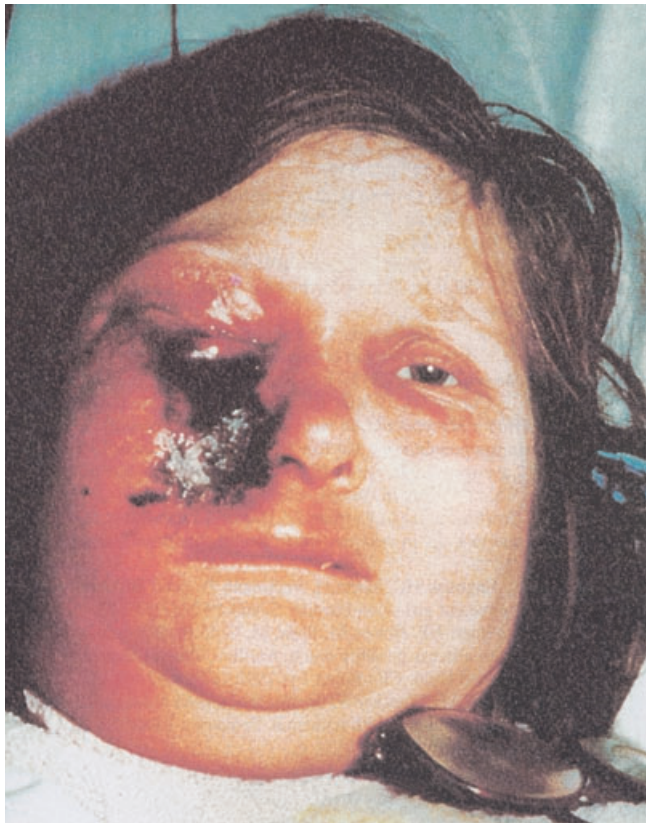


Figure 50.2 Rhinocerebral mucormycosis. Typical appearance in a 45-year-old woman with poorly controlled type 1 diabetes. Periorbital and facial swelling had been present for 3–4 days before admission. Major reconstructive surgery was required. From Rupp ME. Rhinocerebral mucormycosis. *N Engl J Med* 1995; **333**:564.

common in people with diabetes. Melioidosis has also been discussed above as an example of organism-specific factors that interact with diabetes to increase risk of infection. People with diabetes are also thought to be at increased risk for *S. aureus* pneumonia and this may result from the well-documented higher rates of nasal carriage of *S. aureus* in people with diabetes (up to 30%) compared to 11% in healthy individuals [63].

Any respiratory infection in patients with diabetes is associated with increased mortality. In the USA, people with diabetes are reportedly 4 times more likely to die from pneumonia or influenza than are people without diabetes [64].

The importance of diabetes as the most common underlying predisposing factor for thoracic empyema has also long been recognized. A recent report indicates that *Klebsiella* are again notable as the most common pathogens, while other important pathogens include streptococci, *S. aureus* and anaerobes [65].

Diabetes and tuberculosis

An association between diabetes and tuberculosis has been widely accepted in the past, albeit with varying estimates of overall risk (encompassing two- to 11-fold) and variable levels of evidence. The importance of the association is often neglected in the larger arena of public health, for example when compared with the risk of tuberculosis associated with HIV/AIDS.

Diabetes has been confirmed in several recent studies to be associated with increased risk of active tuberculosis. The association of tuberculosis with diabetes presumably reflects impaired innate immunity as well as (in this case at least) a reduced adaptive T-helper type 1 response with reduced secretion of T-helper type 1-related cytokines. A recent review of 13 observational studies published between 1992 and 2007 [66] confirms an increased risk of tuberculosis regardless of study design, population, geographic region and background incidence of tuberculosis, the overall increase in risk being approximately threefold. The risk was greatest among younger people, in areas of high tuberculosis incidence and in non-North American populations. The public health impact may be particularly high in countries such as India and China, which are at the forefront of the diabetes epidemic. The impact of the diabetes epidemic on tuberculosis incidence in India has been modeled by Stevenson *et al.* [67]. They suggest that diabetes accounts for 14.8% (range of uncertainty 7.1–23.8%) of pulmonary tuberculosis and 20.2% (8.3–41.9%) of smear-positive tuberculosis, with an excess risk of the latter in urban areas. This can be compared to an overall estimate of 3.4% for the proportion of adult tuberculosis incidence ascribed to HIV/AIDS in India [68]. Extrapulmonary or unusual manifestations of tuberculosis are also more common in the context of diabetes. In pulmonary tuberculosis, the presence of diabetes, as well as being the most common underlying comorbidity, has also been reported to increase the risk of cavitatory nodules [69].

In addition to the increased risk, there is also evidence that diabetes leads to worse tuberculosis outcomes and has adverse effects upon responses to treatment. A study from Indonesia indicated a doubling of the risk of remaining smear positive at the end of treatment for pulmonary tuberculosis in people with diabetes compared to those without diabetes [70]. The same group in Indonesia has also shown that the presence of T2DM may adversely affect the bioavailability of rifampicin and lead to an increase in dose requirement [71]. In Hong Kong, an area with much pioneering experience of tuberculosis treatment since the 1950s, the Centre for Health Protection recognizes the risk of a worse outcome, and its guidelines recommend a more prolonged period of treatment for people with diabetes compared to those without. For example, when treating pulmonary tuberculosis using a standard regimen of four drugs for the first 2 months followed by two drugs, a total treatment duration of 9 months, rather than 6 months, is recommended. Bidirectionality again needs to be remembered because the presence of tuberculosis is very likely to have a negative impact upon hyperglycemia. Two examples of individuals with tuberculosis in association with diabetes are shown in Figure 50.3. It is perhaps noteworthy that neither was receiving regular follow-up care for the diabetes.

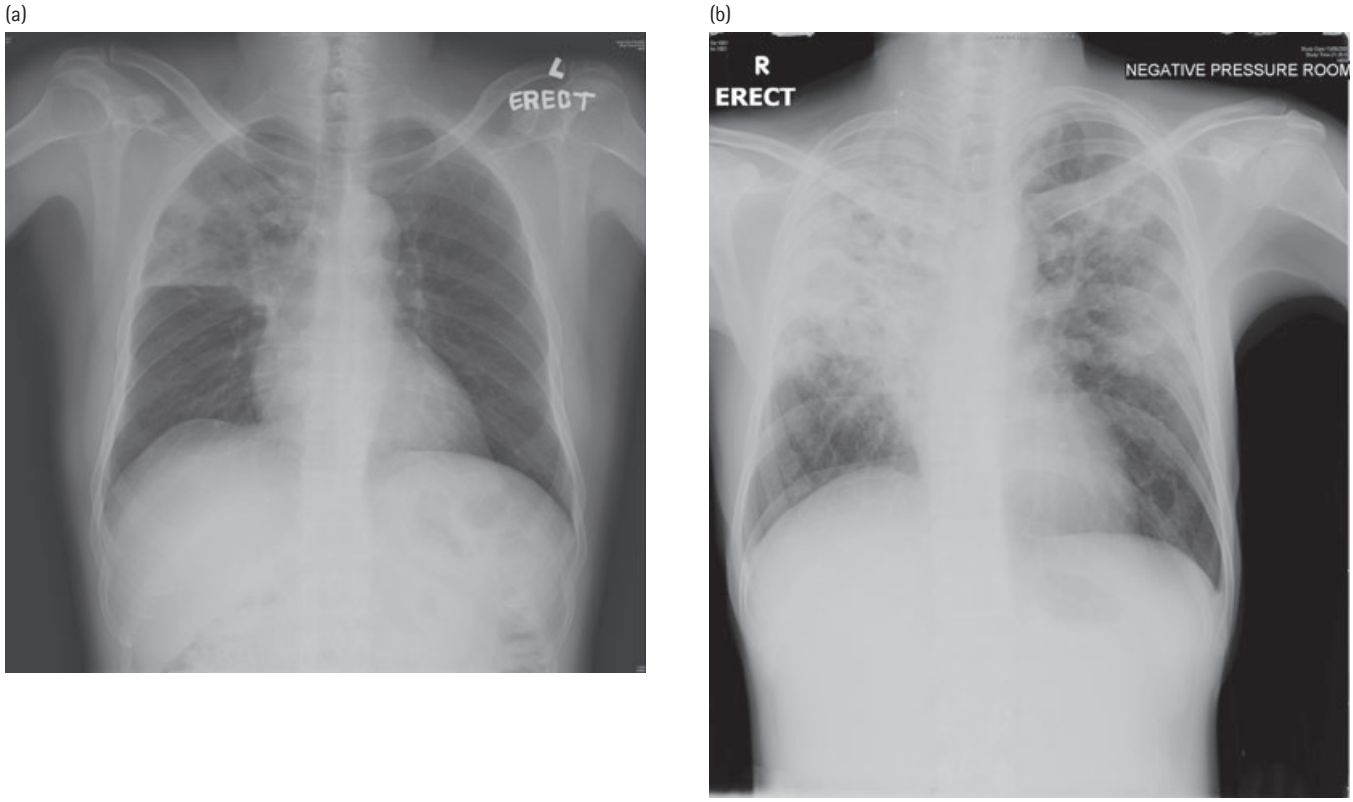


Figure 50.3 (a) A 49-year-old man with diabetes and obesity, not receiving regular follow-up, and presenting with hemoptysis, sputum smear positive for tuberculosis (TB). Chest X-ray shows extensive right upper lobe pneumonic changes. (b) A 30-year-old man with diabetes but no regular follow-up, presents with a cough for 4 months with weight loss, sputum smear positive for TB. Chest X-ray shows extensive bilateral and cavitatory disease.

Infections of the urinary tract

Epidemiology and risk factors

Urinary tract infection (UTI) is frequently encountered in people with diabetes. Asymptomatic bacteriuria also occurs with a higher frequency. One study has demonstrated a prevalence rate for asymptomatic bacteriuria of 26% in women with diabetes, compared to 6% in women without diabetes, a threefold increase [72,73].

A randomized controlled trial of antibiotic treatment for asymptomatic bacteriuria revealed no differences in the development of symptomatic UTI, time to onset of symptoms, risk of pyelonephritis or need for hospitalization [72]. Thus, diabetes does not appear to warrant either screening for, or treating, asymptomatic bacteriuria. This remains a controversial issue and, from the practical standpoint of the physician, ascertaining "asymptomatic status" with confidence, particularly in older women with diabetes, can be difficult or impossible.

A number of studies confirm the increased risk of symptomatic UTI in association with diabetes. In one study of more than 600 women [74], those with T2DM had an overall risk of 20%. A recent study has extended the risk to include recurrence rates as well as risk to males [1].

Diabetes is a risk factor for cystitis in postmenopausal women, leading to a two- to threefold increase in risk [75]. An increased prevalence of asymptomatic vaginal *E. coli* colonization has also been reported in postmenopausal women with diabetes who are receiving insulin treatment. This vaginal colonization may be mediated by greater adherence of type 1 fimbriated *E. coli* to uroepithelial cells in women with diabetes, may be related to impaired cytokine secretion or may reflect a reduced polymorphonuclear inflammatory response [72,76].

Diabetes increases the risk of complications of UTI, serious or unusual forms of infection, and need for prolonged hospitalization [77]. It is a risk factor for acute pyelonephritis in women (odds ratio 4.1), and is the strongest of the various risk factors that have been examined. Among hospitalized patients, 16.7% reported having diabetes compared with 5.8% of non-hospitalized patients [72]. A three- to fivefold increase in risk exists in people with diabetes aged less than 44 years [74].

Diabetic autonomic neuropathy is an important predisposing factor to UTI. This affects the sympathetic and parasympathetic afferent fibers to the bladder and causes decreased reflex detrusor activity. Impaired bladder sensation results in bladder distension, increased residual urine volume, vesicoureteric reflux and recurrent upper UTI [78,79]. Some cases are urinary catheter or instrumentation related [72,78,79]. Additional host factors

predisposing to UTI include: glycosuria, sexual intercourse, history of previous UTI, obstruction, longer duration of diabetes, poor glycemic control, decreased urinary cytokine excretion, increased *E. coli* adhesion, macroalbuminuria and neutrophil dysfunction [78,79]. Renal papillary necrosis and chronic renal failure may also contribute to the complex array of risk to the urinary tract.

Microbiology

E. coli is the most commonly reported organism. *Klebsiella* is also a problem, especially among patients with uncommon severe forms of UTI, such as emphysematous pyelonephritis. Other organisms include *Acinetobacter* species, group B streptococci and *P. aeruginosa* [72]. The latter should be suspected particularly if there is a history of recent instrumentation or hospitalization.

C. albicans in the urine can be associated with incomplete bladder emptying and high glucose concentrations in the urine. Diabetes has been shown to be present in 39% of hospitalized patients with funguria [72]. Candiduria may signify contamination of the urine specimen, benign saprophytic colonization (± catheter), or may be indicative of true invasive infection of the upper and/or lower urinary tract [80]. Diabetes is also a risk factor for multidrug-resistant UTI, perhaps related to recurrent or increased exposure to antibiotics [81].

Clinical features of urinary tract infection in diabetes

Uncomplicated UTIs may be asymptomatic. Symptoms, when present, are generally similar to those experienced by the non-diabetic population. Infection of the lower urinary tract usually presents as dysuria, frequency or urgency. Fever, flank pain, chills and rigors, vomiting and costovertebral angle tenderness raise the suspicion of upper tract infection with renal involvement. Bilateral renal involvement is also more frequent and bilateral pyelonephritis is twice as common in people with diabetes. Bacteremia may be present.

A poor response to appropriate antibiotic therapy should raise the suspicion of the presence of complications. These may include renal papillary necrosis and perinephric abscess. The symptoms of renal papillary necrosis include flank and abdominal pain (which mimic both pyelonephritis and ureteric colic), together with fever. Renal functional impairment is commonly found. Features such as a persisting high fever despite antibiotic treatment, hypotension or septicemic shock, and a palpable tender renal mass may point to the presence of a perinephric abscess. In one series of patients with perinephric abscess, 36% had diabetes [82].

Emphysematous cystitis and emphysematous pyelonephritis

Although uncommon, the severity of these infections warrants their special consideration. Emphysematous cystitis is an uncommon complication of lower UTI characterized by the presence of gas in the bladder wall (Figure 50.4). It presents with hematuria, pneumaturia and abdominal pain. Plain abdominal radiography or CT scan are indicated to detect the presence of gas. Surgical intervention may be required in up to 20% of cases and mortality is reportedly up to 10%. Emphysematous cystitis requires aggressive treatment in hospital and intravenous antibiotic therapy [83].

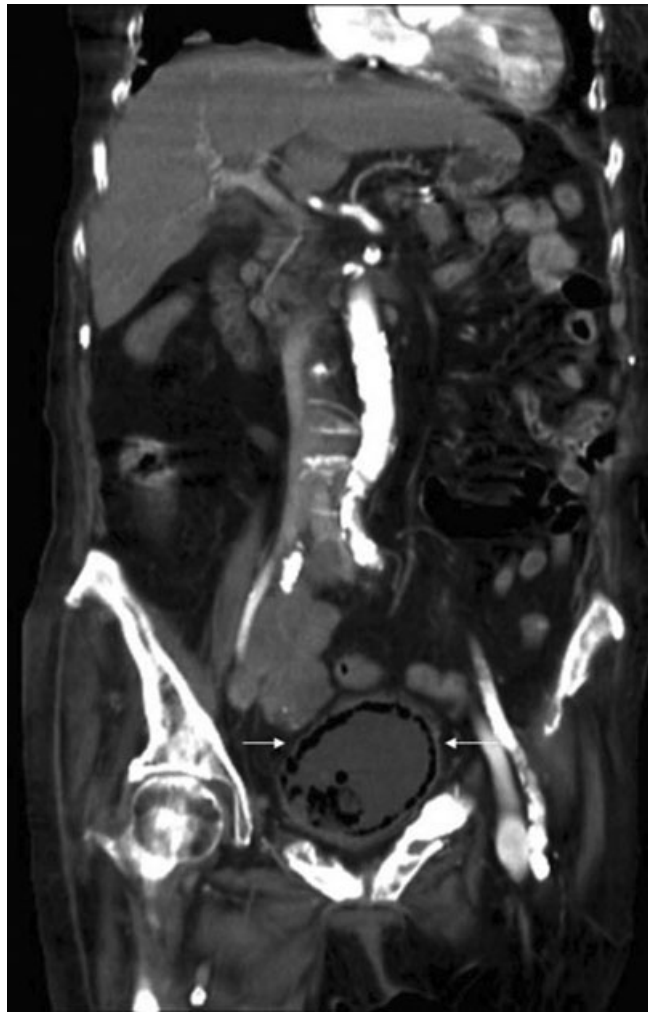


Figure 50.4 Example of emphysematous cystitis in a 67-year-old woman with diabetes and end-stage renal disease (ESRD) requiring hemodialysis. She developed septic shock with lower abdominal tenderness. Blood and urine cultures show *E. coli*. Computed tomography (CT) scan shows air pockets inside the urinary bladder (arrows). From Sun JT, Wang HP, Lien WC. Life-threatening urinary tract infection. *Q J Med* 2009; **102**:223, with permission.

Emphysematous pyelonephritis is an infection that is almost exclusively limited to people with diabetes, who account for 90% of cases (Figure 50.5). It predominantly occurs in females and carries a grave prognosis [84]. It is a necrotizing infection of the renal parenchyma and surrounding areas which can be focal or diffuse and may spread to the collecting system or perinephric tissues. The formation and presence of gas in the renal parenchyma, collecting system or perinephric area may be contributed to by fermentation of glucose when present at high concentra-

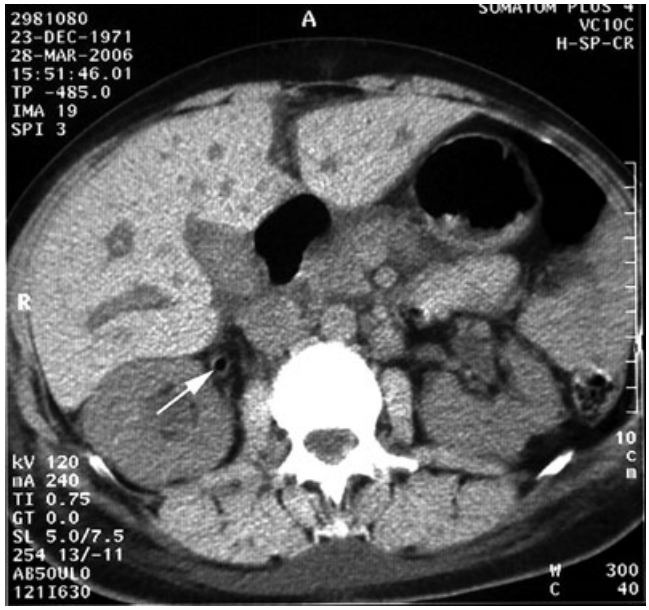


Figure 50.5 Emphysematous pyelonephritis: computed tomography tomography (CT) scan demonstrating gas in the right ureter (indicated by arrow) and a moderate hydronephrosis in a 34-year-old woman with type 1 diabetes. The responsible was organism was *E. coli*. She responded to antibiotics and drainage by nephrostomy, followed by ureteroscopy during which obstructing necrotic slough was removed. From Clark T, Abdalkareem M, Ali K. A case of emphysematous pyelonephritis. *J R Soc Med* 2009; **102**:75–77, with permission.

tions, by the presence of gas-forming organisms and by impaired renal perfusion. Mixed acid fermentation of glucose by Enterobacteriaceae has been suggested as a major pathway of gas formation [85].

A lengthy list of pathogens has been reported; however, as with other UTIs in the context of diabetes, the most common pathogens are *E. coli* (in 70%) and *Klebsiella* (in 30%). Vasculopathy of the renal circulation is believed to be a major factor in the pathogenesis, once again emphasizing the importance of vascular disease in the clinical manifestation of the more severe forms of infection related to diabetes.

Presenting features include fever, abdominal pain, nausea and vomiting and drowsiness or stupor. As a result of these nonspecific symptoms the diagnosis is often delayed. The presence of features such as renal angle tenderness, pyuria or pneumaturia should lead to a high index of suspicion. A flank mass may be detected, often accompanied by crepitus. Disseminated intravascular coagulation, septicemic shock and acute renal failure are all associated with a poor prognosis.

The diagnosis is established by radiologic identification of gas in renal tissue. This is best demonstrated by CT. The plain abdominal X-ray sensitivity is lower. Ultrasonography can also be used, but CT should be regarded as the investigation of choice. In a report of 46 cases in Taiwan, 96% had diabetes with HbA_{1c} higher than 8% (>64 mmol/mol), and 22% also had features of obstruction [86]. Mortality can exceed 50% in patients treated with antibiotics alone. Medical therapy alone is therefore not recommended. Patients may require percutaneous drainage (for localized cases with abscess formation or obstruction) or nephrectomy (in extensive cases). The advent of CT has allowed a more rational approach to the use of these surgical interventions, by allowing more accurate delineation of factors such as gas distribution, obstruction and abscess formation [87].

Diagnosis of urinary tract infection

A high index of suspicion is required, with particular attention in the presence of diabetic neuropathy, renal dysfunction or renal papillary necrosis. Microscopic examination of the urine may reveal leukocytosis and pyuria. Urine culture and sensitivity should always be carried out. In febrile patients or in suspected upper tract infection, blood culture is essential to detect bacteremia or Gram-negative septicemia.

Plain abdominal radiography is useful to help rule out obstructive uropathy, stones and emphysematous infection. Ultrasonography is a sensitive, safe and inexpensive technique for initial screening. Ultrasound or CT can confirm the diagnosis of renal abscess, mass, presence of air in the urinary tract and the extent of perinephric spread of infection. The diagnosis of renal papillary necrosis may require ultimate confirmation by retrograde pyelography.

Treatment of urinary tract infection

Treatment should be tailored to take account of local antibiotic resistance patterns (if known), as well as previous history of UTI, previous antibiotic exposure (and possible allergies) together with other risk factors such as recent instrumentation or catheterization. Uncomplicated UTI may be treated with co-trimoxazole (if the local resistance rate is <15–20%), fluoroquinolones, nitrofurantoin, ampicillin, amoxicillin +/– clavulanate, or sulbactam. Increasing resistance to fluoroquinolones has been noted recently. Co-trimoxazole may potentiate the hypoglycemic effect of some oral antihyperglycemic agents and should be used with caution.

Complicated infections require hospitalization and parenteral antibiotics. Intravenous therapy is continued until fever resolves, following which oral antibiotics can be substituted to complete at least 2 weeks of treatment. Second or third-generation cephalosporins, β-lactam/β-lactamase inhibitor combinations, or fluoroquinolones may need to be considered in patients with risk factors, and the possibility of infection with *Pseudomonas* may influence this choice, particularly in the setting of nosocomial exposure or recent instrumentation.

Because upper urinary tract involvement with UTI may be up to 5 times more frequent in patients with diabetes compared with people without diabetes and may be unsuspected or asymptomatic. More prolonged courses of antibiotics (7–14 days) may be considered wise even in the context of apparently uncomplicated UTI [84]. This may also reduce the risk of subsequent relapse. Repeated urine culture to document bacteriologic cure 2–4 weeks post-treatment is advisable given high rates of relapse or treatment failure.

Distinguishing *Candida* infection from colonization is difficult. Removal of an indwelling catheter, if present, is recommended as an initial intervention. Antifungal agents such as fluconazole may be considered in patients with invasive disease.

Intra-abdominal infections other than those within the urinary tract

Emphysematous cholecystitis

Cholecystitis is probably no more common in patients with diabetes than in the general population; however, severe fulminating infection, especially with gas-forming organisms (enteric Gram-negative rods and anaerobes) is more common.

Emphysematous cholecystitis is a rare variant of acute cholecystitis caused by ischemia of the gallbladder wall and infection with gas-producing organisms. It is strongly associated with diabetes (35–55% of cases have underlying diabetes) [88].

Gangrene and perforation of the gallbladder are more frequent, and the overall mortality is substantially higher (at least 15% compared to less than 4%) when compared with acute cholecystitis.

Clostridium perfringens, *E. coli* and *Bacillus fragilis* are the most frequently encountered pathogens. Emphysematous cholecystitis is thought to result from acalculous cystic duct obstruction, associated with inflammatory edema, which can eventually lead to cystic artery occlusion. Colonization by gas-forming organisms contributes to necrosis of the mucosa, venous congestion, gangrene and, eventually, gallbladder perforation. Gallstones are present in only about half of patients.

The early clinical manifestations may be indistinguishable from those of acute cholecystitis. Right hypochondrial pain and fever are present in all cases, and other important features include nausea and vomiting, septic shock, jaundice and peritonitis. Toxicity is marked, and jaundice may develop in the later stages from biliary obstruction. The gallbladder may be palpable in 25–50% of patients. It should be remembered that Murphy sign (pain and inspiratory arrest on palpation of the right upper quadrant) may be absent in patients with underlying diabetic neuropathy. Crepitus on palpation is an ominous sign. Additional complications include pericholecystic abscess, gallbladder necrosis, generalized or biliary peritonitis, and localized perforation sealed by the omentum.

Plain abdominal X-ray or ultrasound can lead to diagnosis in 95% of cases. In a plain radiograph, gas may be visible in the gallbladder lumen or within the gallbladder wall as a gaseous ring. CT is the most sensitive modality for the detection of intraluminal or intramural gallbladder gas and also demonstrate local complications such as pericholecystic inflammatory changes, abscess formation or perforation.

Initiation of appropriate antibiotics and early cholecystectomy is crucial. Emergency surgery is needed because of the high incidence of gangrene and perforation [89,90].

Liver and other intra-abdominal abscesses

Although liver abscesses may occur in many situations not involving diabetes, the issue is of sufficient importance to justify inclusion in this section.

In keeping with the susceptibility to *Klebsiella* infections described earlier, associations between diabetes and *K. pneumoniae* liver abscess have been reported, notably from Taiwan and Korea [91–93]. Examples from Hong Kong are shown in Figure 50.6.

In Korea, invasive liver abscess is particularly associated both with *K. pneumoniae* (78% of the total, 40% of whom have diabetes)) and with the K1 serotype (60%) [27].

Diabetes is the most common underlying risk factor specifically for the virulent K1 serotype, but not for non-*Klebsiella* abscesses [94]. In a population-based series of pyogenic liver abscess reported from Taiwan and including 29 703 subjects [95], diabetes was a risk factor in 33% leading to an odds ratio of 9 and was associated with an increasing incidence. Liver abscess in people with diabetes was not, however, associated with increased mortality, particularly if therapeutic percutaneous drainage procedures are performed. Eighty percent were associated with *K. pneumoniae* and not as a mixed infection with other organisms. Primary liver abscess in other parts of Asia is also increasing in incidence [27], with 40% reportedly associated with diabetes. Bacteremia is present in 50%, and 8–10% of these cases have metastatic complications (e.g. endophthalmitis, meningitis, brain abscess, pneumonia, skin and soft tissue lesions).

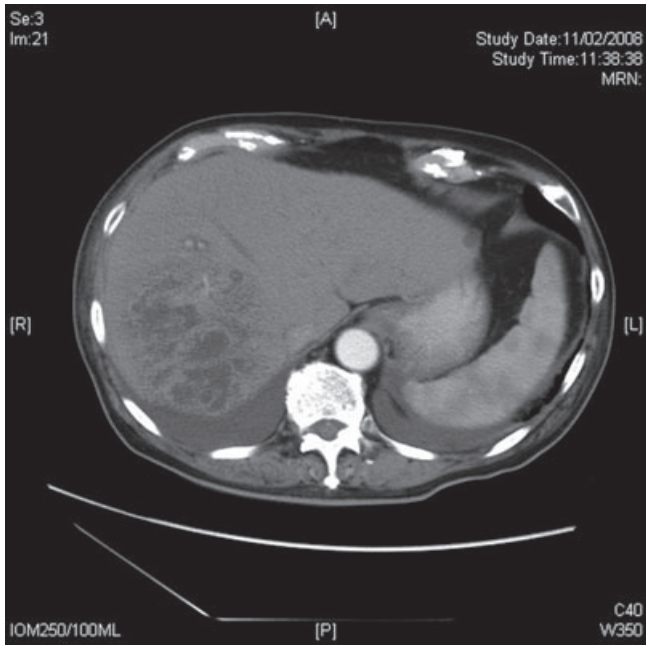
In a series from Europe (n = 1448), the presence of diabetes was associated with a 3.6-fold increase in risk for pyogenic liver abscess, and also with a higher 30-day post-discharge mortality rate compared with patients who did not have diabetes [96].

In the context of the K1 serotype of *Klebsiella* species, a pathogenic role for the magA gene in the serotype-specific region of the K1 capsule gene cluster, together with a K1 capsular polysaccharide per se, is considered as one of the virulence determinants essential for the development of invasive liver abscess. MagA, an outer membrane protein contributing to capsular polysaccharide formation, coexists with serotype K1 and has been identified as the major virulence factor of *K. pneumoniae* [95]. Poor glycemic control also has a role by impairing neutrophil phagocytosis of K1/K2 type *K. pneumoniae*, whereas it does not significantly affect the phagocytosis of non-K1/K2 *K. pneumoniae*. An rmpA-associated hypermuco-viscosity phenotype has also been reported in invasive purulent diseases caused by *K. pneumoniae*.

Most isolates are susceptible to cephalosporins (especially third-generation agents) and fluoroquinolones; however, therapeutic drainage is also needed and also assists with obtaining specimens for culture and susceptibility testing.

Metastatic abscesses may occur elsewhere in the abdomen, either singly or in combination with other sites, as well as within the urinary tract. A notorious, although uncommon, example is psoas abscess where responsible organisms are likely to be *S. aureus*, *Mycobacterium tuberculosis*, *E. coli* or *Klebsiella*.

(a)



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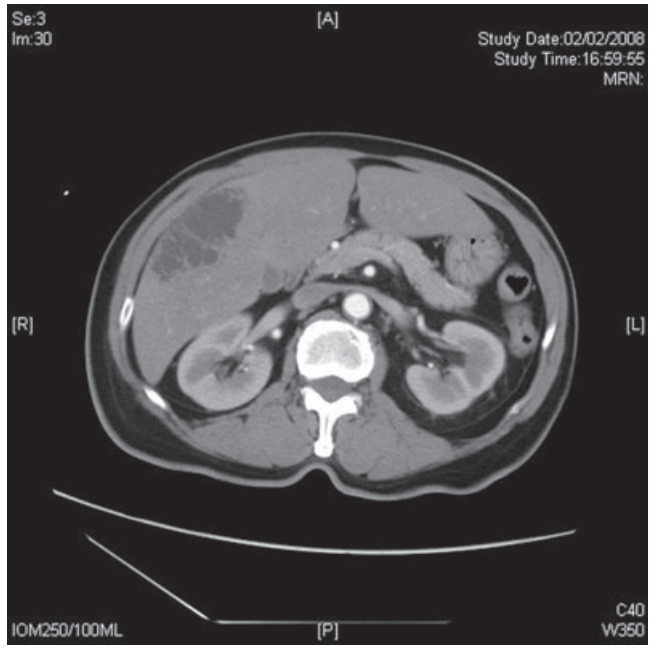

Figure 50.6 (a) CT-scan of an 82-year-old man with fever and newly diagnosed diabetes. Blood culture grew *Klebsiella pneumoniae*. The scan shows an 8 × 8.2 cm heterogeneous lesion in the right lobe of the liver composed of multiple rim enhanced lesions, with septation and hypodense cystic components. A further three smaller similar lesions (1–2.5 cm) were also seen inferiorly. Overall features are suggestive of liver abscesses. The patient recovered with drainage and antibiotics. (b) CT-scan of a 77-year-old woman with underlying diabetes, fever and right upper quadrant pain. Both blood culture and pus (from the liver abscess) grew *K. pneumoniae*. The CT scan shows an irregular ovoid lesion with multiple locules and thin intervening septations in the periphery of liver segment V and measuring 7.3 × 3.2 × 6.1 cm. The features suggest liver abscess with signs of early liquefaction. The patient recovered with drainage and antibiotics. The authors acknowledge the Department of Diagnostic Radiology and Organ Imaging, Prince of Wales Hospital, Chinese University of Hong Kong for kindly supplying the images and permitting their use.

Skin and superficial soft tissue infections

Skin and subcutaneous tissues

Infections involving the skin, nails and subcutaneous tissues are very common, and the skin and subcutaneous tissues are frequent targets of infection in diabetes, particularly in association with poor glycemic control. Candidal infections, bacterial infections such as furunculosis, dermatophycoses and onychophycoses are all commonly seen and may be the reason for diabetes being identified. Cutaneous forms of mucormycosis or other fungal infections may occur and be diagnosed following skin biopsy. More detailed consideration is given to these disorders in Chapter 47 and are not repeated here.

Sensory neuropathy, atherosclerotic vascular disease and hyperglycemia predispose patients with diabetes to skin and soft tissue infections. Additional risk factors for the development of cellulitis include a past history of cellulitis, edema, peripheral vascular disease, tinea infection and dryness of the skin. The predominant organisms involved are group A streptococcus (GAS) and *S. aureus*. Cellulitis can also occur in less usual settings. For example with *S. pneumoniae* (pneumococcal) infections, cellulitis may occur in association with extracutaneous foci of disease, the suggestion being that, in this setting, the cellulitis results from hematogenous spread rather than local infection [97].

People with diabetes, particularly those who inject insulin, often have asymptomatic nasal, mucosal and skin colonization with potential pathogens such as *S. aureus*. Nasal colonization may also contribute to increased risk of staphylococcal pneumonia, for example in association with influenza.

According to data from the National Health and Nutrition Examination Survey (NHANES), people with diabetes who are colonized with *S. aureus* are also more likely to have a methicillin-resistant *S. aureus* isolate than a susceptible one (odds ratio 2.6; 95% CI 1.1–6.1) [98]. A recent increase in community-associated methicillin-resistant *S. aureus* (CA-MRSA) gives additional cause for concern. A recent report evaluating CA-MRSA in three communities found that 77% of skin or soft tissue infections were methicillin-resistant [99]. The underlying conditions identified included smoking (35%), previous skin infection (21%) and diabetes (19%).

Mucosal and skin colonization with *C. albicans* is also common and may involve numerous sites including the genitalia of both sexes as well as the mouth, skin and nails [100]. Balanitis and vulval candidiasis are common presenting features of diabetes.

Colonization may predispose to cutaneous or incisional staphylococcal (or other bacterial) infections as well as transient bacteremia. Entry sites may also include areas of fungal skin infection (e.g. intertrigo). Infection at distant sites with abscess formation or septicemia may then ensue. In two relatively early

studies (each from the 1960s) older patients with diabetes were shown both to be at greater risk of staphylococcal septicemia and also to suffer a substantially higher mortality (69% in the diabetic patients compared to 42% overall) [101,102].

Deeper soft tissue infections

Deeper soft tissue infections also occur with increased frequency in people with diabetes. Examples include pyomyositis, necrotizing fasciitis and Fournier gangrene. Pyomyositis, usually associated with infection by *S. aureus*, occurs in muscles that have undergone trauma, especially when associated with hematoma formation.

Necrotizing fasciitis

Necrotizing fasciitis is a deep-seated life-threatening infection of subcutaneous tissue. Progressive destruction of fascia, fat and muscle ensues. Although relatively uncommon, necrotizing fasciitis is a life-threatening condition. Necrotising fasciitis and Fournier gangrene (a form of necrotizing fasciitis involving the perineum), as well as other necrotizing soft tissue infections resulting from a variety of organisms, all have reported associations with diabetes. Diabetes is the most common of a number of conditions predisposing to necrotizing fasciitis, all of which are associated with compromise to the immune system.

As its name indicates, necrotizing fasciitis spreads initially along fascial planes; however, as infection and inflammation progress, necrosis of muscle, subcutaneous tissues and overlying skin occurs. Necrotizing fasciitis usually follows identifiable episodes of trauma such as burns, insect bites or abrasions, or can result from exposure of non-intact skin to a source of infection. The most common sites are the limbs, abdominal wall and perineum. Involvement of the vulva in women with diabetes may begin as a Bartholin gland ductal abscess, usually associated with obesity [103].

Polymicrobial infection is most commonly observed, with streptococci and Enterobacteriaceae being the most common isolates. The great majority of cases result from infection with anaerobes together with one or more facultative aerobes, whereas about 10% are associated with GAS, with or without *S. aureus*. Thus, GAS is the most common cause of infection by a single organism and can also occur in combination with staphylococci, including CA-MRSA. A recent article describing necrotizing fasciitis caused by CA-MRSA showed that although current or past intravenous drug abuse underlay 43% of patients, 21% occurred in people with diabetes [104].

Vibrio, *Aeromonas*, *Haemophilus* and *Salmonella* infections have also been reported. An interesting example is infection by halophilic marine *Vibrios* either following exposure of non-intact skin to seawater [105] or following bites by marine organisms, such as crabs, and this should be considered when a history of appropriate exposure is present.

Necrotizing fasciitis carries a high mortality, particularly when affecting the lower extremities or perineum, and is rapidly fatal unless diagnosed promptly and treated aggressively. It may be initially misdiagnosed as a benign soft tissue infection and a high index of suspicion is therefore required. Skin changes may be minimal in the early phase of infection.

Early disease may be characterized by severe local pain, which is either disproportionate to or precedes other clinical features such as local inflammation and cellulitis, fever and systemic toxicity. Cellulitis may spread rapidly, unseen in deeper fascial planes. Crepitus is present in about half of cases. Violaceous discoloration of the skin may be noticed and may progress into blistering and bullae. Thrombosis and vasculitis each contribute to necrosis of the superficial fascia and suppuration from liquefactive necrosis. Gangrene and ulceration can result. Anesthesia of overlying skin may indicate destruction of subcutaneous nerves.

Plain radiographs, ultrasound, CT and MRI scan can each assist in both diagnosis and management by identifying the presence of gas in the tissues and by delineating the extent of the disease. Aerobic and anaerobic cultures should be taken from within the lesion, as should blood cultures.

Surgical débridement and fasciotomy are the mainstays of therapy. The single most important issue influencing mortality is time to surgical débridement. Thus, timely diagnosis, empirical broad-spectrum antibiotic therapy (including anaerobic cover) and aggressive surgical débridement of affected tissue are crucial components of management. The antibiotic cover can subsequently be tailored according to culture and sensitivity results. Additional supportive therapy in an intensive care environment should be provided where possible and as necessary.

Fournier gangrene

Fournier gangrene is a specific form of necrotizing fasciitis involving the perineum, scrotum and penis. Overall mortality is very high. As with other forms of necrotizing fasciitis, diabetes is the most common of a number of potential predisposing conditions with a reported presence ranging 32–60% of cases [106,107]. Infection is usually polymicrobial with a lengthy list of potential pathogens which is similar to that seen in other forms of necrotizing fasciitis (*E. coli*, *Bacteroides* spp, staphylococci, streptococci, *Proteus* spp, *Pseudomonas* spp, enterococci). *C. perfringens* is present in the great majority (>90%) of cases in which myonecrosis is present.

Initial malaise and scrotal discomfort or pain is followed by systemic toxicity. Blistering ulceration and necrosis of the skin occur and in the later stages progress to scrotal swelling and a foul purulent discharge. Crepitus may be present. Sources of infection include abnormalities of the urogenital system (most notably urethral trauma, instrumentation or a chronic indwelling catheter, scrotal abscess or injury, insect bite) and local gastrointestinal abnormalities (e.g. ischiorectal or perianal abscess, incarcerated inguinal hernia).

Diagnosis is predominantly clinical. Radiologic imaging techniques may reveal subcutaneous gas and delineate the extent of involvement, as with other forms of necrotizing fasciitis.

Fournier gangrene is a surgical emergency, and extensive débridement is required. Urinary or faecal diversion may be

required, as may laparotomy. Broad-spectrum antibiotic therapies with anaerobic cover, as well as general supportive measures are indicated as with other forms of necrotizing fasciitis. The results of microbiologic investigation may allow subsequent tailoring of antibiotics.

Infected diabetic foot

Foot infection is the most common soft tissue infection associated with diabetes and therefore is a topic of the utmost importance to all who deal with people with diabetes. Detailed coverage of this topic is provided in Chapter 44. In order to avoid duplication, the topic receives only brief discussion in this chapter.

Disease-related peripheral neuropathy and peripheral vascular disease are both important in the etiology of foot infections, although the clinical presentations of the "predominantly ischemic" and the "predominantly neuropathic" foot differ. Serious complications include osteomyelitis, amputation, or even death. Infection often begins after minor trauma, which may be unnoticed, especially in the presence of sensory neuropathy. Cellulitis, soft tissue necrosis and extension into bone, leading to osteomyelitis, may then follow. Involved organisms most commonly include GAS and *S. aureus*, as well as aerobic Gram-positive cocci, Gram-negative rods and anaerobes.

The mainstays of management include exploration and débridement of the necrotic tissue and administration of appropriate antibiotics. In moderate to severe cellulitis or in the presence of osteomyelitis that places the limb at risk, the patient should be hospitalized for broad-spectrum antibiotic therapy and surgical intervention.

As in most diabetes-related infections, poor glycemic control plays an important part, and foot infections remain a common presenting feature of newly diagnosed diabetes, particularly in less developed parts of the world. Prevention of foot ulcers involves a multidisciplinary team approach. Foot care is an essential component of all diabetes education programs and should include proper foot care habits, protective footwear and pressure reduction.

Bone and joint infections

Bone and joint infections remain a significant problem for people with diabetes and can be very difficult to treat. Diabetes is a risk factor for both osteomyelitis and septic arthritis.

The different types of osteomyelitis require differing medical and surgical therapeutic strategies. The three main types, classified according to etiology, include osteomyelitis secondary to a contiguous focus of infection (e.g. after trauma, surgery or insertion of a joint prosthesis); osteomyelitis secondary to vascular insufficiency (e.g. diabetic foot infections); or osteomyelitis secondary to hematogenous spread of infection. The most common reason for septic arthritis is following insertion of joint prostheses. All are more common in people with diabetes, with osteomyelitis of the foot at the forefront. Taking, as an example, osteomyelitis of the spine, then a recurring theme occurs with a combination of both increased risk of hematogenous vertebral osteomyelitis (two- to sixfold) and predisposition to infection involving unusual organisms [108]. Acute osteomyelitis can respond to antibiotics alone but prolonged courses are required for bone and joint infections given the physiologic and anatomical characteristics of the tissues involved. Early diagnosis, together with bone sampling for microbiologic and pathologic examination to allow targeted and long-lasting antimicrobial therapy, allows the best outcomes. As with the diabetic foot, a multidisciplinary approach is required for success, including expertise in orthopedic surgery and infectious diseases, together with vascular surgery. Surgical intervention should be considered if medical treatment fails, for diagnostic confirmation or in the presence of complications.

Chronic osteomyelitis may be associated with avascular necrosis of bone and formation of sequestrum (dead bone), and surgical débridement is then necessary for cure in addition to antibiotic therapy. It is important to remember the possibility of infection by *M. tuberculosis* [109].

Iatrogenic and surgical site infections

Insulin injections

Infections at the site of insulin injections are very uncommon and remain so even when traditional hygienic practices are not applied. Although not advised, administration of insulin through clothing is also not associated with increased risk of infection. Abscesses at needle sites are occasionally seen in individuals receiving subcutaneous insulin infusions [110]. Likewise, pulp infection over the distal phalanges in association with self blood glucose monitoring is exceedingly unusual.

Surgical site infections

An association between diabetes and an increased risk of surgical site infections has been known to exist for many years. Most of the studies addressing this question have focused on the risk of postoperative infection following coronary artery bypass grafting (CABG). The association has been generally assumed to be causally related to the deleterious effect of hyperglycemia on immune function [111].

Three studies support an increased risk of postoperative infection associated with postoperative hyperglycemia among those with diabetes undergoing CABG [112–114]; however, whether or not hyperglycemia imposes an independent risk for infection remains controversial. In none of the studies was mortality increased and, in one, postoperative hyperglycemia was correlated with a higher risk of infection while an elevated HbA_{1c} was not. The studies do demonstrate, however, that improved glucose control during the operative and perioperative period can reduce the risk of postoperative infections in people with diabetes undergoing cardiac surgery. One retrospective study of 1574 patients undergoing CABG at a single institution found no increase in mortality or rates of infection among those with higher postoperative glucose levels and 34.6% of patients in this series had a diagnosis of diabetes. Nevertheless, increased glucose concentra-

tions were associated with increased hospital charges and a longer postoperative stay.

Both allograft rejection and risk for infection appear to be higher in transplant recipients with diabetes. In one study, the risk of serious infection was higher in diabetic heart transplant recipients in the early postoperative period [115]. In another study, renal transplant recipients had a greater risk of both acute allograft rejection and infection when perioperative glycemic control was poor [116].

Dialysis

Ambulatory peritoneal dialysis is a common form of treatment for end-stage renal disease in people with diabetes. For patients receiving continuous ambulatory peritoneal dialysis (CAPD), episodes of catheter-related peritonitis are common, although variable from patient to patient, with some developing multiple episodes. Overall, however, the rate of infection does not appear to be greater in patients with diabetes than patients without diabetes, perhaps reflecting impairment of immunity associated with end-stage renal disease per se.

The issue of peritonitis in patients receiving CAPD is an important one given the large number of people with diabetes receiving this treatment. It is well recognized that peritonitis, despite significant reductions in the last two decades, remains the most important complication of CAPD with an overall mortality of about 3.5%, irrespective of both the underlying cause of the infection and of the renal failure [117]. The degree to which the presence of diabetes adds to the already considerable infection risk remains uncertain. People with diabetes may, however, be generally more unwell and have additional factors and complications such as macrovascular disease, need for hospitalization and predilection to certain infections, such as candidiasis. All of these may, in principle, contribute to the already very considerable risk.

Principles of treatment, prevention and general care

General principles

A high level of awareness is required in people with diabetes and in all health care providers, both to allow prevention and early, prompt recognition and diagnosis. Education, good glycemic control and general measures to maintain health and nutrition are all important measures aimed at minimizing risk. Careful attention to foot care is particularly emphasized. Vigilant measures should be instituted to prevent infection in patients with diabetes. When infections do occur, evolving antibiotic resistance patterns and other local factors must be considered, with CA-MRSA and tuberculosis both providing obvious examples of the importance of this.

The choice of antibiotic therapy follows the same general principles as for any other individual. Use of empirical broad-spectrum antibiotics is generally recommended until microbiologic results can guide treatment. Due caution should be applied in the presence of diabetic complications. For example, the use of potentially nephrotoxic agents in the context of diabetic nephropathy may aggravate renal dysfunction, and in turn impaired renal function requires caution with doses and monitoring of blood levels. The presence of gastroparesis or autonomic neuropathy may hinder, or render unreliable, the absorption of oral drugs. Patients who are blind or partially sighted as a result of eye complications may also be at increased risk, for example when exposed to drugs that impair hearing or balance. Longer courses of antibiotic therapy may be appropriate, for instance in treating UTI.

Antiviral agents are recommended in the setting of influenza, and a more aggressive treatment approach may be appropriate even when presentation is relatively late [62]. Responses to treatment should also be carefully monitored (e.g. in the case of tuberculosis) [70]. The importance of appropriate referral to surgical or other specialist colleagues has been stressed repeatedly. Examples include surgical débridement in the case of necrotizing fasciitis, and incision and drainage of abscesses.

People with diabetes generally have a normal response to vaccines and should receive immunizations according to established guidelines. None of the vaccines currently available are contraindicated on the basis of diabetes alone. Because of increased susceptibility to complications, routine immunization against pneumococcus and influenza is recommended, particularly for the elderly patient with diabetes or for those with additional comorbidity such as chronic respiratory disease. Influenza vaccination has been shown to reduce hospital admissions significantly during influenza outbreaks [118]. Hepatitis B vaccination is also important although some populations may require additional or booster doses over and above standard recommended regimens.

Glycemic control

All physicians need to be aware of the importance of careful monitoring of diabetic control in the presence of infection and should be on guard against destabilization of control or development of complications. Interestingly, in people without diabetes following hospitalization, even mild degrees of hyperglycemia are associated with increased mortality in association with severe illness. Although depressed immune function correlates somewhat variably with traditional measures of glycemic control, there is sufficient evidence to indicate an inverse relationship between the two which is potentially reversible. Previously undiagnosed diabetes may also be first detected following hospitalization and then needs to be distinguished from hospital-related hyperglycemia which later reverts to normal.

Patients with T1DM or others receiving insulin need to be aware of the probability of changing insulin requirements in response to infection and to the risk of severe consequences such as diabetic ketoacidosis. Many patients with T2DM, who are not on insulin, need to be transferred temporarily to insulin therapy as the stress of illness frequently adversely affects glycemic control. Hospital admission is mandatory if severe destabilization of glycemic control occurs, or if symptoms such as nausea and vomit-

ing interfere significantly with oral food intake. In this situation, intravenous insulin-glucose regimens are recommended. While good glycemic control is important, it is also important to avoid hypoglycemia. Interaction between the diabetes care team and other involved specialists should be initiated as early as possible.

The importance of perioperative glycemic control in patients with diabetes undergoing surgery also needs to be emphasized in order to minimize negative impacts upon postoperative infection rates and wound healing (see Chapter 32).

Attention to other risk factors (e.g. neurologic and vascular complications) is also important in order to minimize the risk of infections and infection-related complications. The importance of the presence of microangiopathy and neuropathy in the risk of the more severe forms of infection is again emphasized.

For more detailed description of these aspects of care, readers are referred to clinical practice recommendations, for example those of the American Diabetes Association [119] or to other national or international guidelines, as well as to other relevant chapters in this book.

Awareness among physicians needs to be high, especially with regard to the unusual and severe forms of infection that may occur. The general approach to antibiotic treatment is the same as for patients without diabetes, but details may differ (e.g. doses and duration of therapy). Responses to vaccination are generally normal, and influenza and pneumococcal vaccination is recommended. Careful attention to glycemic control and to other underlying factors is essential.

References

1 Muller L, Gorter KJ, Hak E, Goudzwaard WL, Schellevis FG, Hoepelman AI, *et al*. Increased risk of common infections in patients with type 1 and type 2 diabetes mellitus. *Clin Infect Dis* 2005; **41**:281–288.

2 Shah BR, Hux JE. Quantifying the risk of infectious diseases for people with diabetes. *Diabetes Care* 2003; **26**:510–513.

3 Laupland KB, Gregson DB, Zygun DA, Doig CJ, Mortis G, Church DL. Severe bloodstream infections: a population-based assessment. *Crit Care Med* 2004; **32**:992–997.

4 Bertoni AG, Saydah S, Brancati FL. Diabetes and the risk of infection-related mortality in the United States. *Diabetes Care* 2001; **24**:1044–1049.

5 Kornum JB, Thomsen RW, Riis A, Lerving HH, Schonheyder HC, Sorensen HT. Type 2 diabetes and pneumonia outcomes: a population-based cohort study. *Diabetes Care* 2007; **30**:2251–2257.

6 Booth CM, Matukas LM, Tomlinson GA, Rachlis AR, Rose DB, Dwosh HA, *et al*. Clinical features and short-term outcomes of 144 patients with SARS in the Greater Toronto Area. *JAMA* 2003; **289**:2861–2863.

7 Geerlings SE, Hoepelman AIM. Immune dysfunction in patients with diabetes mellitus (DM). *FEMS Immunol Medical Microbiol* 1999; **26**:259–265.

8 Lederman MM, Schifman GA, Rodman, HM. Pneumococcal immunization in adults. *Diabetes* 1981; **30**:119–121.

9 Beam T, Crigler ED, Goldman, JR, Schifmann G. Antibody response to polyvalent pneumococcal polysaccharide vaccine in diabetics. *JAMA* 1980; **244**:2641–2644.

10 Delamaire M, Maugendre D, Moreno M, Le Goff MC, Allannic H, Genetet B. Impaired leucocyte functions in diabetic patients. *Diabet Med* 1997; **14**:29–34.

11 Llorente L, De La Fuente H, Richaud-Patin Y, Alvarado-De La Barrera C, Diaz-Borjón A, López-Ponce A, *et al*. Innate immune response mechanisms in non-insulin dependent diabetes mellitus patients assessed by flow cytoenzymology. *Immunol Lett* 2000; **74**:239–244.

12 Hostetter MK. Handicaps to host defense: effects of hyperglycemia on C3 and *Candida albicans*. *Diabetes* 1990; **39**:271–275.

13 Katz S, Klein B, Elian I, Fishman P, Djaldetti M. Phagocytotic activity of monocytes from diabetic patients. *Diabetes Care* 1983; **6**:479–482.

14 Park S, Rich J, Hanses F, Lee JC. Defects in innate immunity predispose *db/db* mice to infection by *Staphylococcus aureus*. *Infect Immun* 2009; **77**:1008–1014.

15 Zykova SN, Jenssen TG, Berdal M, Olsen R, Myklebust R, Sljelid R. Altered cytokine and nitric oxide secretion *in vitro* by macrophages from diabetic type II-like db/db mice. *Diabetes* 2000; **49**:1451–1458.

16 Offenbacher S, Salvi GE. Induction of prostaglandin release from macrophages by bacterial endotoxin. *Clin Infect Dis* 1999; **28**: 505–513.

17 Geerlings SE, Hoepelman AL. Immune dysfunction in patients with diabetes mellitus (DM). *FEMS Immunol Med Microbiol* 1999; **26**:259–265.

18 Amano H, Yamamoto H, Senba M, Oishi K, Suzuki S, Fukushima K, *et al*. Impairment of endotoxin-induced macrophage inflammatory protein 2 gene expression in alveolar macrophages in streptozotocin-induced diabetes in mice. *Infect Immun* 2000; **68**:2925–2929.

19 Mazade MA, Edwards MS. Impairment of type III group B streptococcus-stimulated superoxide production and opsonophagocytosis by neutrophils in diabetes. *Mol Genet Metab* 2001; **73**:259–267.

20 Al-Mashat HA, Kandru S, Liu R, Behl Y, Desta T, Graves DT. Diabetes enhances mRNA levels of proapoptotic genes and caspase activity, which contribute to impaired healing. *Diabetes* 2006; **55**:487–495.

21 Li YM. Glycation ligation binding motif in lactoferrin: implications in diabetic infection. *Adv Exp Med Biol* 1998; **443**:57–63.

22 Falagas ME, Kompoti M. Obesity and infection. *Lancet Infect Dis* 2006; **6**:438–446.

23 Ferguson BJ. Mucormycosis of the nose and paranasal sinuses. *Otolaryngol Clin North Am* 2000; **33**:349–365.

24 Tsay WR, Siu LK, Fung CP, Chang FY. Characteristics of bacteraemia between community-acquired and nosocomial *Klebsiella pneumoniae* infection: risk factor for mortality and the impact of capsular serotypes as a herald for community-acquired infection. *Arch Intern Med* 2002; **162**:1021–1027.

25 Yinnon AM, Butnaru A, Raveh D, Jerassy Z, Rudensky B. *Klebsiella* bacteraemia: community versus nosocomial infection. *Q J Med* 1996; **89**:933–941.

26 Lee KH, Hui KP, Tan WC, Lim TK. *Klebsiella* bacteremia: a report of 101 cases from National University Hospital, Singapore. *J Hosp Infect* 1994; **27**:299–305.

27 Chung DR, Lee SS, Lee HR, Kim HB, Choi HJ, Eom JS, *et al*. Emerging invasive liver abscess caused by K1 serotype *Klebsiella* pneumoniae in Korea. *J Infect* 2007; **54**:578–583.

28 Chanchamroen S, Kewcharoenwong C, Susaengrat W, Ato M, Lertmemongkolchai G. Human polymorphonuclear neutrophil responses to *Burkholderia pseudomallei* in healthy and diabetic subjects. *Infect Immun* 2009; **77**:456–463.

29 Van der Werf N, Kroese FGM, Rozing J, Hillebrands JL. Viral infections as potential triggers of type 1 diabetes. *Diabetes Metab Res Rev* 2007; **23**:169–183.

30 Akatsuka H, Yano EC, Gabazza J, Morser J, Sasaki R, Suzuki T, *et al*. A case of fulminant type 1 diabetes with coxsackie B4 virus infection diagnosed by elevated serum levels of neutralizing antibody. *Diab Res Clin Pract* 2009; **84**:e50–e52.

31 Wills-Karp M, Santeliz J, Karp CL. The germless theory of allergic disease: revisiting the hygiene hypothesis. *Nat Rev Immunol* 2001; **1**:69–74.

32 Ling P, Bistrian B, Mendez B, Istfan NW. Effects of systemic infusion of endotoxin, tumour necrosis factor and interleukin-1 on glucose metabolism in the rat: relationship to endogenous glucose metabolism and peripheral tissue glucose uptake. *Metabolism* 1994; **43**:279–284.

33 Mason AL, Lau JY, Hoang N, Qian K, Alexander GJ, Xu L, *et al*. Association of diabetes mellitus and chronic hepatitis C virus infection. *Hepatology* 1999; **29**:328–333.

34 Grimbert S, Valensi P, Lévy-Marchal C, Perret G, Richardet JP, Raffoux C, *et al*. High prevalence of diabetes mellitus in patients with chronic hepatitis C: a case–control study. *Gastroenterol Clin Biol* 1996; **20**:544–548.

35 Knobler H, Stagnaro-Green A, Wallenstein S, Schwartz M, Roman SH. Higher incidence of diabetes in liver transplant recipients with hepatitis C. *J Clin Gastroenterol* 1998; **26**:30–33.

36 Ozyilkan E, Arslan M. Increased prevalence of diabetes mellitus in patients with chronic hepatitis C virus infection. *Am J Gastroenterol* 1996; **91**:1480–1481.

37 Simo R, Hernandez C, Genesca J, Jardi R, Mesa J. High prevalence of hepatitis C virus infection in diabetic patients. *Diabetes Care* 1996; **19**:998–1000.

38 Caronia S, Taylor K, Pagliaro L, Carr C, Palazzo U, Petrik J, *et al*. Further evidence for an association between non-insulin dependent diabetes mellitus and chronic hepatitis C virus infection. *Hepatology* 1999; **30**:1059–1063.

39 Mehta SH, Brancati FL, Sulkowski MS, Steffanie A, Strathdee MS, Thomas DL. Prevalence of type 2 diabetes mellitus among persons with hepatitis C virus infection in the United States. *Ann Intern Med* 2000; **133**:592–599.

40 Knobler H, Schattner A. TNF-α, chronic hepatitis C and diabetes: a novel triad. *Q J Med* 2005; **98**:1–6.

41 Howard AA, Klein RS, Schoenbaum EE. Association of hepatitis C infection and antiretroviral use with diabetes mellitus in drug users. *Clin Infect Dis* 2003; **36**:1318–1323.

42 Samaras K. Prevalence and pathogenesis of diabetes mellitus in HIV-1 infection treated with combined antiretroviral therapy. *J Acquir Immune Defic Syndr* 2009; **50**:499–505.

43 Tebas P. Insulin resistance and diabetes mellitus associated with antiretroviral use in HIV-infected patients: pathogenesis, prevention, and treatment options. *J Acquir Immune Defic Syndr* 2008; **49**(Suppl 2):S86–S92.

44 Wand H, Calmy A, Carey DL, Samaras K, Carr A, Law MG, *et al*. Metabolic syndrome, cardiovascular disease and type 2 diabetes mellitus after initiation of antiretroviral therapy in HIV infection. *AIDS* 2007; **21**:2445–2453.

45 Samaras K, Wand H, Law M, Emery S, Cooper D, Carr A. Prevalence of metabolic syndrome in HIV-infected patients receiving highly active antiretroviral therapy using International Diabetes Foundation and Adult Treatment Panel III criteria: associations with insulin resistance, disturbed body fat compartmentalization, elevated C-reactive protein, and [corrected] hypoadiponectinemia. *Diabetes Care* 2007; **30**:113–119.

46 Ledergerber B, Furrer H, Rickenbach M, Lehmann R, Elzi L, Hirschel B, *et al*. Factors associated with the incidence of type 2 diabetes mellitus in HIV-infected participants in the Swiss HIV Cohort Study. *Clin Infect Dis* 2007; **45**:111–119.

47 Wohl DA, McComsey G, Tebas P, Brown TT, Glesby MJ, Reeds D, *et al*. Current concepts in the diagnosis and management of metabolic complications of HIV infection and its therapy. *Clin Infect Dis* 2006; **43**:645–653.

48 Lundgren JD, Battegay M, Behrens G, *et al*.; EACS Executive Committee). European AIDS Clinical Society (EACS) guidelines on the prevention and management of metabolic diseases in HIV. *HIV Med* 2008; **9**:72–81.

49 Schambelan M, Benson CA, Carr A, Currier JS, Dubé MP, Gerber JG, *et al*. Management of metabolic complications associated with antiretroviral therapy for HIV-1 infection: recommendations of an International AIDS Society-USA panel. *J Acquir Immune Defic Syndr* 2002; **31**:257–275.

50 Papatheodoridis GV, Chrysanthos N, Savvas S, Sevastianos V, Kafiri G, Petraki K, *et al*. Diabetes mellitus in chronic hepatitis B and C: prevalence and potential association with the extent of liver fibrosis. *J Viral Hepat* 2006; **13**:303–310.

51 Cheng AY, Kong AP, Wong VW, So WY, Chan HL, Ho CS, *et al*. Chronic hepatitis B viral infection independently predicts renal outcome in type 2 diabetic patients. *Diabetologia* 2006; **49**:1777–1784.

52 Chandler JR. Malignant external otitis. *Laryngoscope* 1968; **78**:1257–1294.

53 Grandis JR, Branstetter IV BF, Yu VL. The changing face of malignant (necrotising) external otitis: clinical, radiological, and anatomic correlations *Lancet Infect Dis* 2004; **4**:34–39.

54 Lee FYW, Mossad SB, Adal KA. Pulmonary mucormycosis: the last 30 years. *Arch Intern Med* 1999; **59**:1301–1307.

55 Roden MM, Zaoutis TE, Buchana WL, Knudsen TA, Sarkisova TA, Walsh TJ. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. *Clin Infect Dis* 2005; **41**:634–653.

56 Ghadiali MT, Deckard NA, Farooq U, Astor F, Robinson P, Casiano RR. Frozen-section biopsy analysis for acute invasive fungal rhinosinusitis. *Otolarngology* 2007; **136**:714–719.

57 Walmsley RS, David DB, Allan RN, Kirkby GR. Bilateral endogenous *Escherichia coli* endophthalmitis: a devastating complication in an insulin-dependent diabetic. *Postgrad Med J* 1996; **72**:361–363.

58 Karacal H, Kymes SM, Apte RS. Retrospective analysis of etiopathogenesis of all cases of endophthalmitis at a large tertiary referral center. *Int Ophthalmol* 2007; **27**:251–259.

59 Oliver RC, Tervonen T. Periodontitis and tooth loss: comparing diabetics with the general population. *J Am Dent Assoc* 1993; **124**:71–76.

60 Ljubic S, Balachandran A, Pavlic-Renar I. Pulmonary infections in diabetes mellitus. *Diabetol Croat* 2005; **4**:115–124.

61 Marrie TJ. Bacteraemic pneumococcal pneumonia: a continuously evolving disease. *J Infect* 1992; **24**:247–255.

62 Lee N, Chan PK, Hui DC, Rainer TH, Wong E, Choi KW, *et al*. Viral loads and duration of viral shedding in adult patients hospitalized with influenza. *J Infect Dis* 2009; **200**:492–500.

63 Lipsky BA, Pecoraro RE, Chen MS, Koepsell TD. Factors affecting staphylococcal colonization among NIDDM outpatients. *Diabetes Care* 1987; **10**:483–486.

64 Valdez R, Narayan KM, Geiss LS, Engelgau MM. Impact of diabetes mellitus on mortality associated with pneumonia and influenza among non-Hispanic black and white US adults. *Am J Public Health* 1999; **89**:1715–1721.

65 Cheu KY, Hsueh PR, Liaw YS, Yang PC, Luh K. A 10 year experience with bacteriology of acute thoracic empyema. *Chest* 2000; **117**:1685–1689.

66 Jeon CY, Murray MB. Diabetes mellitus increases the risk of active tuberculosis: a systematic review of 13 observational studies. *PLoS Medicine* 2008;**5**; e152: doi:10.1371/journal.pmed.0050152.

67 Stevenson CR, Forouhi NG, Roglic G, Williams BG, Lauer JA, Dye C, *et al*. Diabetes and tuberculosis: the impact of the diabetes epidemic on tuberculosis incidence. *BMC Public Health* 2007; **7**:234.

68 Corbett EL, Watt CJ, Walker N, Maher D, Williams BG, Raviglione MC, *et al*. The growing burden of tuberculosis: global trends and interactions with the HIV epidemic. *Arch Intern Med* 2003; **163**:1009–1021.

69 Wang JY, Lee LN, Hsueh PR. Factors changing the manifestation of pulmonary tuberculosis. *Int J Tuberc Lung Dis* 2005; **9**:777–783.

70 Alisjahbana B, Sahiratmadja E, Nelwan EJ, Purwa AM, Ahmad Y, Ottenhoff TH, *et al*. The effect of type 2 diabetes on presentation and treatment response of pulmonary tuberculosis. *Clin Infect Dis* 2007; **45**:428–435.

71 Nijland HM, Ruslami R, Stalenhoef JE, Nelwan EJ, Alisjahbana B, Nelwan RH, *et al*. Exposure to rifampicin is strongly reduced in patients with tuberculosis and type 2 diabetes. *Clin Infect Dis* 2006; **43**:848–854.

72 Harding GM, Zhanel GG, Nicolle L, Cheung M. Antimicrobial treatment in diabetic women with asymptomatic bacteriuria. *N Engl J Med* 2002; **347**:1576–1583.

73 Stapleton A. Urinary tract infections in patients with diabetes. *Am J Med* 2002; **113**:80S–84S.

74 Geerlings SE, Stolk RP, Camps MJL, Netten PM, Collet JT, Schneeberger PM, *et al*. Consequences of asymptomatic bacteriuria in women with diabetes mellitus. *Arch Intern Med* 2001; **161**:1421–1427.

75 Hu KK, Boyko EJ, Scholes D, Normand E, Normand E, Chen CL, Grafton J, *et al*. Risk factors for urinary tract infections in postmenopausal women. *Arch Intern Med* 2004; **164**:989–993.

76 Scholes D, Hooton TM, Roberts PL, Gupta K, Stapleton AE, Stamm WE. Risk factors associated with acute pyelonephritis in healthy women. *Ann Intern Med* 2005; **142**:20–27.

77 Efstathiou SP, Pefanis AV, Tsioulos DL, Zacharos ID, Tsiakou AG, Mitromaras AG, *et al*. Acute pelonephritis in aults: prediction of mortality and failure of treatment. *Arch Intern Med* 2003; **163**:1206–1212.

78 Meiland R, Geerlings SE, Hoepelman ALM. Management of bacterial urinary tract infections in adult patients with diabetes mellitus. *Drugs* 2002; **62**:1859–1868.

79 Geerlings SE, Stolk RP, Camps MJL, Netten PM, Collet TJ, Hoepelman AI; Diabetes Women Asymptomatic Bacteriuria Utrecht Study Group. Risk factors for symptomatic urinary tract infection in women with diabetes. *Diabetes Care* 2000; **23**:1737–1741.

80 Vasquez JA, Sobel JD. Fungal infections in diabetes. *Infect Dis Clin North Am* 1995; **9**:97–116.

81 Wright SW, Wrenn KD, Haynes M, Haas DW. Prevalence and risk factors for multidrug resistant uropathogens in ED patients. *Am J Emerg Med* 2000; **18**:143–146.

82 Edelstein H, Mccabe RE. Perinephric abscess: modern diagnosis and treatment in 47 cases. *Medicine (Baltimore)* 1988; **67**:118–131.

83 Grupper M, Kravtsov A, Potasman I. Emphysematous cystitis: illustrative case report and review of the literature. *Medicine* 2007; **86**:47–53.

84 Stamm WE, Hooton TM. Management of urinary tract infections in adults. *N Engl J Med* 1993; **329**:1328–1334.

85 Moutzouris DA, Michalakis K, Manetas S. Severe emphysematous pyelonephritis in a diabetic patient. *Lancet Infect Dis* 2006; **6**: 614.

86 Huang JJ, Tseng CC. Emphysematous pyelonephritis: clinicoradiological classification, management, prognosis, and pathogenesis. *Arch Intern Med* 2000; **160**:797–805.

87 Pontin AR, Barnes RD. Current management of emphysematous pyelonephritis. *Nat Rev Urol* 2009; **6**:272–279.

88 Tellez LG, Rodrigues-Montes JA, de Lis SF, Marten LG. Acute emphysematous cholecystitis: report of twenty cases. *Hepatogastroenterol* 1999; **46**:2144–2148.

89 Elsayes KM, Menias CO, Sierra L, Dillman JR, Platt JF. Gastrointestinal manifestations of diabetes mellitus: spectrum of imaging findings. *J Comput Assist Tomogr* 2009; **33**:86–89.

90 Shrestha Y, Trottier S. Images in clinical medicine: emphysematous cholecystitis. *N Engl J Med* 2007; **357**:1238.

91 Chang FY, Chou MY. Comparison of pyogenic liver abscesses caused by *Klebsiella pneumoniae* and non-*K pneumoniae* pathogens. *J Formos Med Assoc* 1995; **94**:232–237.

92 Chang FY, Chou MY, Fan RL, Shaio MF. A clinical study of *Klebsiella* liver abscess. *J Formos Med Assoc* 1988; **88**:1008–1011.

93 Wang JH, Liu YC, Lee SS, Yen MY, Chen YS, Wang JH, *et al*. Primary liver abscess due to *Klebsiella pneumoniae* in Taiwan. *Clin Infect Dis* 1998; **26**:1434–1438.

94 Kim JK, Chung DR, Wie SH, Yoo JH, Park SW. Risk factor analysis of invasive liver abscess caused by the K1 serotype *Klebsiella pneumoniae*. *Eur J Clin Microbiol Infect Dis* 2009; **28**:109–111.

95 Tsai FC, Huang YT, Chang LY, Wang JT. Pyogenic liver abscess as endemic disease, Taiwan. *Emerg Infect Dis* 2008; **14**:1592–1600.

96 Thomsen RW, Jepsen P, Sorensen HT. Diabetes mellitus and pyogenic liver abscess: risk and prognosis. *Clin Infect Dis* 2007; **44**:1194–1201.

97 Grau I, Vadillo M, Cisnal M, Pallares R. Bacteremic pneumococcal cellulitis compared with bacteremic cellulitis caused by *Staphylococcus aureus* and *Streptococcus pyogenes*. *Eur J Clin Microbiol Infect Dis* 2003; **22**:337–341.

98 Graham PL 3rd, Lin SX, Larson EL. A US population-based survey of *Staphylococcus aureus* colonization. *Ann Intern Med* 2006; **144**:318–325.

99 Fridkin SK, Hageman JC, Morrison M, *et al*.; for the Active Bacterial Core Surveillance Program of the Emerging Infections Program Network. Methicillin-resistant *Staphylococcus aureus* disease in three communities. *N Engl J Med* 2005; **352**:1436–1444.

100 Tapper-Jones LM, Aldred MJ, Walker DM, Hayes TM. Candidal infections and populations of *Candida albicans* in mouths of diabetics. *J Clin Pathol* 1981; **34**:706–711.

101 Farrer SM, Macleod CM. Staphylococcal infections in a general hospital. *Am J Hyg* 1960; **72**:38–58.

102 Cluff LE, Reynolds RC, Page DL. Staphylococcal bacteraemia: demographic, clinical and microbiological features of 185 cases. *Trans Am Clin Climatol Assoc* 1968; **79**:905–915.

103 Farley DE, Katz VL, Dotters D. Toxic shock syndrome associated with vulva necrotizing fasciitis. *Obstet Gynaecol* 1993; **82**:660–662.

104 Miller LG, Perdreau-Remington F, Rieg G, Mehdi S, Perlroth J, Bayer AS, *et al*. Necrotizing fasciitis caused by community-associated methicillin-resistant *Staphylococcus aureus* in Los Angeles. *N Engl J Med* 2005; **352**:1445–1453.

105 Howard RJ, Bennett NT. Infections caused by halophilic marine *Vibrio* bacteria. *Ann Surg* 1993; **217**:525–531.

106 Clayton MD, Fowler JE Jr, Sharifi R, Pearl RK. Causes, presentation and survival of 57 patients with necrotizing fasciitis of the male genitalia. *Surg Gynaecol Obstet* 1990:49–55.

107 Smith GL, Bunker CB, Dinneen MD. Fournier's gangrene. *Br J Urol* 1998; **81**:347–355.

108 Cunningham ME, Girardi F, Papadopoulos EC, Cammisa FP. Spinal infections in patients with compromised immune systems. *Clin Orthop Relat Res* 2006; **444**:73–82.

109 Lew DP, Waldvogel FA. Osteomyelitis. *Lancet* 2004; **364**:369–379.

110 Brink SJ, Stewart C. Insulin pump treatment in insulin-dependant diabetic children, adolescents and young adults. *JAMA* 1986; **255**:617–621.

111 Latham R, Lancaster AD, Covington JF, Pirolo JS, Thomas CS. The association of diabetes and glucose control with surgical-site infections among cardiothoracic surgery patients. *Infect Control Hosp Epidemiol* 2001; **22**:607–612.

112 Golden SH, Peart-Vigilance C, Kao WH, Brancati FL. Perioperative glycemic control and the risk of infectious complications in a cohort of adults with diabetes. *Diabetes Care* 1999; **22**:1408–1414.

113 Guvener M, Pasaoglu I, Demircin M, Oc M. Perioperative hyperglycemia is a strong correlate of postoperative infection in type II diabetic patients after coronary artery bypass grafting. *Endocr J* 2002; **49**:531–537.

114 Estrada CA, Young JA, Nifong W, Chitwood WR Jr. Outcomes and perioperative hyperglycemia in patients with or without diabetes mellitus undergoing coronary artery bypass grafting. *Ann Thorac Surg* 2003; **75**:1392–1399.

115 Marelli D, Laks H, Patel B, Kermani R, Marmureanu A, Patel J, *et al*. Heart transplantation in patients with diabetes mellitus in the current era. *J Heart Lung Transplant* 2003; **22**:1091–1097.

116 Thomas MC, Mathew TH, Russ GR, Rao MM, Moran J. Early peri-operative glycaemic control and allograft rejection in patients with diabetes mellitus: a pilot study. *Transplantation* 2001; **72**: 1321–1324.

117 Davenport A. Peritonitis remains the most important complication of peritoneal dialysis: the London, UK, peritonitis audit 2002–2003. *Perit Dial Int* 2009; **29**:297–302.

118 Colquhoun AJ, Nicholson KG, Botha JL, Raymond NT. Effectiveness of influenza vaccine in reducing hospital admissions in people with diabetes. *Epidemiol Infect* 1997; **119**:335–341.

119 American Diabetes Association. Clinical practice recommendations 2009. *Diabetes Care* 2009; **32**(Suppl.1):S13–S61.