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PULMONARY INFECTIONS IN DIABETES MELLITUS

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SUMMARY

Pulmonary infections in diabetes mellitus are characterized by alterations in host defense, in the entire body, and in the lung locally as well as in the function of respiratory epithelium and ciliary motility. They are characterized by serious clinical features, longer duration, more frequent complications, and increased mortality. The pulmonary infection mortality among diabetic patients with end-stage renal disease is 10-fold that in the general population. The importance of hyperglycemia has to be emphasized, as it can cause an alteration in host defense and, consequently, increased susceptibility to infections.

INTRODUCTION

Chronic hyperglycemia due to absolute or relative insulin deficiency characterizes metabolic disturbances in persons with diabetes mellitus, resulting in typical signs and symptoms. Insulin is a very important driver of anabolic processes. The magnitude and duration of hyperglycemia is strongly associated with the severity of microvascular and neurologic complications (1). The presence of these complications adds to the risk of

infections. The predisposition for infection may also be based on conditions that interfere with normal clearance mechanisms, and on disturbance of pulmonary immune cell function (2).

There are several reasons for changes in the clinical course of infection, which are elaborated below.

THE IMMUNE SYSTEM

A wide range of neutrophil and macrophage functions are impaired: chemotaxis, adherence, phagocytosis (may be slightly affected), and ability to kill the phagocytosed microorganisms (1). Reduction in intracellular killing of microbes with free radicals, superoxides and hydrogen peroxide, the “respiratory burst”, is impaired (3). The occurrence of free radicals depends on the presence of nicotinamide adenine dinucleotide phosphate (NADPH). NADPH is normally generated through hexose-monophosphate shunt. If more glucose enters the cells (hyperglycemia, diabetes mellitus), it is metabolized by the polyol pathway. Enzyme aldose-reductase, which is involved in the polyol pathway of glucose metabolism, also requires NADPH. Because of this competition for NADPH, the production of free radicals (respiratory burst) and intracellular killing are reduced.

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There is a valuable observation that treatment with ponalrestat, an aldose reductase inhibitor, improved intracellular killing of microbes by neutrophils. However, data from clinical studies to support this finding are lacking (1).

Serum complement levels (25% of type 1 diabetic patients have low C4) and T-4 lymphocytes are also reduced in diabetes. Alterations in T-lymphocyte subsets, including relative reductions in T-helper lymphocytes, could interfere with immune defense against infection (4).

As a response to infection and cytokine release, insulin resistance in peripheral tissues occurs, resulting in the elevation of blood sugar (1).

Hyperglycemia and the immune system

Hyperglycemia impairs a wide range of functions in neutrophils and monocytes (macrophages) (3,4). This is particularly important in limiting invasion by pyogenic and other bacteria. Adherence and phagocytosis depend on recognition of specific molecules on the bacteria surface, including bacterial glycoproteins as well as attached complement and IgG produced as a result of the immune response to the infection (5). The movement of phagocytic cells to the sites of infection is generally impaired in diabetics but improves with glycemic control (6).

Changes in the microcirculation

The presence of healthy microcirculation is essential to certain infectious insults. Alteration in the function of capillary endothelium, the rigidity of red blood corpuscles and changes in the oxygen dissociation curve that occur as a result of chronic hyperglycemia are factors which affect the host's ability to combat infections. It is therefore no surprise that patients with longstanding diabetes with complications are at a much greater risk of infections than nondiabetics or diabetics without complications. The reduced oxygen supply to tissues as a result of microvascular changes predisposes them to infections by anaerobic microorganisms which grow best under such conditions (7,8).

Other reasons

Diabetic gastroparesis may increase the risk of aspiration (9). Some medications may impair host defense: calcium channel blockers may impair phagocyte function, whereas digoxin may decrease clearance of pneumococci from the lower respiratory tree. Abnormalities in ciliary motility are also important. Pneumonia, lung tuberculosis, fungal infections and parasitic infections have a different course in diabetics than in the general population (1).

BACTERIAL PNEUMONIA

Infections with increased frequency may be due to *Staphylococcus aureus* and gram-negative organisms such as *Klebsiella*, *Escherichia coli*, *Enterobacter*, *Pseudomonas* and *Acinetobacter*.

Infections with a possibly increased morbidity and mortality may be due to *Streptococcus* (group B, *S. pneumoniae*), *Legionella* and viral infections (influenza). Viral infections in diabetic patients are often complicated with bacterial pneumonia.

Anaerobic bacteria may cause pneumonia as a result of esophageal disorders (motility), disorders of ciliary motility, and bronchial and impaired bronchiolar reactivity (clearance mechanism).

Infections with increased frequency

Staphylococcal infection. *Staphylococcus* is a major pathogen in the etiology of both community-acquired and nosocomial pneumonia in diabetic patients. On the basis of a high nasal carriage rate, diabetics are thought to be at an increased risk of staphylococcal pneumonia. Up to 30% of diabetics are nasal carriers of *Staphylococcus aureus* as compared to 11% of healthy individuals (10). Although the carriage rate was previously reported to be higher for diabetics who required insulin injections than in those on oral hypoglycemic agents or diet alone (11,12), it is apparently more influenced by the degree of glycemic control. The rate of nasal carriage of *Staphylococcus aureus* is directly related to the glycosylated hemoglobin (A1c) level (13,14).

Pneumonia due to *Staphylococcus aureus* may be either primary, following aspiration of organisms from the upper airway, or secondary to hematogenous spread of

distant infection (1). The skin and soft tissue structures are the most common infection sites leading to hematogenous spread, followed by endocarditis. Although *Staphylococcus aureus* pneumonia typically presents as an acute process with lobar or segmental consolidation, no clinical or radiographic features can distinguish this from other types of pneumonia. Diabetics are at a risk of developing complications of bacteremia in *Staphylococcus aureus* pneumonia, with an attendant increase in mortality (14).

An emerging problem in the treatment of *Staphylococcus aureus* pneumonia is infection due to methicillin-resistant *Staphylococcus aureus* (MRSA) (15). Pneumonia caused by MRSA is usually bilateral and multilobar. The mortality rate is 38%. Thus, the choice of empiric antimicrobial therapy in diabetic patients with evidence for staphylococcal pneumonia (as suggested by sputum gram stain or in association with soft tissue infection) should be guided by the prevalence of MRSA at the institution (1,10).

Gram-negative organisms

Gram-negative aerobes cause approximately 10%-20% of all community-acquired pneumonia and 60%-80% of all nosocomial pneumonia (16). In general, gram-negative bacteria are acquired by one of the three following routes:

- aspiration of the pathogen from the colonized pharynx,
- hematogenous spread of extrapulmonary infection, or
- acquisition *via* contaminated equipment such as contaminated nebulizers.

Although the latter two mechanisms are sometimes encountered, aspiration is the most common way of lung infection. The upper airway colonization occurs within 24-48 hours of hospitalization even in normal individuals; however, healthy individuals are resistant to upper airway colonization by gram-negative aerobic bacteria (9). The predisposition of diabetics to the development of gram-negative aerobic pneumonia is attributed to an increased rate of upper airway colonization with these organisms (17). Diabetics have an increased susceptibility to laryngeal trauma during intubation, which predisposes them to gram-negative colonization (18). The ability of gram-negative aerobes to adhere to the upper respiratory epithelium is also increased in diabetic patients. Upon adherence, the

bacteria are aspirated into the lungs, where host defense may be further impaired by factors such as coexisting pulmonary edema and impaired phagocytosis. Retrograde colonization of the pharynx from the stomach may be an additional factor at medical intensive care units (9,19). The concomitant use of histamine (H₂)-blockers may increase the gram-negative colonization from the stomach. The subsequent risk of aspiration is increased by diabetic gastroparesis (19,20).

Acinetobacter pneumonia has been associated with a mortality rate exceeding 60%. The risk of pneumonia is increased in the presence of coexistent diabetes (1,9).

Pulmonary infections with possibly increased morbidity and mortality

Gram-positive cocci such as *S. pneumoniae* are responsible for the majority of infections in diabetic patients, followed by agents such as *H. influenzae* (21,22). Diabetics may develop a more severe disease due to the organisms such as *S. pneumoniae*, and have higher rates of hospitalization and development of complications such as bacteremia. Diabetes has been associated with an increased risk of recurrent bacterial pneumonia (23). *H. influenzae* is not more common in diabetics, although it may be more common in the elderly, in whom type 2 diabetes is also prevalent (24).

Aerobic gram-negative organisms and staphylococcal infections typically are the most important causes of nosocomial pneumonia in diabetic patients (16). Furthermore, approximately 25% of nosocomial infections are polymicrobial (25). Bacterial pneumonia in diabetic individuals, especially when caused by *Klebsiella* and *Staphylococcus*, is associated with the more severe course of the disease and more frequent need of mechanical ventilatory support (26). Mortality rates for all hospitalized patients with nosocomial pneumonia range from 30%-50% and are even higher in diabetic patients (27).

Streptococcal infections

Although diabetes may have a slightly higher rate of carriage of group A streptococcus, which can cause severe pneumonia, it is unclear whether diabetes can be separated as a risk factor from the attendant variables of age and severity of illness (13). Of all

streptococcal species, group B streptococcus is the most severe microorganism in diabetic patients (28). When invasion with group B streptococcus occurs, diabetes is the most important factor with an influence on host defense. The lung may be a portal of entry (1).

Although diabetes is often considered to be a risk factor for the development of pneumococcal diseases, controlled studies have shown that diabetes apparently does not represent an independent risk factor for pneumococcal infections (13,21). Diabetes is a risk factor for the development of bacteremia in pneumococcal pneumonia resulting in a significantly higher and more rapid mortality (29). Despite earlier controversy, diabetic patients generally respond normally to pneumococcal vaccination. Immunization against pneumococcal disease is cost-effective as a preventive strategy (30).

Anaerobic bacteria

Aspiration of oropharyngeal contents, composed of anaerobic bacteria, frequently occurs in the normal host but rarely results in pneumonia in the presence of intact pulmonary clearance mechanisms. Although diabetes mellitus is not specifically identified as a risk factor for developing anaerobic pulmonary infections, diabetic patients are probably at risk because of altered cough and clearance mechanisms, esophageal disorders and depressed mental status (hypoglycemic seizures), which are identified as risk factors for developing aspiration pneumonia (1,31).

Atypical pathogens

For other types of community-acquired or nosocomial pneumonia associated with atypical organisms, such as mycoplasma and the chlamydial strain, there is no reported association between diabetes and either increased prevalence or increased morbidity. *Legionella*, an important cause of community-acquired pneumonia, is associated with excess morbidity in diabetics, possibly on the basis of impaired cell-mediated immunity (32,33). *Legionella* species are responsible for 5%-22% of patients to require intensive care unit admission. A large series of community-acquired legionellosis were reviewed, and diabetics were found to be at an increased risk of acquiring legionella infections, with the mortality in this series being 19%

(34). In the presence of diabetes alone, the relative risk of acquiring legionella infections is 1.3 compared to nondiabetic individuals, whereas in diabetic patients with coexisting end-stage renal disease the relative risk dramatically increases to 340 (35).

The most common complications of pneumonia in diabetics are pleural effusion, empyema (because of the increased risk of aspiration, esophageal disease, neurologic abnormalities), and bacteremia (*Klebsiella* infection is the most common cause of bacteremia and associated with a high incidence of metastatic infections), which increases the mortality twofold in diabetics (1,31).

Therapy

- Start with antibiotic therapy as soon as possible (based on antibiogram results if possible) (10,16).
- Priority should be given to antibiotics from the group of quinolones and aztreonam (these groups have better intracellular penetration and efficacy in immunocompromised patients). Attention must be paid to the possibility of the development of resistance to antibiotics (36).
- Good glycemic regulation because of the influence on the immune system (3-5).

Management should involve a comprehensive approach to all aspects of patient care. The importance of glycemic control with regard to immune cell function has been described. Additionally, fluid management and resuscitation in diabetic patients with coexistent cardiovascular or renal failure may complicate therapy (1,5). Even in the absence of elevated serum creatinine level, these patients may have renal dysfunction manifested only by the presence of micro- or macroalbuminuria. Many of the antibiotics used in the treatment of pulmonary infections must be adjusted in patients with renal dysfunction. Aminoglycosides are especially prone to exacerbate renal dysfunction in diabetics.

Cytokines/immunomodulators. Because immune cell defects may be partially responsible for the increased incidence of infection and the related high morbidity and mortality in diabetics, agents capable of augmenting host cell function theoretically offer an

attractive therapeutic modality to supplement current antimicrobial agents. Exogenous cytokine therapy may serve as adjuvant therapy in complicated infections such as multiple drug resistant mycobacterium tuberculosis or multiple drug-resistant bacterial species, reduce the severity of infection, protect the high risk host, or be used as a vaccine immunoadjuvant. In the future, cellular immune defects possibly present in a diabetic host may be the target of cytokine therapy (1,5).

PULMONARY TUBERCULOSIS

The onset of lung tuberculosis is not more common in diabetics than in the general population (1). Lung tuberculosis is a common accompaniment of diabetes and the cause of insulin resistance and "brittleness". In autopsy studies prior to 1900, 50% of cases of diabetes had pulmonary tuberculosis (1,37). Similarly, the incidence of diabetes amongst pulmonary tuberculosis patients was much higher compared to normal population. In some parts of the world with still endemic tuberculosis, a higher than expected proportion of patients with tuberculosis have diabetes. When persons with diabetes do not respond in spite of appropriate treatment, they should be screened for tuberculosis, as weakness, sweating and weight loss are common for both lung tuberculosis and diabetes. The presence of anorexia in a diabetic may point to associated tuberculosis (1,37).

Some important points about lung tuberculosis in diabetes

- The development of lung tuberculosis is not more common in diabetic individuals than in the general population (1).
- The duration of diabetes mellitus has no effect on the prevalence of pulmonary tuberculosis.
- The incidence of lung tuberculosis is increased in uncontrolled diabetics and in patients with severe diabetes requiring large doses of insulin.
- The problems in diabetics with lung tuberculosis include a severe form and more aggressive course of the disease, a higher tendency to destruction

and cavitation, and more common resistance to antitubercotics (especially in patients with poor glycemic control) (37).

- Atypical chest x-ray findings: lower lobe or multiple lobe involvement, higher incidence of cavitation lesions, and higher incidence of pleural effusions in diabetic than in nondiabetic patients (38).
- Complete resolution occurs in patients with HLA A1 and DR2.
- In patients with HLA A2 and DR3, large caseous focus of tuberculoma is formed (1).

The probable reasons for the high association of tuberculosis and diabetes (1,37,38)

- hyperglycemia favors the growth, viability and propagation of tubercle bacilli
- disturbance in electrolyte balance and local tissue acidosis favor infection
- impaired phagocytosis and impaired cellular immunity in persons with diabetes allow for the spread of the disease over neutralizing antibodies in bronchial secretion
- lower resistance due to vascular damage to lung tissue
- disordered nutritional balance

Although earlier reports have suggested that persons with diabetes tend to have tuberculosis confined to lower lobes, these features are no longer evident. Multiple lobe involvement now predominates in diabetic and nondiabetic population alike, however, diabetic subjects more often have cavitating disease under nonsegmental distribution. If reactivation does occur, the tubercle bacillus is more likely to show multiple antibiotic resistance (37,38).

Therapy

If diabetes is well controlled, response to antitubercotic therapy is the same as in nondiabetic groups. Patients with type 2 diabetes on oral therapy may need insulin supplementation or insulin replacement (39). Type 1 patients may require intensification of treatment. Therapy should start with

a combination of four antituberculars over a 2-month period (isoniazid, 300 mg; rifampicin, 600 mg; ethambutol, 15mg/kg; pyrazinamide 1.5-2 g), followed by isoniazid and rifampicin over a 4-month period (1).

The possible therapy related problems may include impaired gastrointestinal drug absorption and hyperglycemic state that may interfere with achieving adequate tissue levels, alveolar macrophage function and CD4+ cell function. Measurement of serum levels of antitubercular drugs in diabetic patients as compared with nondiabetic persons could be useful. Based on clinical experience, some authors suggest that the treatment be prolonged to nine months or even one year. Initial hospitalization improves compliance and response to treatment (40).

Many antitubercular drugs are metabolized in the liver. As rifampicin induces hepatic enzymes that inactivate sulphonylureas metabolized by the liver, sulphonylureas may become less effective and should preferably be avoided. Some antitubercular agents have metabolic and endocrine effects which can affect the diabetic state, e.g., rifampicin has been implicated to cause acute adrenal failure already within few weeks of starting the therapy. Isoniazid and rifampicin both lead to abnormal vitamin D metabolism and hypocalcemia. Para-aminosalicylic acid therapy is associated with hypoglycemia, goiter and hypothyroidism. Although generally of low clinical significance, these effects must be kept in mind (40).

VIRAL INFECTIONS

Influenza

Influenza is a substantial cause of morbidity and mortality in diabetics. During epidemics of influenza pneumoniae, the rate of pneumonia, ketoacidosis and mortality increase sharply in diabetics (41). Death rates attributable to influenza may increase by 5%-15% during the epidemic, especially in elderly patients who have a coexisting cardiovascular disease (42). Influenza infection results in reduced ciliary clearance of inhaled or aspirated bacteria and predisposes the infected host to bacterial superinfection. Combined with the increased rate of nasal carriage of *Staphylococcus aureus* in diabetic patients, this reduced clearance leads to a high risk of developing postinfluenza staphylococcal pneumonia, which has an associated mortality of 30% (43).

Some important points about influenza in diabetes:

- influenza virus grows to significant titers in diabetic lungs
- increased glucose levels impair collective surfactant protein D-mediated host defenses of the lung
- prophylactic influenza vaccination is advised in diabetics
- diabetics have a poor immune response to the influenza vaccine

Diabetes and human immunodeficiency virus (HIV)

A few case reports of diabetes, both type 1 and type 2, have been attributed to the acquired immunodeficiency syndrome (AIDS), however, whether or not these were directly due to the viral infection is unclear (44). Pentamidine used to treat *Pneumocystis* pneumonia in AIDS can have profound effects on glucose homeostasis. Initially, it causes B-cell necrosis, massive insulin release and hypoglycemia. Later, permanent glucose intolerance or clinical diabetes may supervene, and may require insulin administration. This complication is dose-related but can occur with aerosol administration of the drug, and is more likely to develop in renal impairment (45).

CD4 cell-mediated immunity and macrophage function are essential in the control of tuberculosis infection.

Hallmarks of HIV infection (44,46)

- depletion of CD4 cells (CD4 count <200/ μ L can be considered significant)
- defects in macrophage and monocyte functions
- immune response in patients with tuberculosis might enhance HIV viral replication

Radiographic image in immunocompromised patients (HIV) can be determined by T-cell count as follows (45):

Mean CD4 T-cell count	X-ray finding of the lung
389	Upper zone infiltrates and cavitations
185	Pleural effusion
105	Lower or midzone infiltrates, lymphadenopathy, interstitial pattern or normal radiograph, dissemination in tissues

Considerations for antituberculous therapy in HIV-infected diabetic patients treated with antiretroviral agents

Interactions between protease inhibitors (ritonavir, saquinavir) and rifamycins (rifampin, rifabutin) have been established:

- rifamycin-related CYP450 induction decreases blood concentrations of drugs metabolized by CYP450 (such as protease inhibitors)
- rifampin (a potent CYP450 inducer) markedly decreases blood concentration of protease inhibitors (antiviral drugs); conversely, antiviral drugs (potent CYP450 inhibitors) markedly increase blood concentration of rifabutin and its toxicity (46).

FUNGAL INFECTIONS

Primary pneumonia might be caused by mucormycosis, *Aspergillus* spp, *Coccidioides immitis*, and *Cryptococcus neoformans* (1). Attention must be paid to patients on antibiotics. Although mucormycosis typically causes a fulminant rhinocerebral infection, mucormycosis rarely presents as a primary pulmonary infection with hemoptysis (47). Poorly controlled diabetics are more prone to *Mucor* infections. Bronchoalveolar macrophages have decreased ability to inhibit spore generation, resulting in rapidly progressive pulmonary infection with hematogenous dissemination and death. In case of vascular invasion, massive hemoptysis can occur. Mucormycosis is more common in diabetics with renal transplants. Early treatment with amphotericin B therapy with surgical debridement and rapid correction of hyperglycemia and acidosis may be beneficial.

Aspergillus can cause fungal pneumonia in diabetics. This infection may present as an intracavitary mass or mycetoma (typically within tuberculous cavity), and acute or chronic pneumonia (1). The major causes of intracavitary lung colonization are *Aspergillus fumigatus*, *Aspergillus niger*, *Aspergillus flavus* and *Pseudallescheria boydii*. Initially, this process may appear similar to lung abscess caused by bacterial anaerobes, whereas the development of intracavitary mass or mycetoma occurs later in the course of the disease. In chronic *Aspergillus* pneumonia, symptoms are nonspecific and include fever and a productive cough (41). Symptoms are more often present for 1 to 6 months before diagnosis, highlighting the difficulties encountered in making this diagnosis (1,48). Therapy of choice is amphotericin B, or rimantadin (less adverse events) and recombinant MF-CSF (1).

Although rare, both coccidioidomycosis and cryptococcal pneumonia may be more common in diabetics than in nondiabetics (49). Although diabetic patients may have a high carrier rate of *Candida albicans* and a higher risk of infectious complications of *Candida* spp., including oral candidiasis, vulvovaginal candidiasis, and fungal urinary tract infections, pneumonia is not a usual complication (50).

PARASITIC INFECTIONS

In the absence of other risk factors such as immunosuppression following renal transplantation, HIV-associated risk factors, or specific travel to an endemic area, there is no particular predisposition to parasitic infections in diabetic patients. Jacobs *et al.* have recently described a cluster of five patients who developed *Pneumocystis carinii* pneumonia with no known or previously recognized predisposing condition for the development of this opportunistic infection (51). Two of the five patients had type 2 diabetes as an underlying medical condition, with the availability of more sensitive diagnostic stains of respiratory material of *Pneumocystis carinii* (52). Although most cases of *Pneumocystis carinii* pneumonia are related to the AIDS epidemic, *Pneumocystis carinii* pneumonia can occur in individuals with other forms of immunodeficiency (53,54).

CONCLUSION

Although diabetes is often identified as an independent risk factor for developing lower respiratory tract infections, the available literature is rare. There appear to be certain types of pulmonary infections that may be more common in diabetics than in nondiabetics. Diabetic patients also appear to be at an increased risk of complications of pneumonia, such as bacteremia, or recurrent or chronic bacterial pneumonia, and have an increase in mortality that may be related to the coexistent medical disease. The predisposition may be based on conditions that interfere with normal clearance mechanisms or

disturbance of pulmonary immune cell function. The predisposition is further to be complicated by coexisting medical conditions including malnutrition, cardiovascular disease, vascular insufficiency, and chronic renal disease. Current knowledge regarding the interaction of the host defense with respiratory pathogens is limited due to incomplete knowledge about specific pulmonary immune mechanisms in persons with diabetes mellitus. Further studies might provide an insight into the basic mechanisms of the disease and allow the development of improved prophylaxis and treatment regimens for lower respiratory tract infections in diabetic patients.

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