

# Mycoses in diabetes — difficult diagnostic and therapeutic problem. Review of literature



## Agata Drozdowska, MD, PhD

Born in 1975, graduated from Faculty of medicine within individual program of study at the Chair and Department of Biology and Clinical Parasitology of Medical University of Lodz. Afterwards, in 2006 she was awarded a doctoral degree by the Medical University of Lodz, Department of Biology, Clinical Parasitology and Molecular Genetics. In 2006 she worked at the Hospital Emergency Care Department in Zgierz, and since november 2006 she hosts a post of assistant at the Department of Internal Medicine, Diabetology and Clinical Pharmacology of the Medical University of Lodz. Her scientific interests involve parasitology and infections, therein mycotic ones. She is an author and co-author of 6 works and several national and international conference reports. She is also a member of Polish Society of Metabolic Disorders.



## Jozef Drzewoski

Jozef Drzewoski is a full professor at the Medical University of Lodz and the head of the Department of Internal Medicine, Diabetology and Clinical Pharmacology. He is the author or the co-author of several hundred original papers, review papers and casuistic studies; of more than ten books including "Type 2 diabetes — selected pathophysiological, diagnostic and treatment issues"; of the "Clinical pharmacology of oral antidiabetic drugs" series, including "Clinical pharmacology of rosiglitazone, metmorfin, glimepiride, glipizide and gliclazide"; as well as of the "Reference lexicon of diabetology". The main scientific interests include the pathogenesis, diagnostics, treatment and complications of diabetes, as well as the clinical pharmacology of antidiabetic drugs. In recognition of his scientific achievements and overall didactic attainments he has several times been awarded the Health Minister's Prize.

## Abstract

Prevalence of superficial and systemic mycoses has increased in recent years. The most common etiological factors responsible for those infections are fungi of the genus *Candida*, mainly *Candida albicans*; however approximately 35–65% of candidemia cases are caused by other species of this particular genus, described in literature as *Candida non-albicans* pathogens.

Fungal infections have deleterious impact on metabolic control of diabetes; their course is usually more severe than

in people without diabetes, long-lasting and characterized by frequent relapses and standard anti-fungal treatment resistance.

The aim of this review was to summarize the current knowledge on diagnostic and therapeutic problems of fungal infections in people with diabetes mellitus.

*Diabet Dośw i Klin* 2008; 8: 1–11

**key words:** diabetes mellitus, fungal infections, anti-fungal treatment

Address for correspondence: dr med. Agata Drozdowska  
Klinika Chorób Wewnętrznych z Oddziałem Diabetologii  
i Farmakologii Klinicznej Uniwersytetu Medycznego w Łodzi  
Wojewódzki Szpital Specjalistyczny w Zgierzu  
ul. Parzęczewska 35, 95–100 Zgierz  
Tel/fax (+48 42) 714 45 51  
e-mail: adrozdowska@poczta.onet.pl



Diabetologia Doświadczalna i Kliniczna 2008, 8, 1, 1–11  
Copyright © 2008 Via Medica, ISSN 1643–3165

## Introduction

Incidence of mycoses, both superficial and systemic, has increased during recent years. This is due to the prevalence of fungi in human's environment as well as to the ability of those organisms to develop on the surface of skin and mucous membranes, in saliva, vagina, faeces, urine and internal organs. The most common etiological factors responsible for mycoses are fungi of genus *Candida*, mainly *C. albicans*, however other species of this genus are more and more often identified, causing numerous diagnostic and therapeutic problems.

Mycoses caused by moulds and dermatophytes, keratin decomposing fungi, affecting skin with its appendages, are also diagnosed more frequently.

It has been established that the risk of mycoses is determined both by pathogenic properties of fungal strains and host characteristics, i.e.: age, dietary habits, social conditions, invasive diagnostic and therapeutic procedures (e.g. dialysis, hyperalimentation), use of broad-spectrum antibacterial antibiotics, inherited and acquired immunological deficiencies (e.g. AIDS, tumors, diabetes and other endocrinopathies). It should be remembered that fungal infections are often identified during autopsy because their significance is underestimated and proper diagnostic procedures are not conducted.

Fungi — considered by many authors as physiological components of different ontocenoses of human organism — reveal immunosuppressive and allergic features and may be the cause of patient's deterioration without producing symptoms of systemic mycosis (silent mycosis), however in some cases they can lead to death due to disseminated infection. Therefore, it should be pointed out that carriage of those pathogens can be an important risk factor for development of symptomatic mycoses [1, 2].

There is a widespread clinical belief, supported by many observations, that community-acquired bacterial, viral and fungal infections occur more frequently in diabetics than in general population. It has been demonstrated that some infections appear to have a specific predilection for patients with diabetes and can be of more severe course with higher risk of serious complications and standard treatment resistance. Diabetes may predispose to certain types of infections including pneumonias, acute bacterial cystitis, emphysematous pyelonephritis, perinephric abscesses, fungal cystitis, necrotizing fasciitis, invasive external otitis, rhinocerebral mucormycosis and emphysematous cholecystitis [3–6]. It should be also stressed that diabetics are more susceptible to hospital-acquired infections, particularly in post-operative cardiac and critically ill surgical patients [7].

Mechanism(s) responsible for close association between diabetes and increased susceptibility to infections has not been yet well explained. There is also lack of large epidemiological studies concerning this issue. It has been suggested that hyperglycemia can impair a wide range of functions in neutrophils, monocytes and macrophages, including adherence, chemotaxis and phagocytosis with intracellular killing of microorganisms, immunological response of T cells and skin reaction to antigens. Local factors related to decreased blood flow and nerves damage may also be of great importance in people with diabetes [3, 8–11]. Hostetter [12] underlined the significant influence of hyperglycemia on the third

component of complement (C3). It is suggested that glycation of C3 inhibits its attachment to the surface of bacteria and thereby impairs opsonization, which plays the crucial role in phagocytosis. *Candida albicans* has the ability to express proteins on its surface that are structurally and functionally homologous to complement receptors on mammalian phagocytes. Chronic hyperglycemia induces their expression that in turn leads to the attachment of C3 to them and results in a lack of fungus recognition as a pathogen. This particular kind of molecular mimicry contributes to easier colonization and infection.

Clinical observations indicate that fungal infections in diabetics can dramatically worsen glycaemic control and increase insulin requirement; in some cases leading to acidosis and other severe complications of diabetes, including death [2].

The aim of this review was to summarize available data related to clinical picture of mycoses in diabetics, regarding to sites of their occurrence, stressing diagnostic and therapeutic problems.

---

## Oral cavity

---

Despite the fact that patients with diabetes have higher rates of fungal colonization of oral cavity, data from literature suggest that colonization is not always associated with symptomatic infection. It has been shown that increased adherence of fungi to epithelial cells and impaired processes of binding, phagocytosis and intracellular killing of those pathogens by neutrophils, favour colonization of the oral cavity [13, 14]. Among clinically significant fungal infections of the oral cavity, the most typical of diabetes are: recurrent angular cheilitis and blastomycotic stomatitis, denture stomatitis, median rhomboid glossitis (central papillary atrophy), atrophic glossitis and pseudomembranous candidiasis [1, 2, 15].

It should be remembered that the presence of fungi in the oral cavity of diabetics can be asymptomatic. Bartholomew et al. [16] detected among 60 patients without clinical features of mycosis the presence of fungi in the oral cavity in almost 75% of subjects. Fisher et al. [17] revealed the carriage of species of genus *Candida* in 51% of 412 patients; 6% of patients had more than one species of this genus. Goncalves et al. [18] examining 175 diabetics treated with insulin found fungal colonization of the oral cavity in 53% of them.

It has been proven that the most common fungal pathogen isolated from the oral cavity in patients with diabetes, as well as in general population, is *Candida albicans* [17, 19]. However, it is worth mentioning that in recent years *non-albicans* species have been identified more often. This situation has important clinical implica-

tions due to common antifungal drugs resistance among these strains.

Very good differentiation of species inhabiting the ontocenosis of the oral cavity was documented by Gonçalves et al. [18]: *C. albicans* was found in 56% of all isolates, *non-albicans* species (*C. parapsilosis*, *C. tropicalis*, *C. glabrata*, *C. krusei*, *C. rugosa*, *C. guilliermondii*) were identified in 39.8% of cases, whereas other (4.3% of all cases) included genera: *Pichia*, *Trichosporon* and *Geotrichum*. Dorko et al. [20] isolated from diabetics with fungal denture stomatitis: *C. albicans*, *C. tropicalis*, *C. parapsilosis* and *C. guilliermondii*.

In our own studies fungi were found in oral cavity in 58.1% of patients with diabetes and chronic renal failure. In accordance with above mentioned observations the presence of fungi was not associated with any clinical symptoms of infections. *C. albicans* strains were isolated most often (66.7% of all isolates). *Non-albicans* species were found in the following order: *C. guilliermondii*, *C. parapsilosis*, *C. rugosa* and *C. lambica*. *Geotrichum penicillatum* was identified only in one patient [21].

It is worth mentioning that Sahin et al. [22] and Manfredi et al. [23] isolated *Candida dubliniensis*, species was mistaken with *C. albicans* till 1995. It is of great clinical value due to fluconazole resistance presented by majority of *C. dubliniensis* strains. *C. dubliniensis* is isolated mostly from ontocenosis of the oral cavity and stool samples in HIV-positive patients and those with AIDS. It is assumed that its presence is influenced by impairment of cellular immunity that is also observed in diabetes [24]. Interestingly enough, type 2 diabetes (T2DM) occurs frequently in HIV-infected people. This coexistence can be explained partially by the HIV virus deleterious influence and side effects of anti-HIV drugs.

During recent years *C. glabrata* has been identified in the oral cavity of diabetics more often than previously. Compared to *C. albicans*, *C. glabrata* is characterized by lower ability of adherence to oral cavity keratinocytes but significantly higher to the denture surface. Among the most important factors responsible for the virulence of this specific pathogen there are: lower susceptibility to fungicidal properties of beta-defensins (natural epithelial peptides with antibacterial and antifungal activity), different degree of resistance to antifungal activity of salivary histatins and mucins and both innate and acquired resistance of this species to azole drugs [25, 26].

Cisto et al. [1] found the presence of fungi in the oral cavity in 92.2% of children with type 1 diabetes (T1DM) and showed that species composition of this ontocenosis is more differentiated than in healthy children. Coexistence of yeast-like fungi and moulds (from genera *Aspergillus* and *Penicillium*) was also more often found in diabetics. In oral cavity washings obtained from children with diabetes the density of fungal population was

significantly higher. The degree of inhabiting of this ontocenosis and the growth intensity of yeast-like fungi were dependent on glycaemic control, whereas it was not related to the duration of diabetes. Factors influencing quicker and more intensive growth of fungi in the oral cavity of diabetics include: vascular-dependent disturbances of mucous membrane's alimentation, decreased secretion of saliva, lower pH and high glucose concentration in saliva.

Data concerning association between the presence of fungi in the oral cavity and blood glucose concentration are inconsistent [17,19]. Several authors did not find any correlation between prevalence, species differentiation and growth density of *Candida spp.* in the oral cavity of diabetics with glycaemic control and the mode of anti-diabetic treatment [29–32]. On the other hand, Hill et al. [27] revealed significantly higher prevalence of fungi in this ontocenosis in patients with elevated concentration of glycosylated hemoglobin ( $HbA_{1c}$ )  $\geq 12\%$ . It was not supported by Bartholomew et al. [16] who did not find any relation between these two variables.

Of note, Kadir et al. [28] examining 55 patients with diabetes previously treated with oral hypoglycemic agents observed higher colonization by *Candida spp.* after implementation of insulin-therapy.

Many studies revealed higher fungal colonization, especially by yeast-like fungi, in patients with diabetes wearing dentures [17, 19, 22, 23, 28]. It has been established that under a plate of a denture covering the mucous membrane of prosthetic base several unwanted effects occur including: difficulties in backflow of saliva, lack of self-cleaning, restricted oxygen access, increased temperature, retention of alimentary debris and disturbances of biocenotic balance. Prosthesis, used for many years, is often characterized by impaired stabilization and therefore leads to disruption of tissue integrity and damage of epithelium under its plate that allows infiltration of fungal cells deep into tissues.

Belazi et al. [29] noticed that it is impossible to make direct association between increased prevalence of fungi in the oral cavity and using dentures in diabetics. Our own studies revealed similar frequency of fungi both in patients with diabetes and chronic renal failure wearing dentures (58.3%) and in diabetics who did not use them (57.9%) [21]. It is worth mentioning that even in healthy persons wearing dentures fungi are detected more often. In addition, the rate of fungal infections in different groups of patients with prosthetic inflammation of the oral cavity (*stomatitis prothetica mycotica*) is evaluated by different investigators at the level of 65% up to 100%. Based on these data, wearing dentures seems to be the independent risk factor for higher prevalence of fungi in the oral cavity than diabetes *per se*. Some studies revealed association between using dentures and

increased density of fungal population and greater differentiation of identified species of genus *Candida* in the ontocenoses of diabetics' oral cavities [18, 19, 23, 28].

Among other risk factors increasing the incidence of fungi in the oral cavity in patients with diabetes: smoking, older age, use of antibiotics, intensive teeth brushing, lower pH and increased blood glucose concentration are considered [19, 22, 28]. Bartholomew et al. [16] did not notice an influence of previous antibiotic-therapy and higher glucose levels on the prevalence of fungi. However, other investigation revealed positive correlation between antibacterial treatment and carriage of *C. glabrata* and high leucocytosis and carriage of *C. albicans* [28].

Manfredi et al. [33, 34] evaluated genetic relation of *Candida spp.* strains isolated from the oral cavity of patients with diabetes from different countries. Strains obtained from patients from Great Britain showed greater differentiation which was probably related to the mode of antifungal treatment. Those strains were more often resistant to fluconazole, miconazole and ketoconazole in comparison to strains collected from Italian patients. These findings indicate the necessity of drug sensitivity evaluation which can be dependent on geographic region where mycosis was diagnosed.

In diabetics impairment of immunological system and frequent fungal colonization of the oral cavity may cause chronic hyperplastic candidosis, known as candidal leukoplakia. This particular kind of oral cavity candidosis undiagnosed and untreated, especially in patients with immune system disturbances, leads to dysplasia and in some cases to cancer [35].

---

## Lower part of gastrointestinal tract

---

It has been demonstrated that factors predisposing to fungal colonization of gastrointestinal (GI) tract include: older age, malnutrition, diabetes, steroid therapy, immunosuppressive treatment, injuries, burns, surgical procedures, parenteral hyperalimentation, vascular and urinary catheters, treatment with H<sub>2</sub> receptor antagonists and proton pump inhibitors, use of broad-spectrum antibiotics. In general population people with three or more risk factors are at the highest risk of developing mycosis [36, 37]. In diabetics additional factors may play an important role; among them: young age, smoking, shorter duration of diabetes, hospitalization within last year [22].

Of note, there are cases of intensive colonization of GI tract in healthy persons, which do not lead to systemic dissemination. In studies conducted on healthy mice de Repentigny et al. [38] showed that chronic colonization was accompanied by partial da-

mage of mucous membrane of a large intestine by surrounding mycelium cells. It is extremely important considering the fact that the mucous membrane of GI tract is the commonest way of invasion and hematogenous spread of fungi in the organism — dissemination is therefore most often endogenous. In patients suffering from systemic mycoses Greenfield et al. [39] revealed initially submucosal invasion by blastoconidia and pseudohyphae, whereas Cole et al. [40] and Sanchez et al. [41] proved that damage of the mucous membrane of GI tract in neutropenic patients may lead to candidal microabscesses within the mucous membrane and blood-related dissemination.

In the available literature there are only few reports on fungal colonization of GI tract and clinically evident fungal infections in patients with diabetes. Cisto et al. [2] showed that the mucous membrane of a large intestine in children with T1DM was more often colonized by moulds and yeast-like fungi with greater differentiation of fungal species in this ontocenosis than in healthy children. Pathological fungal cell count (> 10<sup>5</sup> colonies in 1 g of stool) was detected in 64.7% of affected children. This is a higher prevalence than noticed previously in quantitative stool cultures obtained from adults with non-specific symptoms from GI tract (42.3%), as well as from children with similar complaints (48.1%) [42, 43]. Colonization and intensity of yeast-like fungi growth were related to the levels of serum HbA<sub>1c</sub> but had no association with the duration of diabetes [2].

Our own studies conducted on patients with diabetes and chronic renal failure revealed mainly *Candida albicans* strains in stool. Less frequently, *C. glabrata*, *C. guilliermondii*, *C. humicola*, *C. kefir*, *C. parapsilosis*, *C. rugosa* were found. None of the patients showed clinical symptoms of mycosis [21].

---

## Skin and its appendages

---

It has been established that ratio of epidermis/serum glucose concentration is higher in patients with diabetes than in healthy individuals, and it is suggested that it may favour fungal growth. On the other hand, Skorepova [44] underlined that the frequency of skin mycoses in diabetics is not significantly higher than in general population. It was nicely demonstrated by Garcia-Humbria et al. [45] who revealed superficial mycoses in 75% of examined patients with diabetes and in 65% of healthy individuals adjusted for gender and age, stressing no significant difference in the prevalence of infections between both groups. Clinical experience indicates that only certain types of skin mycoses, including: tinea pe-

dis, onychomycosis and fungal balanitis caused by *Candida* spp. occur more frequently in diabetics than in general population. For example, onychomycosis was found nearly 2,5 to 6-fold more often in diabetics than in people without diabetes [46, 47].

It has also been reported that diabetes and onychomycosis increased the risk of gangrene and foot ulceration to greater extent than diabetes without coexisting fungal nail infection [46]. Onychomycosis in patients with diabetes was also associated with the increased risk of other foot diseases (secondary bacterial infections or cellulites due to the infection of surrounding skin) even leading to amputation [48].

Dermatophytes, such as *Trichophyton rubrum* and *Trichophyton mentagrophytes*, are the most common pathogens responsible for more than 90% of infections. Despite the fact that mould infections are quite rare in general population, some studies revealed their prevalence in almost 20% of diabetics with onychomycoses with predominance of *Scopulariopsis brevicaulis*, *Fusarium* spp., *Acremonium* spp. and *Aspergillus* spp. It is believed that fungi from genus *Candida* can cause nail infections in almost 2.7% of diabetics [49, 50].

Saunte et al. [51] revealed in 22% of 271 diabetics with onychomycosis the presence of dermatophytes and yeast-like fungi (93% and 7%, respectively). However, Dogra et al. [47] found in fungal nail lesions: yeast-like fungi (48.1% of all cases), dermatophytes (37%) and non-dermatophytic moulds (14.8%). The presence of mycosis was related to age, severity of nail damage, male gender, duration of diabetes, impairment of peripheral circulation and neuropathy.

It is interesting enough that Bouguerra et al. [52] confirmed infection in diabetics with clinical symptoms of skin mycoses by mycological culture of biological material in only 30% of subjects. He found that almost 94% of mycoses were caused by *T. rubrum*.

Mayer et al. [53] mycologically confirmed tinea pedis in almost 70% of 95 patients with long-term (mean 35.8 years) T1DM with predominance of *T. rubrum* strains (69.2% of all isolates). This species was also most frequently found (78% of diabetics vs. 50% of controls) by Garcia-Humbria et al. [45]. However, in Romano's et al. [54] investigations *T. mentagrophytes* was predominantly isolated from tinea pedis and distal subungual onychomycosis.

Mlinaric-Missoni et al. [55] detected fungi in interdigital spaces in 24% of 509 ambulatory treated diabetics and showed a great species differentiation. Fungi of genera: *Candida*, *Rhodotorula*, *Cryptococcus*, *Trichosporon*, *Saccharomyces*, *Blastoschizomyces*, *Geotrichum*, *Debaryomyces*, *Ustilago*, *Trichophyton* and *Epidermophyton* were identified with predominance of

*C. parapsilosis* (in 11.6% of patients) and *T. mentagrophytes* (in 3.1%). Coexistence of yeast-like fungi and dermatophytes was rare and concerned only 0.6% of diabetics. Although no relationship was found between the fungal colonization and gender, age and the duration of diabetes; fungi were significantly more often isolated from patients with T2DM (30.1%) than from T1DM (19.8%). Poblete-Gutierrez et al. [56] described, for the first time, onychomycosis in patient with T1DM caused by *T. gallinae*, which only sporadically infects people.

---

## Diabetic foot

---

Fungal infections may complicate the course of diabetic foot and in such cases species of *Candida* genus are mostly isolated. Species of genera: *Cryptococcus*, *Trichosporon* and *Rhodotorula* were detected less frequently [55, 57]. It should be noticed that Dorko et al. [20] discovered in ulcerations *C. krusei* and *C. robusta* [20]. It has been established that higher risk of fungal infections of diabetic foot was in insulin-treated diabetics with long-term ulceration. Fungal infections in patients treated with oral hypoglycemic agents were not related to the duration of foot ulceration [57].

---

## Urogenital system

---

There are several studies indicating more frequent occurrence of vulvovaginal mycosis in women suffering from diabetes in comparison to healthy individuals [58–60]. It was suggested that chronic, recurrent fungal infection may even be the marker of diabetes [61, 62]. However, most studies did not examine the association between asymptomatic carriage of *Candida* genus fungi or clinically evident vulvovaginal mycoses and glycaemic control or type of diabetes [58, 63, 64]. Drews et al. [65] showed that diabetes and increased body mass index (BMI) were among important risk factors responsible for the development of vaginal mycosis in pregnant women and patients with malignancies of uterus.

De Leon et al. [58] noticed almost three times higher ratio of colonization by *Candida* species in women with T1DM in comparison to women with T2DM. Fungal colonization was associated with increased HbA<sub>1c</sub> concentration, use of antibiotics, coexisting *Chlamydia* spp. infection and performing oral sex in the last two weeks before examination. It is interestingly enough that *C. non-albicans* species (with predominance of *C. glabrata*) were more prevalent in women with T2DM, whereas *C. albicans* was found mainly in patients with T1DM. Goswami et al. [66] suggested significant correlation between hyperglycemia and vulvovaginal candidosis

and the role of pathogens other than *C. albicans*. He stressed that *C. tropicalis* was detected only in women with diabetes. Ray et al. [25] examining 111 diabetic women with vulvovaginal candidosis found *C. glabrata* in majority of them, while *C. albicans* and *C. tropicalis* were isolated less frequently. It should be underlined that the prevalence of *C. glabrata* infections often resistant to conventional antibiotics has increased during recent years also in general population [67–69]. Fortunately, the resistance of a fungal strain to one antibiotic does not indicate the lack of sensitivity to other antifungal agents [70–72]. Preliminary observations suggest the effectiveness of flucytosine and boric acid vaginal suppositories against *C. glabrata* related vulvovaginal candidosis [25, 73–76].

Giannopoulos et al. [77] analyzing six described in the literature cases of fungal epididymitis in diabetics noticed that two of them were caused by *C. glabrata*.

Glycosuria is recognized as a risk factor of fungal urinary tract infections (UTIs) with *C. albicans*, *C. parapsilosis*, *C. tropicalis* and *C. krusei* being the commonest etiological pathogens [20]. Carvalho et al. [78] analyzing fungal UTIs in children and adults found diabetes in 9.5% and 28% of cases, respectively. However, there are no significant evidences that diabetes is the independent risk factor for fungal UTIs. The presence of fungi in urinary tract can be asymptomatic colonization or clinically evident infection.

In people without diabetes obtaining  $10^5$  colonies in 1 ml of urine is considered to be a cut-point for diagnosis UTI. However, it should be stressed that symptomatic infections in diabetics are associated with much lower value [3, 79]. There are still many controversies concerning the presence of *Candida spp.* in the urinary tract. In many cases it is unclear whether fungi colonizing urinary bladder or if their presence, especially in kidneys, is always related to infection. It is also questionable if finding fungi in urine is the result of hematogenous dissemination or is the evident of ascending infection. According to these, very important clinical issue should be considered — whether all patients with asymptomatic candiduria without pyuria should be treated?

In 1997, during International Conference for the Development of a Consensus on the Management and Prevention of Severe Candidal Infections, it was established that treatment of fungal UTI should be introduced only in patients with diabetes, patients with functional impairment of urogenital tract and renal transplant recipients. In other cases, urine culture must be repeated after Foley's catheter removal and the end of antibacterial antibiotic-therapy, the main risk factors of candiduria [80]. Although Joshi et al. [3] suggested implementation of antibiotic-therapy in diabetics only when clinically evident infection is diagnosed basing on the presence of pyuria. It is diffi-

cult to accept this opinion taking into account the histopathological examinations of kidneys in patients with persistent candiduria. They revealed the presence of microabscesses in renal glomerules or within interstitial layer, renal papillary necrosis, infiltrations of renal tubules and blood vessels. Those changes, despite diabetic nephropathy itself, can be additional factors associated with development of renal failure [81, 82].

In men with diabetes the possibility of fungus balls formation — clusters of pseudohyphae localized in renal pelvis or ureters — should be taken into consideration as a kind of ascending infection. This complication may often require surgical management. Fungus balls formation in patients with diabetes may be associated with *Candida spp.* and *Aspergillus spp.* infection [83].

---

## Specific fungal infections

---

It was well documented that zygomycosis is strongly associated with diabetes. Mycosis is caused by species of genera: *Mucor*, *Rhizopus* and *Absidia*. In humans four main kinds of this disease are observed: rhinocerebral — most often diagnosed in diabetic ketoacidosis; gastro-intestinal — related to malnutrition; pulmonary and disseminated — accompanying leukemia and lymphomas but also found in diabetics [84].

Fungi initially colonizing the mucous membrane of nose and paranasal sinuses continuously reach orbit's tissue, invading the central nervous system (CNS) through blood vessels causing granulomatous meningitis. Infection with CNS involvement is characterized by very rapid, sometimes fulminant course frequently resulting in death. Some experimental studies indicate that development of fungal CNS infections can be related to cellular immunity disorders, which are also observed in diabetes [85–87].

Roden et al. [88] reviewing 929 reports of zygomycosis in the English-language literature since 1885, found coexisting diabetes in 36% of patients. Zygomycosis caused death in 44% of them. However, Chakrabarti et al. [89] analyzing 178 cases of zygomycosis in hospitalized patients in north India found coexisting, uncontrolled diabetes in 73.6% of patients. Moreover, Schwartz et al. [90] noticed that cerebro-rhino-orbital phycomycosis (CROP), caused mainly by *Rhizopus spp.*, occurs predominantly in individuals with diabetic ketoacidosis. CROP leads to proptosis, loss of vision, ophthalmoplegia and death resulting from cerebral involvement. Higher prevalence of rhinocerebral mucormycosis in patients with uncontrolled diabetes was reported by many other authors [91–96].

Considering above cited data it should be underlined that in diabetics physicians should always pay special attention to infections within facial skeleton, especially non-responding to antibiotic-therapy.

Tsaousis et al. [97] reported for the first time a case of patient with diabetes and simultaneous liver and brain mucormycosis. Patients with diabetes and coexisting symptoms of pneumonia, especially with sudden and severe course, non-responding to antibiotic-therapy, should always be checked for the presence of pulmonary mucormycosis [98–100].

Of note, Kontoyiannis [101] noticed that despite the increase in the incidence of diabetes in developed countries, the prevalence of zygomycosis in diabetics has decreased since 1990. Further investigations in order to explain this phenomenon are necessary. The author proposed the hypothesis that widespread use of statins in diabetics underlines such a trend because of direct inhibitory activity of those drugs, revealed both *in vitro* and *in vivo*, against fungi causing zymomycoses.

Patients with diabetes are more susceptible to mycoses caused by *Aspergillus spp.*, such as: sino-orbital, pulmonary or cerebral aspergillosis [102–104].

Santelli et al. [105] examining 329 cases of coccidioidomycosis, found coexisting diabetes in 13.4% of patients. Mycosis, caused by *Coccidioides immitis*, presented non-characteristic symptoms, including: lung infections, skin and bones changes, meningitis. It was noticed that diabetics were significantly more likely to have cavitary lung diseases and relapsed infections than non-diabetics. Moreover, patients with glucose concentration  $\geq 220$  mg/dL were predisposed to develop disseminated infection, required intensive treatment and were less susceptible to complete recovery.

---

## Fungemia

Diabetes may predispose to fungemia with its late complications. This association was supported by many studies indicating that mortality rate of fungal sepsis was up to 39% [106–109]. Additionally, Bader et al. [110] noticed that mean blood glucose concentration  $\geq 13.9$  mmol/L (7 days after the outset of the disease) was a significant marker of increased in-hospital mortality in patients with diabetes and candidemia.

In diabetics fungemia can even be developed due to administration of probiotic agents containing fungi considered to be non-pathogenic. Lestin et al. [111] reported the case of a patient with micro- and macroangiopathic complications, including peripheral artery disease with necrosis in several digits of both feet. Complications occur after using agents with *Saccharomyces cerevisiae* (synonym: *S. boulardii*) because of chronic post-antibiotic diarrhoea. Therefore, therapeutic usage of probiotics should be carefully considered regarding their risk-benefit potential especially in patients with immunity disorders.

It has been established that species of *Candida* genus are responsible for almost 10% of hematogenous nosocomial infections in the US being the fourth leading cause of them (after coagulase-negative staphylococci, *Staphylococcus aureus* and *Enterococcus sp.*) According to many authors, mortality due to invasive fungal infections has increased more than twice reaching even 49% during last two decades. It should be stressed that *Candida non-albicans* species, such as: *C. glabrata*, *C. parapsilosis*, *C. tropicalis* and *C. krusei* can be responsible for 35% up to even 65% of all candidemia cases [108, 112–120].

Considering above mentioned data further investigations on the prevalence of foci of candidosis in patients with diabetes, as a group more frequently hospitalized because of different complications, are of great importance. In Poland we still have little data concerning the frequency of infections, mostly candidemia cases, caused by *non-albicans* species.

Frequent isolation of *C. parapsilosis* from diabetics is noticeable. This species was found in oral cavity, urinary tract, interdigital spaces of feet, crural ulcerations, eyes and ears of patients with diabetes [20, 55, 57]. It is extremely important considering study conducted by Nucci et al. [121] who reported increased prevalence of *C. parapsilosis* candidemia cases in some countries of Latin America. *C. parapsilosis* infections are often related to the maintenance of intravenous catheters, artificial prostheses, invasive medical procedures, intravenous hyperalimentation. It should be mentioned that infection can be developed in articulations and heart muscle [113, 122]. In our own study *C. parapsilosis* comprised 5.26% of all isolated *Candida* strains obtained from diabetics with chronic renal failure.

---

## Treatment modalities

It should be stressed that during treatment of fungal infections in patients with diabetes the possibility of interaction between antifungal drugs and insulin or oral hypoglycemic agents may occur. Hryncewicz-Gwózdź et al. [123] analyzed the pathway of anti-diabetics and antifungal agents metabolism. Azole drugs such as: itraconazole, fluconazole, ketoconazole and terbinafine, belong nowadays to the most common anti-fungals used in treatment of superficial mycoses. Both azoles and most anti-diabetics are metabolized by cytochrome P-450, but by various enzymes in case of itraconazole and ketoconazole (anti-diabetics — CYP 2C9, itraconazole — CYP 3A4, ketoconazole — CYP 3A4, fluconazole — CYP 2C9 and CYP 3A4). Terbinafine is not metabolized by cytochrome P-450. Clinical observations indicate that itraconazole and terbinafine are safe and well tolerated by diabetics but further investigations are necessary.

## Conclusions

High prevalence of fungi in diabetics, possible severe complications of mycoses and increasing number of species resistant to standard antifungal agents, force considering whether the mycological examination should be introduced into the panel of methods evaluating clinical condition of diabetics both in outpatient clinics and hospital departments. It is worth mentioning that it can be extremely helpful in controlling systemic infections. Higher accessibility of antifungal agents for disinfection purposes and faster introduction of new, effective, easily absorbed in gastrointestinal tract antifungal drugs maintaining fungicidal concentration in all body fluids, also in urine, will also contribute to control mycoses in diabetics.

Necessity of permanent examination of patients with diabetes in order to look for foci of fungal colonization and clinically evident infections and after their discovery — constant elimination of pathogens in each predilection site, mostly on the skin surface and mucous membranes — should be carefully considered. Rieth [124] in the eighties underlined the need of eradication of fungi from oral cavity in diabetics each time of their occurrence. He also stressed that intensive blastomycosis (mainly in cases seemingly resistant to treatment or in cases of continuous relapses) requires extension of diagnostic procedures from the point of view of diabetes or other endocrinopathies.

## References

- Cisło M, Baran E, Noczyńska A, Hryniewicz-Gwóźdź A, Wąsikowa R, Ziarkiewicz M. Występowanie grzybów drożdżopodobnych i grzybów pleśniowych w przewodzie pokarmowym dzieci chorych na cukrzycę typu 1. Część I. Jakościowa i ilościowa ocena grzybów w ontocenozie jamy ustnej. *Mikol Lek* 2001; 8: 147–152.
- Cisło M, Wąsik-Kuprianowicz A, Baran E, Noczyńska A. Występowanie grzybów drożdżopodobnych i grzybów pleśniowych w przewodzie pokarmowym dzieci chorych na cukrzycę typu 1. Część I. Jakościowa i ilościowa ocena grzybów w kale. *Mikol Lek* 2003; 10: 193–198.
- Joshi N, Caputo GM, Weitekamp MR, Karchmer AW. Infections in patients with diabetes mellitus. *N Engl J Med* 1999; 16: 1906–1912.
- Shah BR, Hux JE. Quantifying the risk of infectious diseases for people with diabetes. *Diabetes Care* 2003; 26: 510–513.
- Wheat LJ. Infection and diabetes mellitus. *Diabetes Care* 1980; 3: 187–197.
- Vazquez JA, Sobel JD. Fungal infections in diabetes. *Infect Dis Clin North Am* 1995; 9: 97–116.
- Peleg AY, Weeraratna T, McCarthy JS, Davis TME. Common infections in diabetes: pathogenesis, management and relationship to glycaemic control. *Diabetes Metab Res Rev* 2007; 23: 3–13.
- Muller LMAJ, Gorter KJ, Hak E, et al. Increased risk of common infections in patients with type 1 and type 2 diabetes mellitus. *Clin Inf Dis* 2005; 41: 281–288.
- Moutschen MP, Scheen AJ, Lefebvre PJ. Impaired immune response in diabetes mellitus: analysis of the factors and mechanisms involved. Relevance to the increased susceptibility of diabetic patients to specific infections. *Diab Metab* 1992; 18: 187–201.
- Geerlings SE, Hoepelman AI. Immune dysfunction in patients with diabetes mellitus (DM). *FEMS Immunol Med Microbiol* 1999; 26: 259–265.
- Pozzilli P, Leslie RD. Infections in diabetes: mechanisms and prospects for prevention. *Diabet Med* 1994; 11: 935–941.
- Hostetter MK. Handicaps to host defense. Effects of hyperglycemia on C3 and *Candida albicans*. *Diabetes* 1990; 39: 271–275.
- Darwazeh AM, Lamey PJ, Samaranyake LP, et al. The relationship between colonization, secretor status and in vitro adhesion of *Candida albicans* to buccal epithelial cells from diabetics. *J Med Microbiol* 1990; 33: 43–49.
- Ueta E, Osaki T, Yoneda K, Yamamoto T. Prevalence of diabetes mellitus in odontogenic infections and oral candidiasis: an analysis of neutrophil suppression. *J Oral Pathol Med* 1993; 22: 168–174.
- Vernillo AT. Dental considerations for the treatment of patients with diabetes mellitus. *JADA* 2003; 134: 24S–33S.
- Bartholomew GA, Rodu B, Bell DS. Oral candidiasis in patients with diabetes mellitus: a thorough analysis. *Diabetes Care* 1987; 10: 607–612.
- Fisher BM, Lamey PJ, Samaranyake LP, MacFarlane TW, Frier BM. Carriage of *Candida* species in the oral cavity in diabetic patients: relationship to glycaemic control. *J Oral Pathol* 1987; 16: 282–284.
- Goncalves RH, Miranda ET, Zaia JE, Giannini MJ. Species diversity of yeast in oral colonization of insulin-treated diabetes mellitus patients. *Mycopathologia* 2006; 162: 83–89.
- 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.
- Dorko E, Baranova Z, Jenca A, Kizek P, Pilipcinec E, Tkacikova L. Diabetes mellitus and candidiasis. *Folia Microbiol* 2005; 50: 255–261.
- Drozdowska A. Cechy morfologiczne i biochemiczne grzybów wyodrębnionych od pacjentów z niewydolnością nerek. Rozprawa doktorska. Uniwersytet Medyczny, Łódź 2006.
- Sahin I, Oksuz S, Sencan I, et al. Prevalence and risk factors for yeasts colonization in adult diabetic patients. *Ethiop Med J* 2005; 43: 103–109.
- Manfredi M, McCullough MJ, Al-Karaawi ZM, Hurel SJ, Porter SR. The isolation, identification and molecular analysis of *Candida* spp. isolated from the oral cavities of patients with diabetes mellitus. *Oral Microbiol Immunol* 2002; 17: 181–185.
- Sullivan D, Coleman D. *Candida dubliniensis*: characteristics and identification. *J Clin Microbiol* 1998; 36: 329–334.
- Ray D, Goswami R, Banerjee U, et al. Prevalence of *Candida glabrata* and its response to boric acid vaginal suppositories in comparison with oral fluconazole in patients with diabetes and vulvovaginal candidiasis. *Diabetes Care* 2007; 30: 312–317.
- Li L, Redding S, Dongari-Bagtzoglou A. *Candida glabrata*, an emerging oral opportunistic pathogen. *J Dent Res* 2007; 86: 204–215.
- Belazi M, Velegraki A, Fleva A, et al. Candidal overgrowth in diabetic patients: potential predisposing factors. *Mycoses* 2005; 48: 192–196.
- Soyza NS, Samaranyake LP, Ellepola AN. Diabetes mellitus as contributory factor in oral candidosis. *Diabet Med* 2006; 23: 455–459.
- Kumar BV, Padshetty NS, Bai KY, Rao MS. Prevalence of *Candida* in the oral cavity of diabetic subjects. *J. Assoc. Physicians India* 2005; 53: 599–602.

30. Chomicz L, Szubińska D, Piekarczyk J. et al. Occurrence of oral subclinical infections in insulin treated diabetics. *Wiad Parazyt* 2004; 50: 177–180.
31. Hill LV, Tan MH, Pereira LH, Embil JA. Association of oral candidiasis with diabetic control. *J Clin Pathol* 1989; 42: 502–505.
32. Kadir T, Pisiriciler R, Akyuz S, Yarat A, Emekli N, Ipbuker A. Mycological and cytological examination of oral candidal carriage in diabetic patients and non-diabetic control subjects: thorough analysis of local aetiological and systemic factors. *J Oral Rehabil* 2002; 29: 452–457.
33. Manfredi M, McCullough MJ, Al-Karaawi ZM, Vescovi P, Porter SR. Analysis of the strain relatedness of oral *Candida albicans* in patients with diabetes mellitus using polymerase chain reaction-fingerprinting. *Oral Microbiol Immunol* 2006; 21: 353–359.
34. Manfredi M, McCullough MJ, Polonelli L. et al. In vitro antifungal susceptibility to six antifungal agents of 229 *Candida* isolates from patients with diabetes mellitus. *Oral Microbiol Immunol* 2006; 21: 177–182.
35. Sitheequ MAM, Samaranyake LP. Chronic hyperplastic candidosis/candidiasis (candidal leukoplakia). *Crit Rev Oral Biol Med* 2003; 14: 253–267.
36. Zwolińska-Wcisło M, Brzozowski T, Kwiecień S. et al. Kolonizacja grzybicza przewodu pokarmowego w badaniach klinicznych i doświadczalnych. *Przew Lek* 2003; 6: 81–89.
37. Donskey CJ. The role of the intestinal tract as a reservoir and source for transmission of nosocomial pathogens. *Clin Infect Dis* 2004; 39: 219–226.
38. De Repentigny L, Phaneuf M, Mathieu LG. Gastrointestinal colonization and systemic dissemination by *Candida albicans* and *Candida tropicalis* in intact and immunocompromised mice. *Infect Immunol* 1992; 60: 4907–4914.
39. Greenfield RA, Joyce WA. Gastric colonization with *Candida albicans*. *Mycopathologia* 1993; 122: 1–5.
40. Cole GT, Halawa AA, Anaissie EJ. The role of the gastrointestinal tract in hematogenous candidiasis; from the laboratory to the bedside. *Clin Infect Dis* 1996; suppl 2: S73–S88.
41. Sanchez V, Vazquez JA, Barth-Jones D, Demby L, Sobel JD, Zervos MJ. Epidemiology of nosocomial acquisition of *Candida lusitanae*. *J Clin Microbiol* 1992; 30: 3005–3008.
42. Pawlik B, Macura A. Grzyby występujące w kale osób z nieswoistymi dolegliwościami ze strony przewodu pokarmowego. *Mikrob Med* 2002; 1: 18–21.
43. Pawlik B, Macura A, Bialek-Kaleta J. Występowanie grzybów w kale u dzieci. *Med. Dośw Mikrobiol* 2002; 54: 273–279.
44. Skorepova M. Mycoses and diabetes. *Vnitr Lek* 2006; 52: 470–473.
45. Garcia-Humbria L, Richard-Yegres N, Perez-Bianco M et al. Superficial mycoses: comparative study between type 2 diabetic patients and a non-diabetic control group. *Invest Clin* 2005; 46: 65–74.
46. Blume P, Wilkinson JT, Key JJ. Treating difficult nails in diabetic patients. *Podiatry Today* 2006; 3: 91–98.
47. Dogra S, Kumar B, Bhansali A, Chakrabarty A. Epidemiology of onychomycosis in patients with diabetes mellitus in India. *Int J Dermatol* 2002; 41: 647–651.
48. Winston JA, Miller JL. Treatment of onychomycosis in diabetic patients. *Clin Diab* 2006; 24: 160–166.
49. Gupta AK, Konnikov N, MacDonald P. et al. Prevalence and epidemiology of toenail onychomycosis in diabetic subjects: a multicentre survey. *Br J Dermatol* 1998; 139: 665–671.
50. Rich P, Harkless LB, Atillasoy ES. Dermatophyte test medium culture for evaluating toenail infections in patients with diabetes. *Diabetes Care* 2003; 26: 1480–1484.
51. Saunte DM, Holgersen JB, Haedersdal M. et al. Prevalence of toe nail onychomycosis in diabetic patients. *Acta Derm Venereol* 2006; 86: 425–428.
52. Bouguerra R, Essais O, Sebai N. et al. Prevalence and clinical aspects of superficial mycosis in hospitalized diabetic patients in Tunisia. *Med Mal Infect* 2004; 34: 201–205.
53. Maysen P, Hensel J, Thoma W. et al. Prevalence of fungal foot infections in patients with diabetes mellitus type 1 — underestimation of moccasin-type tinea. *Exp Clin Endocrinol Diab* 2004; 112: 264–268.
54. Romano C, Massai L, Asta F, Signorini AM. Prevalence of dermatophytic skin and nail infections in diabetic patients. *Mycoses* 2001; 44: 83–86.
55. Mlinaric-Missoni E, Kalenic S, Vazic-Babic V. Species distribution and frequency of isolation of yeasts and dermatophytes from toe webs of diabetic patients. *Acta Dermatovenereol Croat* 2005; 13: 85–92.
56. Poblete-Gutierrez P, Abuzahra F, Becker F, Krause H, Merk HF, Frank J. Onychomycosis in a diabetic patient due to *Trichophyton gallinae*. *Mycoses* 2006; 49: 254–257.
57. Missoni EM, Kalenic S, Vukelic M. et al. Role of yeasts in diabetic foot ulcer infection. *Acta Med Croatica* 2006; 60: 43–50.
58. de Leon EM, Jacober SJ, Sobel JD, Foxman B. Prevalence and risk factors for vaginal *Candida* colonization in women with type 1 and type 2 diabetes. *BMC Inf Dis* 2002, 2. <http://www.biomedcentral.com/1471-2334/2/1>.
59. Reed BD. Risk factors for *Candida* vulvovaginitis. *Obstet Gynecol Surv* 1992; 47: 551–560.
60. Krigoriou O, Baka S, Makrakis E, Hassiakos D, Kapparos G, Kouskouni E. Prevalence of clinical vaginal candidiasis in an university hospital and possible risk factors. *Eur J Obstet Gynecol Reprod Biol* 2006; 126: 121–125.
61. Ringdahl EN. Treatment of recurrent vulvovaginal candidiasis. *Am Family Phys* 2000; 61: 3306–3318.
62. Sobel JD. Vaginitis. *N Eng J Med* 1997; 337: 1896–1903.
63. Rahman T, Khan IH, Begum J. High vaginal swab, routine microscopy and culture sensitivity in diabetic and non-diabetic, a comparative retrospective study of five years. *Indian J Med Sci* 1990; 45: 212–214.
64. Rowe BR, Logan MN, Farrell I, Barnett AH. Is candidiasis the true cause of vulvovaginal irritation in women with diabetes mellitus? *J Clin Pathol* 1990; 43: 644–645.
65. Drews K, Markowska A, Kuszerska A, Markowska J. Zakażenia grzybicze pochwy u kobiet ciężarnych, u kobiet leczonych z powodu nowotworów łagodnych i złośliwych macicy. *Mikol Lek* 2006; 13: 181–184.
66. Goswami R, Dadhwal V, Tejaswi S. et al. Species-specific prevalence of vaginal candidiasis among patients with diabetes mellitus and its relation to their glycaemic status. *J Infect* 2000; 41: 162–166.
67. Saporiti AM, Gomez D, Levalle S. et al. Vaginal candidiasis: etiology and sensitivity profile to antifungal agents in clinical use. *Rev Argent Microbiol* 2001; 33: 217–222.
68. Goswami D, Goswami R, Banerjee U. et al. Pattern of *Candida* species isolated from patients with diabetes mellitus and vulvovaginal candidiasis and their response to single dose oral fluconazole therapy. *J Infect* 2006; 52: 111–117.
69. Garcia HM, Garcia SD, Copolillo EF. et al. Prevalence of vaginal candidiasis in pregnant women. Identification of yeasts and susceptibility to antifungal agents. *Rev Argent Microbiol* 2006; 38: 9–12.
70. Nawrot U, Cisło M, Noczyńska A, Włodarczyk K, Baran E. Podatność grzybów drożdżopodobnych zasiedlających przewód pokarmowy dzieci z cukrzycą typu 1 na wybrane leki przeciwgrzybicze. *Mikol Lek* 2006; 13: 35–38.
71. Vacheva-Dobrevski R, Kovachev S, Nacheva A, Stoev S, Vasilev N. Comparative study of itraconazole and fluconazole therapy in vaginal candidosis. *Akush Ginekol* 2004; 43: 20–23.
72. Urunsak M, Ilkit M, Evruke C, Urunsak I. Clinical and mycological efficacy of single-day oral treatment with itraconazole (400 mg) in acute vulvovaginal candidosis. *Mycoses* 2004; 47: 422–427.
73. Sobel JD, Chaim W, Nagappan V, Leaman D. Treatment of vaginitis caused by *Candida glabrata*: use of topical boric

- acid and flucytosine. *Am J Obstet Gynecol* 2003; 189: 1297–1300.
74. Sobel JD, Chaim W. Treatment of *Toluopsis glabrata* vaginitis: retrospective review of boric acid therapy. *Clin Infect Dis* 1997; 24: 649–652.
  75. Redondo-Lopez V, Lynch M, Schmitt C, Cook R, Sobel JD. *Toluopsis glabrata* vaginitis: clinical aspects and susceptibility to antifungal agents. *Obstet Gynecol* 1990; 76: 651–655.
  76. Drews K, Adamski Z, Bieszczad E. Zastosowanie itrakonazolu w ginekologii. *Mikol Lek* 2006; 13: 219–222.
  77. Giannopoulos A, Giamarellos-Bourboulis EJ, Adamakis I, Georgopoulou I, Petrikos G, Katsilambros N. Epididymitis caused by *Candida glabrata*. A novel infection in diabetic patients? *Diabetes Care* 2001; 24: 2003–2004.
  78. Carvalho M, Guimaraes CM, Junior JRM, Bordignon GPF, Queiroz-Telles F. Hospital-associated funguria: analysis of risk factors, clinical presentation and outcome. *BJID* 2001; 5: 313–318.
  79. Garrison MW, Campbell RK. Identifying and treating common and uncommon infections in the patient with diabetes. *The Diabetes Educator* 1993; 19: 522–529.
  80. International Conference for the Development of a Consensus on the Management and Prevention of Severe Candidal Infections. *Clin Infect Dis* 1997; 25: 43–59.
  81. Wendland SL. Fungal infections/antifungal agents. In: Dipro JT, Talbert RL, Yee GC. ed. *Pharmacotherapy — a pathophysiologic approach*. McGraw-Hill, New-York 2005.
  82. Kwaśniewska J. Grzyby jako czynnik etiologiczny zakażeń narządów moczowych i płciowych. *Mikrobiol Med* 1998; 4: 24–28.
  83. Prkacin I, Sabljarić Matutinović M, Skegrod D. et al. Fungus balls in ureter in a diabetic patient with generalized *Candida* mycoses. *Diabet Croat* 1999; 28: 15–18.
  84. Sugar AM. Mucormycosis. *Clin Infect Dis* 1992; suppl 1: S126–S129.
  85. Boelaert JR, de Locht M, Van Cusem J, Kerrels V, Cantiniaux B, Verdonck A. Mucormycosis during deferoxamine therapy is a siderophore-mediated infection: *In vitro* and *in vivo* animal studies. *J Clin Invest* 1993; 91: 1979–1996.
  86. Weng DE, Wilson WH, Little R, Walsh TJ. Successful medical management of isolated renal zygomycosis: case report and review. *Clin Infect Dis* 1998; 26: 601–605.
  87. Van den Saffele JK, Boelaert JR. Zygomycosis in HIV-positive patients: a review of the literature. *Mycoses* 1996; 39: 77–84.
  88. Roden MM, Zaoutis TE, Buchanan WL. et al. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. *Clin Infect Dis* 2005; 41: 634–653.
  89. Chakrabarti A, Das A, Mandal J. et al. The rising trend of invasive zygomycosis in patients with uncontrolled diabetes mellitus. *Med Mycol* 2006; 44: 335–342.
  90. Schwartz JN, Donnelly EH, Klintworth GK. Ocular and orbital phycomycosis. *Surv Ophthalmol* 1977; 22: 3–28.
  91. Robibaro B, Pammer J, Leber J, Knapp S, Vorbach H, Prestler E. Mucormycosis—a rare complication in patients with diabetes mellitus. *Wien Klin Wochenschr* 1996; 108: 24–27.
  92. Ferchichi L, Chadli-Debbiche A, Koubaa W. et al. Rhinocerebral mucormycosis in four diabetics. *J Mal Vasc* 2006; 31: 85–87.
  93. Chadli-Chaieb M, Bchir A, Fathallah-Mili A. et al. Mucormycosis in the diabetic patient. *Presse Med* 2005; 34: 218–222.
  94. Szalai G, Fellegi V, Szabo Z, Vitez LC. Mucormycosis mimicks sinusitis in a diabetic adult. *Ann N Y Acad Sci* 2006; 1084: 520–530.
  95. Moll GW, Raila FA, Liu GC, Conerly AW. Rhinocerebral mucormycosis in IDDM. Sequential magnetic resonance imaging of long-term survival with intensive therapy. *Diabetes Care* 1994; 17: 1348–1353.
  96. Pellacchia V, Terenzi V, Moricca LM, Buonaccorsi S, Indrizzi E, Fini G. Brain abscess by mycotic and bacterial infection in a diabetic patient: clinical report and review of literature. *J Craniofac Surg* 2006; 17: 578–584.
  97. Tsaousis G, Koutsouri A, Gatsiou C, Paniara O, Peppas C, Chalevelakis G. Liver and brain mucormycosis in a diabetic patient type II successfully treated with liposomal amphotericin B. *Scand J Infect Dis* 2000; 32: 335–337.
  98. Vichova Z, Beuret P, Boyer M, Chanoz J. Fatal pulmonary mucormycosis in a diabetic patient. *Ann Fr Anesth Reanim* 2006; 25: 40–42.
  99. Anuradha K, Lakshmi V, Umabala P, Rao MN. Pulmonary zygomycosis in a diabetic patient. *Indian J Med Microbiol* 2006; 24: 222–224.
  100. Virally ML, Riveline JP, Virally J. et al. Pulmonary mucormycosis in a diabetic patient with HIV. *Diabetes Care* 2002; 25: 2105.
  101. Kontoyiannis DP. Decrease in the number of reported cases of zygomycosis among patients with diabetes mellitus: a hypothesis. *Clin Infect Dis* 2007; 44: 1089–1090.
  102. Sharada DM, Arunkumar G, Vandana KE, Rao PS. Sino-orbital aspergillosis in a diabetic patient. *Indian J Med Microbiol* 2006; 24: 138–140.
  103. Komase Y, Kunishima H, Yamaguchi H, Ikehara M, Yamamoto T, Shinagawa T. Rapidly progressive invasive pulmonary aspergillosis in a diabetic man. *J Infect Chemother* 2007; 13: 46–50.
  104. Norlinah MI, Ngow HA, Hamidon BB. Angioinvasive cerebral aspergillosis presenting as acute ischaemic stroke in a patient with diabetes mellitus. *Singapore Med* 2007; 48: e1–e4.
  105. Santelli AC, Blair JE, Roust LR. Coccidioidomycosis in patients with diabetes mellitus. *Am J Med* 2006; 119: 964–969.
  106. Haruyama N, Masutani K, Tsuruya K. et al. *Candida glabrata* fungemia in a diabetic patient with neurogenic bladder: successful treatment with micafungin. *Clin Nephrol* 2006; 66: 214–217.
  107. Gumbo T, Chemaly RF, Isada CM, Hall GS, Gordon SM. Late complications of *Candida (Toluopsis) glabrata* fungemia: description of a phenomenon. *Scand J Infect Dis* 2002; 34: 817–818.
  108. Jakubowska I, Łukasiewicz D. Serious course of sepsis in diabetic patients. *Przegl Epidemiol* 2006; suppl 1: 46–50.
  109. Bader MS, Lai SM, Kumar V, Hinthorn D. Candidemia in patients with diabetes mellitus: epidemiology and predictors of mortality. *Scand J Infect Dis* 2004; 36: 860–864.
  110. Bader MS, Hinthorn D, Lai SM, Ellerbeck EF. Hyperglycaemia and mortality of diabetic patient with candidaemia. *Diabet Med* 2005; 22: 1252–1257.
  111. Lestin F, Pertschy A, Rimek D. Fungemia after oral treatment with *Saccharomyces boulardii* in a patient with multiple comorbidities. *Dtsch Med Wochenschr* 2003; 128: 2531–2533.
  112. Ascioğlu S, Rex JH, de Pauw B. et al. on behalf of the Invasive Fungal Infections Cooperative Group of the European Organization for Research and Treatment of Cancer and Mycoses Study Group of the National Institute of Allergy and Infectious Diseases: Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: An international consensus. *Clin Infect Dis* 2002; 34: 7–14.
  113. Segal E. *Candida*, still number one — what do we know and where are we going from there? *Mycoses* 2004; suppl 1: 3–11.
  114. Krajewska-Kutak E, Lewko J, Rolka H. et al. Grzybicze zakażenia szpitalne — narastający problem. *Mikol Lek* 2000; 7: 159–163.
  115. Gudlaugsson O, Gillespie S, Lee K. et al. Attributable mortality of nosocomial candidemia, revisited. *Clin Infect Dis* 2003; 37: 1172–1177.

116. McNeil MM, Nash SL, Hajjeh RA. et al. Trends in mortality due to invasive mycotic diseases in the United States, 1980–1997. *Clin Infect Dis* 2001; 33: 641–647.
117. Pfaller MA, Diekema DJ. Rare and emerging opportunistic fungal pathogens: concern for resistance beyond *Candida albicans* and *Aspergillus fumigatus*. *J Clin Microbiol* 2004; 42: 4419–4431.
118. Nguyen MH, Peacock JE, Morris AJ. et al. The changing face of candidemia: emergence of non-*Candida albicans* species and antifungal resistance. *Am J Med* 1996; 100: 617–623.
119. Marchetti O, Bille J, Fluckiger U. et al. Epidemiology of candidemia in Swiss tertiary care hospitals: secular trends, 1991–2000. *Clin Infect Dis* 2004; 38: 311–320.
120. Szymankiewicz M, Kowalewski J. Zakażenia wywołane przez grzyby *Candida*. Czynniki predysponujące. *Mikol Lek* 2005; 12: 189–192.
121. Nucci M, Marr KA. Emerging fungal diseases. *Clin Infect Dis* 2005; 41: 1058–1063.
122. Kotlarek-Haus S. Kliniczne aspekty uogólnionych zakażeń grzybiczych. *Mikol Lek* 1995; 2: 175–182.
123. Hrynczewicz-Gwóźdź A, Plomer-Niezgoda E, Baran E. Trudności lecznicze grzybicy u chorych na cukrzycę. *Mikol Lek* 2006; 13: 315–317.
124. Rieth H. Mycoses and antimycotics. III. Diagnostic and therapeutic guidelines. *Pharm Unserer Zeit* 1982; 11: 1–17.