Original Article

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Progress in clinical research complicated infection with diabetes mellitus

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Abstract: Patients with diabetes are prone to concurrent infection. The mechanism of concurrent infection is related to factors such as hyperglycemia and weakened defense function. The infections of patients with diabetes include general and special infections. General infection includes infections in the respiratory system, urinary system, hepatobiliary system, and skin mucosa. Meanwhile, special infection includes invasive otitis externa, nasal mucormycosis, necrotizing fasciitis, and emphysema infection. Patients with special infections also have a higher mortality rate than those with general ones. Complicated infection with diabetes is difficult to treat and has poor prognosis. Therefore, a patient requires active treatment once infected with this infection.

Keywords: diabetes, infection, complicated infection with diabetes mellitus, review

With the increased prevalence of diabetes, related acute and chronic metabolic disorders and various complications, such as complications in the blood vessels and nerves, also increase significantly, thereby posing the challenges for the overall survival of patients with diabetes. Patients with diabetes suffer from T-lymphocyte and neutrophil dysfunction, decreased humoral immune function, oxidative–antioxidative imbalance, and defects in opsonization and phagocytosis [1]. Patients with diabetes are significantly prone to infection, which is difficult to control. Many specific infections are common in patients with diabetes, whereas some infections occur almost exclusively in patients with diabetes. This article reviews the progress in clinical research on complicated infection with diabetes.

1 Pathogenesis

The mechanism underlying the susceptibility of patients with diabetes to suffer from concurrent infection lacks research and is related to a variety of factors, such as hyperglycemia and weakened body defense. Hyperglycemia inhibits the chemotaxis, adhesion, phagocytosis of leukocytes, and intracellular killing, thereby reducing the body's resistance to infection. A multicenter study including 55,408 postoperative patients with diabetes showed that if the blood glucose concentration exceeds 8.3 mmol/L, then the risk of postoperative infection increases significantly. Hence, the risk of infection in patients with diabetes is closely related to blood glucose levels [2]. In terms of weakened body defense, many studies have shown that patients with diabetes suffer from impaired leukocyte function and are prone to infection [3-4].

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2 Clinical features

2.1 Common complicated infection in patients with diabetes

The common complicated infections in patients with diabetes are generally consistent with infections in general patients without diabetes in terms of pathogens, clinical manifestations, and diagnostic methods.

2.1.1 Respiratory infection

The incidence of certain specific respiratory pathogens in patients with diabetic respiratory infections, such as *Staphylococcus aureus*, Gram-negative bacteria, and *Mycobacterium tuberculosis* infections, is increased. The increased incidence of *S. aureus* and Gram-negative bacterial pneumonia in patients with diabetes can be associated with the increased colonization of these pathogens in the upper respiratory tract. Patients with diabetes are threefold more likely to carry nasal pharyngeal *S. aureus* than patients without diabetes. Therefore, patients with diabetes are prone to suffer from *S. aureus* pneumonia, especially after the occurrence of influenza; *S. aureus* is also easy to colonize due to impaired respiratory cilia function and weakened clearing ability [5-6]. Chen *et al.* [7] showed that elevated blood glucose levels are associated with the adverse outcomes of diabetes with community-acquired pneumonia, such as acute respiratory failure, acute kidney injury, septic shock, long hospital stays, and ventilator maintenance time.

2.1.2 Urinary system infection

Diabetes is associated with an increased risk of asymptomatic bacteriuria and urinary tract infections. Asymptomatic bacteriuria is a major risk factor for the development of symptomatic urinary tract infections, whereas emphysema pyelonephritis is almost exclusive in patients with diabetes [4]. Hirji *et al.* [8] showed that type 2 diabetes patients have an increased risk of urinary tract infections of approximately 60% compared with patients without diabetes. Gender, age, duration of diabetes, history of urinary tract infection, urinary tract obstruction, and use of urinary tract devices are the risk factors for the urinary tract infection in patients with type 2 diabetes.

2.1.3 Hepatobiliary infection

For patients with diabetes, due to the reduced defense mechanism of the body, autonomic neuropathy often occurs, which tends to lead to hepatobiliary infection. Among them, cholecystitis and liver abscess are commonly observed. Diabetes is associated with an increased incidence of acute cholecystitis, and this disease complicated with acute cholecystitis is associated with increased cholecystectomy, intraoperative complications, laparoscopic conversion to open cholecystectomy, and increased overall adverse outcomes in patients without diabetes [9]. A total of 50% of patients with suppurative liver abscess complicated with diabetes and recessive liver abscess show that diabetes is one of the potential causes of unexplained fever in patients with type 2 diabetes, and *Klebsiella* is the most common pathogen [10-11].

2.1.4 Skin mucosal infections

Diabetes is an independent risk factor for the diagnosis of skin mucosal infections in the emergency department, thereby leading to long hospital stays and death from infection. *S. aureus* is the one of the most important pathogens of skin mucosal infection, following *Pseudomonas aeruginosa* and anaerobic bacteria [12].

2.2 Special complicated infection with diabetes

Considering glucose metabolism disorders, a variety of complex changes can occur in patients with diabetes, including the changes in cell membrane structure, peripheral blood lymphocyte subunits, and protein biochemical metabolic abnormalities, thereby observing some specific infections in patients with diabetes that are uncommon in patients without diabetes.

2.2.1 Malignant otitis externa

Malignant otitis externa is a potentially fatal sacral osteomyelitis that can affect the surrounding soft tissue, cranial nerves, and skull base, which is represented by facial nerve palsy and bone destruction. In 1959, Meltzer *et al.* [13] reported this potentially fatal sacral osteomyelitis in patients with diabetes for the first time and was first named as malignant otitis externa by Chandler [14] in 1968. Diabetes is a major risk factor for malignant otitis externa, and these diseases often occur concurrently. However, the research of Hobson *et al.* [15] involving 20 patients with malignant otitis externa showed that diabetes is found in all patients with *Pseudomonas* infection, while it is found in only in one out of three patients infected by methicillin-resistant *S. aureus* and 55% of patients infected by non-*Pseudomonas* pathogens. These results suggested that malignant otitis externa is observed in any patients with refractory otitis externa, including those without diabetes. *P. aeruginosa* is previously believed as the main pathogen of malignant otitis externa. However, recent studies have shown that *P. aeruginosa* infection is gradually reduced, and the positive rate of bacterial culture ranges from 27% to 54%. The number of patients with malignant otitis externa uninfected with *Pseudomonas*, such as methicillin-resistant *S. aureus* infection, gradually increases. In terms of treatment, as the microbial environment of malignant otitis externa changes, selecting effective antibacterial therapy against pathogenic bacteria becomes crucial. Ciprofloxacin was first recognized as an empirical antibacterial agent for malignant otitis externa treatment. However, with the increase in patients with malignant otitis externa and non-*Pseudomonas* infection, these patients become resistant to cyclopropane. This approach lacks effectivity due to the inability of the antibacterial spectrum of ciprofloxacin to be covered by Gram-positive bacteria, ineffective effects against methicillin-resistant *S. aureus*, and the increase in *Pseudomonas sinensis*. Compounds sulfamethoxazole, amoxicillin, and clavulanate potassium may be provided, and mastoid incision may be performed if necessary for patients with non-*Pseudomonas* infection [15].

2.2.2 Nasal mucormycosis

Nasal mucormycosis, which is mainly found in patients with diabetes and immunosuppression, is a fulminant, opportunistic fungal infection that can invade the nasal and paranasal sinuses directly or through the blood. This disease was previously considered rare. However, due to the prevalence of immunosuppressed patients, especially patients with diabetes, mucormycosis detection also gradually increases. Nasal mucormycosis is the most invasive fungal infection that can kill 80% of patients with diabetic ketoacidosis and other immunosuppressed patients. Diabetes without sound control is a common susceptible factor to nasal mucormycosis, especially for patients with ketoacidosis. The specific reasons are unclear and can be associated with the following factors: reduced granulocyte phagocytosis, diabetic microangiopathy and atherosclerosis that lead to local tissue ischemia and increased susceptibility to infection, decreased ability of transferrin to bind Fe, and increased serum Fe levels, thereby leading to the circumstance wherein mucormycosis disease tends to occur. *Rhizopus*, *Trichoderma*, and *Mucor* are the common pathogenic strains of the disease, among which *Rhizopus* is the most common, found in 90% of patients with nasal mucormycosis and diabetes complicated with ketoacidosis. The patient's clinical manifestations include facial pain, headache, lethargy, blindness, eyeball protrusion, and ankle ulcer, but the abovementioned symptoms are unspecific. Given that pathogenic bacteria can be spread rapidly, early disease diagnosis is crucial to save the patient's life.

Diagnosis relies on the biopsy of the affected tissue, which is represented by a wide, zonal, and membrane-free hyphae. The main treatments include controlling diabetes, removing necrotic bone tissue, and applying antifungal treatments, such as amphotericin B [16-17].

2.2.3 Necrotizing fasciitis

Necrotizing fasciitis is considered as a serious soft tissue infection that leads to extensive necrosis of subcutaneous tissue and fascia. As the disease progresses, the thrombosis of the affected skin through the vessel can lead to skin necrosis and blood bubble formation. Once the infection is formed, bacteremia and sepsis occur. Despite active treatment, the mortality rate of bad fasciitis is still high, reaching up to 34% [18]. Diabetes is a potential disease commonly observed in patients with bad fasciitis, accounting for 44.5%–72.3% [19]. Necrotizing fasciitis is divided into three types according to the bacterial culture results: type I refers to multiple bacterial infections, type II refers to type A streptococci with or without staphylococcal infection, and type III refers to *Vibrio* infection. However, recent studies showed that necrotizing fasciitis can occur as a single consistent pathogen for infection, such as methicillin-resistant *S. aureus*. These results suggested that the pathogen spectrum of bad fasciitis constantly changes. Necrotizing fasciitis is most likely to affect the lower extremities, and patients with diabetes exhibit a higher amputation rate than those without diabetes mainly due to diabetic neuropathy and vascular disease, thereby making the maintenance of limbs with concurrent fasciitis difficult. During treatment, early and thorough surgical debridement and fasciotomy are necessary to save the patient's life. The negative pressure treatment of the wound aids in controlling the infection and facilitate wound healing. Sensitive antibiotics should be provided according to bacterial culture results. The use of ampicillin or sulbactam and clindamycin or metronidazole in combination is recommended [20].

2.2.4 Emphysema infection

Emphysema cholecystitis: Emphysema cholecystitis is an uncommon, fatal, and acute cholecystitis caused by gas-producing bacteria. Pathogenic bacteria are generally anaerobic bacteria, such as *Clostridium*, and other pathogens, such as *Escherichia coli*, Gram bacterium, *Proteus*, *Staphylococcus*, *Streptococcus*, and *Salmonella*. This infection mainly occurs in men aged 50–70 years. Approximately 50% of patients have diabetes and peripheral vascular disease and 40% have gallstones, which are found in 90% of patients with acute cholecystitis. Different from acute and chronic cholecystitis caused by cholelithiasis, emphysema cholecystitis is mainly associated with the occlusion of the gallbladder artery, the ischemic necrosis of the gallbladder walls, and gallbladder gangrene and secondary gas-borne pathogen infection. The mortality rate of emphysema cholecystitis can reach as high as 15%, while the mortality rate of general acute cholecystitis is only 4%. Clinical manifestations include upper right abdominal pain, fever, nausea, and vomiting. However, patients with emphysema and diabetes can only exhibit fever, which can be related to undiagnosed diabetic neuropathy, thereby covering the symptoms of abdominal pain. Hyperglycemia and microcirculatory disorder in patients with diabetes can lead to ischemia, thereby leading to emphysema cholecystitis. Diagnosis relies on abdominal imaging studies, including X-ray, B-ultrasound, and computed tomography (CT), to detect the presence of gas in the gallbladder wall, gallbladder cavity, or the tissues surrounding the gallbladder. For treatment, early acute cholecystectomy is necessary due to the rapid progression of the disease quality. Broad-spectrum antibiotics that cover anaerobic bacteria and intestinal Gram-positive and Gram-negative pathogens should be used as early as possible [21-22].

Epileptic liver abscess: Epileptic liver abscess refers to a liver abscess with gas formation, accounting for 6%–24% of bacterial liver abscesses. It is commonly observed in patients with diabetes and poor glycemic control, which is easy for sepsis and abscess with a mortality rate of 27%. The most common pathogen

is *Klebsiella*, accounting for approximately 70% of the emphysema liver abscess. Abdominal ultrasound and X-ray examination aid diagnosis, but abdominal CT is the most sensitive method for gas detection in abscesses. Clinical manifestations can include abdominal pain, nausea, and fever. However, emphysema liver abscess in patients with diabetes can only represent as fever and fatigue without abdominal symptoms, which can be associated with diabetic neuropathy. Therefore, if patients with diabetes and poor glycemic control experience long-term fever and fatigue, then the possibility of this fatal infection should be alerted and requires considerable attention. In addition to the application of effective antibiotics and good control of blood sugar, performing percutaneous abscess drainage, especially for patients with abscess diameters of >5 cm, is necessary for certain cases. Emergency surgery is considered if abscess rupture and peritonitis occur [23].

Epileptic pyelonephritis: Emphysema pyelonephritis is an acute, severe, and necrotic infection involving the renal parenchyma and perirenal tissues, which can be found in the renal parenchyma, collecting system, or perirenal tissue. Diabetes is the most common susceptibility factor; the factors include urinary tract obstruction, neurogenic bladder, alcohol abuse, drug abuse, and urinary tract malformations. Emphysema pyelonephritis is more commonly observed in women than in men, and the age of onset ranges from 40 years to 80 years. *E. coli* is the most common pathogen found in 70% of patients with emphysema pyelonephritis. Other pathogenic bacteria include *Klebsiella*, *Proteus mirabilis*, *P. aeruginosa*, and intestinal bacilli. Therefore, initial antibiotic treatment should cover Gram-negative bacteria, such as fluoroquinolone ketones. CT is the most effective method for the early diagnosis of emphysema pyelonephritis. According to CT findings, emphysema pyelonephritis is divided into types I and II: type I is considered as the dry type characterized by renal parenchymal necrosis with mottled gas without liquid, while type II is considered as the wet type characterized by the presence of gas in the kidney or perirenal fluid accompanied by a bubble gas or in a collection system. Treatment options have some controversy. In the past, emergency nephrectomy is a commonly used treatment method, but increasing percutaneous drainage has been applied recently because the latter can keep the kidneys and restore damaged kidney function. Percutaneous drainage can be used as part of the initial treatment of emphysema pyelonephritis, the mortality of which is lower than that of drug-only or nephrectomy treatment. Delayed selective nephrectomy is mainly used for patients after percutaneous drainage, especially for patients with long-term fever, sepsis, and nonfunctional one-sided kidney. For nonsurgical patients, percutaneous drainage is recommended together with medication [24].

Emphysema cystitis: Emphysema cystitis is a rare complex urinary tract sensation characterized by visible gas in the bladder wall and lumen and mainly observed in elderly women with diabetes who have poor glycemic control. Risk factors include diabetes, neurogenic bladder, recurrent urinary tract infection, and urinary tract obstruction. Among these risk factors, diabetes is the most important risk factor, and 70% of the patients with emphysema cystitis have diabetes. *E. coli* and *Klebsiella* are two major pathogens, while others include *Enterobacter*, *P. mirabilis*, *Streptococcus*, *P. aeruginosa*, and *S. aureus*.

The most common clinical manifestation is abdominal pain, which is found in 80% of patients. Fever and gross hematuria can also be observed. Although gas urine is a highly specific symptom, it is rare. Acute cystitis is observed in approximately 50% of patients, but the abovementioned symptoms are unspecific because approximately 7% of patients are asymptomatic. Therefore, diagnosis can be delayed easily. Emphysema cystitis can spread up and develop into emphysema pyelonephritis. Abdominal imaging is critical for the diagnosis of emphysema cystitis, among which abdominal CT is the most common and sensitive method of examination. In addition to finding the bladder wall and lumen gas, CT can also detect ascending emphysema infection, intra-abdominal abscess or tumor, and other sources of gas in the pelvic cavity, such as gas from bladder rectal fistula, vesicovaginal fistula, intestinal wall cystic gas, uterine gas gangrene, and emphysema vaginitis. Treatments include the use of sensitive antibiotics (including fluoroquinolones, ceftriaxone, carbapenems, and aminoglycosides), bladder drainage, and treatment for susceptible factors, such as blood sugar control. For patients with concurrent emphysema cystitis and emphysema pyelonephritis, early percutaneous renal drainage can be considered. Severe patients with poor response or severe necrotizing infections need early surgical intervention [25].

3 Prevention and treatment

3.1 Prevention

In the flu season, vaccination with influenza vaccine and pneumococcal vaccine can effectively prevent the occurrence of bacterial pneumonia [26]. The prevention of urinary tract infections in diabetes focuses in preventing bacteria from entering the urinary tract and enhancing the resistance of the urinary tract to bacteria. Urinary tract devices should be avoided to be used for any operation in the urinary tract. For example, catheterization and intubation must be performed under aseptic conditions to allow the removal of the catheter as soon as possible. Skin should be kept clean, and skin infections should be prevented.

3.2 Treatment

Patients with diabetes are prone to infection, and treatment is difficult and has high mortality rate. Once an infection occurs, it should be actively treated. The specific principles are as follows.

3.2.1 Principles of antibiotic treatment

The following should be noted for the application of antibiotics: (1) select sensitive antibiotics under the guidance of bacterial culture and drug susceptibility results of various secretions, (2) the intravenous administration of severe infections as much as possible, and (3) sufficient drugs and adequate course of treatment. For common respiratory and urinary tract infections, as the infection rates of *S. aureus* (respiratory), Gram-negative bacilli (such as *E. coli*), and *Proteus* (urinary tract) are increased, three generations of cephalosporins, aminoguanidines, and quinolone antibiotics can be administered when the pathogens are still unclear. For digestive system infections, pathogenic bacteria are commonly found in Gram-negative bacilli and anaerobic bacteria. Meanwhile, ampicillin, aminoglycoside antibiotics, and metronidazole are often used. Skin mucosal infections include diabetic foot, which is often infected by various microorganisms, such as *S. aureus*, *Pseudomonas*, and anaerobic bacteria. β-lactams and glycopeptides, such as vancomycin, carbapenems, and fluoroquinolone antibiotics, are commonly used [27-28].

3.2.2 Controlling blood glucose

A retrospective, multicenter cohort study showed that 2471 patients with community-acquired pneumonia possess a significantly higher risk of death from the blood glucose levels of >11.0 and <11.0 mmol/L. Therefore, patients with diabetes complicated by infection should actively control blood sugar to reduce the occurrence of adverse clinical outcomes. Insulin is preferred for hypoglycemic treatment. Preprandial (<7.8 mmol/L) and postprandial or random blood glucose (<10.0 mmol/L) are considered the control targets for reasonable blood glucose, which can effectively reduce the incidence of infection-related complications and hypoglycemia [29,30].

3.2.3 Treatment of special infections due to diabetes

Refer to the “Clinical features” section.

3.2.4 Treatment of severe infections

The following should be noted in the treatment of diabetes complicated with severe infections. (1) Blood sugar control: insulin therapy is recommended when blood glucose exceeds 10.0 mmol/L. The goal of blood

glucose control is to control the blood glucose level between 7.8 and 10.0 mmol/L, thereby avoiding hypoglycemia and large blood sugar fluctuations. (2) Antibiotic treatment: delaying antibiotic treatment is associated with an increased mortality rate in severe infections. Therefore, once the severe infection is diagnosed, a sufficient amount of effective broad-spectrum antibiotics is administered intravenously within 3 h. Once the pathogenic bacteria are determined, the antibiotics are given as a step-down treatment. The most effective single-agent treatment is selected to cover pathogenic bacteria and reduce the occurrence of drug-resistant bacteria and drug side effects with the course of treatment for 7–10 days. If the infection is uncontrolled or occurs with staphylococcemia, fungal, or viral infection and concurrent immunodeficiencies, including neutropenia, then the course of treatment may be extended. (3) Primary infection treatment: within 12 h after severe infection diagnosis, primary infection (such as necrotizing soft tissue infection, peritonitis, cholecystitis, intestinal necrosis, or liver abscess) should be identified as soon as possible, and the infected necrotic tissue, abscess wear puncture, or tube drainage should be removed as soon as possible. (4) Hemodynamic support and auxiliary support treatment: the crystal solution is preferred for severe infection treatment. If the blood volume is low, then it should be administered with at least 30 mL/kg of crystal solution to avoid administration of hydroxyethyl starch. If the mean arterial pressure is lower than 8.67 kPa, then norepinephrine is preferred for vasopressor drugs. Dopamine is used as an alternative drug for only people with low-risk tachyarrhythmia, and the use of a low dosage of this drug is discouraged for kidney protection. (5) Cardiac drug: if the patient still shows a decrease in cardiac output or tissue hypoperfusion after adequate rehydration, then dobutamine should be injected. If the hemodynamics of glucocorticoid of severely infected and shocked patients remains unstable after treatment, then 200 mg/day hydrocortisone can be injected through intravenous infusion, and the dose can be gradually reduced as the condition improves while monitoring the changes in blood glucose. (6) Deep vein thrombosis prevention: patients with severe infection need daily anticoagulant drugs to prevent venous thrombosis formation, such as low-molecular-weight heparin. (7) Stress ulcer prevention: stress ulcer can be prevented by using a proton pump inhibitor or a H2 receptor blocker. (8) Nutrition support treatment: within 48 h after the severe infection onset, if the patient can tolerate, then the patient should eat or be provided with enteral nutrition rather than simply fasting or intravenous glucose or complete parenteral nutrition to prevent bacterial translocation [31,32].

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