10.17951/c.2018.73.1.47-59

ANNALES
UNIVERSITATIS MARIAE CURIE-SKŁODOWSKA
LUBLIN – POLONIA

VOL. LXXIII, 1 SECTIO C 2018

MARTA DĄBROWSKA[1,2], MONIKA SIENKIEWICZ[1*], PAWEŁ KWIATKOWSKI[3], HANNA ZIELIŃSKA-BLIŹNIEWSKA[1], MICHAŁ DĄBROWSKI[1]

[1]Department of Allergology and Respiratory Rehabilitation, 2nd Chair of Otolaryngology, Medical University of Łódź, Poland
[2]Department of Gynecology and Obstetrics, District Hospital in Garwolin, Poland
[3]Department of Diagnostic Immunology, Chair of Microbiology, Immunology and Laboratory Medicine, Pomeranian Medical University in Szczecin, Poland
*Correspondence to: e-mail: monika.sienkiewicz@umed.lodz.pl

Diagnosis and treatment of invasive *Candida* infections – a review article

SUMMARY

Candida albicans is the most common cause of fungal infections worldwide. Invasive candidiasis comprises candidemia and deep-seated candidiasis. Most yeast invasive infections are endogenous with a high mortality. Pathogenesis of candidiasis depends on avoiding host immune responses, as well as the virulence factors of the fungus enabling colonization and invasion of tissues. Adequate source control and antifungal therapy administered within a short time is critical to get a better prognosis. The emergence of drug resistance and the side effects of currently available antifungals are becoming the major problem in the management of *Candida* spp. infection.

Keywords: *Candida* spp., candidemia, invasive candidiasis, treatment, recommendation

INTRODUCTION

Invasive fungal infection is associated with a high mortality ranging from 29 to 90% (1). In Europe invasive fungal infections include invasive yeast infections with *Candida* spp. as the absolutely dominating pathogen (41). Invasive *Candida* spp. infections are the most common non-mucosal fungal diseases among hospitalized patients in the developed world. *Candida* spp. is also

by far the most common fungal blood stream pathogen (25). Invasive candidiasis comprises candidemia and deep-seated candidiasis. Yeasts are part of our normal microflora and the reason of disease process is the disturbance of the balance between yeast and host. In the majority of yeats invasive infections are endogenous, exogenous infections are rare (62). *C. albicans, C. glabrata, C. krusei, C. parapsilosis*, and *C. tropicalis* are five most common *Candida* species in human infections, in addition there are rarer species like *C. guilliermondii*, *C. lusitaniae* and *C. kefyr*. In Japan in 2009 for the first time was described *C. auris*, an emerging multidrug-resistant yeast (57). *C. auris* can cause invasive candidiasis and is associated with high mortality. *C. auris* infections, specifically fungemia, have been reported on five continents. The strains isolated in each region are genetically distinct, indicating that this species is emerging in different locations (14). Pathogenesis of candidiasis depends on avoiding host immune responses, as well as the virulence factors of the fungus enabling colonization and invasion of tissues. Yeasts virulence factors include: complexity of cell wall structure, adhesion, pleomorphism, enzymatic activity, molecular mimicry, phenotypic variation (36). The risk factors for a patient's candidiasis include: immunosuppressant or steroids treatments, long-term catheterization, invasive medical procedures, treatment with broad-spectrum antibiotic, destruction of skin by deep skin burns, local disorders of the gastrointestinal tract, diabetes mellitus, premature very low birth weight infants, immunologically compromised individuals, spread of HIV infection (41, 52).

Diagnosis of fungal infections is based on microscopic studies, microbiological cultures and identification of cultured fungal species, serological tests (detection of antigens and antibodies) and molecular ones (24). Diagnosis by culturing allows subsequent susceptibility testing of causative species (34). Sensitivity of blood culture is far from ideal, with a sensitivity reported to be 21–71% (34). Standard diagnostic tests (blood or deep-tissue site cultures) are low sensitive, have turnaround times of several days, and often turn positive late in the disease (13). Deep-tissue cultures are further limited by need for invasive procedures, which are often contra-indicated due to underlying medical conditions. Non-culture diagnostics (such as β-d-glucan or polymerase chain reaction – PCR) used judiciously as adjuncts to cultures can identify more patients with invasive candidiasis, at earlier disease stages (13). However, there is uncertainty about the performance of non-culture diagnostics in routine practice, and their roles in patient management.

Patients with invasive candidiasis are often already sick from other medical conditions, so it can be difficult to know which symptoms are related to a *Candida* spp. infection. The most common symptoms of invasive candidiasis are fever and chills that do not improve after antibiotic treatment for suspected bacterial infections. If the infection spreads to other parts of the body, such as the heart, brain, eyes, bones, or joints, other symptoms of invasive candidiasis can develop (67).

Infectious Diseases Society of America in 2016 carried out a revision of the clinical practice guideline for candidiasis depending on the site of infection and its severity (49). Candidiasis is treated with antimycotics like: clotrimazole, nystatin, fluconazole, voriconazole, amphotericin B, and echinocandins. Low carbohydrate diet and probiotic preparations are the supplementation of pharmacological treatment.

Candidemia

The most common form of invasive candidiasis is *Candida* spp. bloodstream infection, which is called candidemia (50). Its overall incidence raised fivefold in the past ten years and *Candida* spp. is the most frequently isolated species, however there are geographical differences emerging in epidemiology between different countries demonstrating a shift towards non-albicans species (2, 4). In the United States and Europe, candidemia is one of the most common causes of bloodstream infections in hospitalized patients, and it often results in long hospital stays, high medical costs, and poor outcomes (38, 39). Barchiesi et al. study shows that candidemia is a significant source of mor-

bidity and mortality. Mortality of candidemia is very high, ranging to 63% depending on the patients population. The elderly population is particularly vulnerable to *Candida* spp. infections, this can be due to several factors such as: high frequency of comorbidities, aging-related physiological changes, polypharmacy, and high colonization rate (4). Early initiation of effective antifungal therapy is critical in the successful treatment of candidemia. There is much higher mortality rates among patients with candidemia whose therapy was delayed (4).

The identification of the etiological factor followed by the direct preparation blood cultures is usually negative in the case of disseminated candidiasis, making diagnosis difficult. In the case of candidemia, blood should be collected again after 24 h. In candidiasis or severe organ candidalysis, there should be determined azoles susceptibility (echinocandin susceptibility indicated in previously treated patients and in *C. glabrata* and *C. parapsilosis* infection). In candidiasis, it is recommended to repeat blood cultures daily until negative results are obtained (28).

The selection of drug for the treatment of candidemia should optimally take into account any history of recent azole exposure, a history of intolerance to an antifungal agent, the dominant *Candida* species and current susceptibility data in a particular clinical unit or location, severity of illness, relevant comorbidities, and evidence of involvement of the CNS, cardiac valves, and/or visceral organs (49).

Fluconazole (≥6 mg/kg/24 h) is first-line therapy for patients who are hemodynamically stable, who have no previous exposure to azoles, and who do not belong to a group at high risk of *C. glabrata*. Patients with candidemia and suspected concomitant endocardial or CNS candidiasis should receive amphotericin B-AmB in ≥7 mg/kg daily dose (for endocardial or CNS candidiasis) or echinocandin (for endocardial candidiasis). The echinocandins demonstrate significant fungicidal activity against all *Candida* species. Because of their efficacy, favorable safety profile, and very few drug interactions, the echinocandins are favored for initial therapy for patients who have a recent history of exposure to an azole, moderately severe to severe illness (hemodynamically unstable). They are also recommended for patients with allergy or intolerance to azoles or AmB, or high risk of infection with *C. krusei* or *C. glabrata*. A short course of intravenous echinocandin therapy (3–5 days) followed by transition to oral fluconazole or voriconazole (for *C. krusei* infection) is recommended by Infectious Diseases Society of America (49).

According to Polish recommendations, preferred treatment includes echinocandins – caspofungin every 24 h, the first dose of 70 mg, the next 50 mg; or micafungin 100 mg every 24 h; or anidulafungin first dose of 200 mg, then 100 mg every 12 h (28). Echinocandin is favored as initial therapy for patients with moderately severe to severe disease due to invasive candidiasis, but in the opinion of most experts it should not be used in all episodes (49).

In *C. glabrata* susceptible to fluconazole or voriconazole, voriconazole 400 mg (6 mg/kg) maintenance therapy every 12 h or fluconazole 800 mg (12 mg/kg) per maintenance therapy should be used. In supportive therapy for *C. krusei* candidiasis voriconazole is recommended in standard doses: 400 mg (6 mg/kg) twice daily for 2 doses, then 200 mg (3 mg/kg) twice daily. Treatment should be continued for 14 days after negative blood culture if no organ spreading occurs (28, 49). If it is not dangerous for the patient, intravenous catheter removal is recommended for nonneutropenic patients with candidemia (26, 49).

Candidemia in neutropenic patients is associated with acute disseminated candidiasis, a sepsis-like syndrome, multiorgan failure, and death. *C. tropicalis* is particularly virulent in neutropenic patients. Echinocandins are the first-line option for therapy and have a better safety profile than other agents (1). Duration of therapy for candidemia in neutropenic patients should be 14 days after resolution of attributable signs and symptoms and clearance of the bloodstream of *Candida* species, provided that there has been recovery from neutropenia (49). Intravenous catheter removal should be considered for neutropenic patients who have persistent candidemia and in whom it is logistically feasible (68). Granulocyte colony-stimulating factor (G-CSF) mobilized granulocyte transfusions

can be considered in cases of persistent candidemia with anticipated protracted neutropenia (49). Chronic disseminated candidiasis can ensue as a complication of candidemia in neutropenic patients despite antifungal therapy.

Empirical treatment for suspected invasive candidiasis

Candida species are an increasing cause of sepsis among nonneutropenic patients receiving intensive care (4, 66). Identification of patients at risk of *Candida* spp. infections and prompt adequate antifungal treatment and catheter removal could be critical to decrease early mortality (53). *Candida* spp. colonization, severity of illness, number of broad-spectrum antibiotic agents used and duration of use, previous surgery (especially bowel surgery), receipt of dialysis, use of central venous catheters, receipt of parenteral nutrition, and length of ICU stay are important risk factors for invasive candidiasis (26). Empirical antifungal therapy is recommended in critically ill patients with risk factors for invasive candidiasis and no other known cause of fever. Echinocandin are preference in hemodynamically unstable patients, in patients previously exposed to an azole, and in those known to be colonized with azole-resistant *Candida* species. Liposomal *amphotericin* B-LFAmB and *amphotericin* B-desoxycholate (AmB-d) are alternatives, but the risk of toxicity is quite big. Empirical therapy with fluconazole may be considered in non-critically ill patients who are known to be colonized with azole-susceptible *Candida* species or who have no prior exposure to azoles (49).

In neutropenic patients LFAmB (3–5 mg/kg daily), caspofungin (70 mg loading dose, then 50 mg daily) or voriconazole (6 mg/kg twice daily for 2 doses, then 3 mg/kg twice daily) are recommended for empirical antifungal therapy (49). Caspofungin has been shown to be as effective as and better tolerated than L-AmB for empirical therapy (65). Alternative agents are fluconazole 800 mg (12 mg/kg) loading dose, then 400 mg [6 mg/kg] daily, which is less toxic than amphotericin B, but its usefulness is limited by its relatively narrow spectrum and itraconazole 200 mg (3 mg/kg) twice daily, but it is available only as an oral formulation and has variable oral bioavailability and frequent gastrointestinal adverse effects (5, 38, 49).

AmB-d is an effective alternative, but there is a higher risk of toxicity than there is with LFAmB.

Chronic disseminated (hepatosplenic) candidiasis

Chronic disseminated candidiasis (CDC) is the syndrome seen after previous bloodstream; it mainly involves the liver, spleen, and occasionally kidneys and other organs. Chronic disseminated candidiasis occurs mostly in patients after profound and prolonged neutropenia, which is more often seen in patients with acute haematological malignancies (53). *Candida* spp. infection frequently misdiagnosed for the late onset of clinical and radiological manifestations, this kind of complication is much more rare nowadays (46). Clinical symptoms of disseminated candidiasis are usually not characteristic and include: fever, right upper quadrant discomfort, nausea, and elevation of liver enzymes. The symptoms occur following return of neutrophils and persist for a long time unless treatment is initiated (53). Organ changes in the course of candidiasis can be visualized in imaging such as ultrasonography, computed tomography, magnetic resonance imaging or positron emission tomography-CT (15). The diagnosis of probable hepatosplenic candidiasis requires the presence of typical clinical symptoms and imaging findings, as well as an episode of candidemia within the preceding 2 weeks. Biopsy of the hepatic or splenic lesion(s) is not required.

Lipid formulation AmB 3–5 mg/kg/d or echinocandins (caspofungin every 24 h, first dose 70 mg, next 50 mg or micafungin 100 mg every 24 h or anidulafungin first dose 200 mg, then 100 mg every 12 h) for several weeks is recommended as an initial treatment. Followed by oral fluconazole, 400 mg (6 mg/kg) daily is prescribed, for patients who are unlikely to have a fluco-

nazole-resistant isolate (49). Duration of pharmacotherapy is unspecified, usually several months, until the regression has resolved radiographically in order to prevent relapse. Therapy should be continued for a period of immunosuppression, including during chemotherapy. As an additional treatment nonsteroidal anti-inflammatory drugs or corticosteroids for 1–2 weeks can be used in patients with chronic fever (15, 53).

Intra-abdominal candidiasis

Intra-abdominal candidiasis is the most common type of deep-seated candidiasis. Intra-abdominal candidiasis occurs: in patients who have had recent abdominal surgery and includes peritonitis, abdominal abscess, and purulent or necrotic infection at sites of gastrointestinal perforation or anastomotic leak. Patients with secondary or tertiary peritonitis and with recurrent gastroduodenal perforation, anastomotic leaks, or acute necrotizing pancreatitis have a high risk to develop intra-abdominal candidiasis with a high mortality rate (5). Intra-abdominal candidiasis encompasses a range of disease manifestations, which are usually not characteristic. Diagnosis is hampered by the lack of specific clinical signs and symptoms. The clinical significance of *Candida* spp. in cultures of samples from intra-abdominal sites is controversial and blood cultures are often negative. There are limited data on the utility of using surrogate markers (42, 43). Because of diagnostic difficulties, empiric antifungal therapy should be considered for patients with clinical evidence of intra-abdominal infection and significant risk factors for candidiasis, including recent abdominal surgery, anastomotic leaks, or necrotizing pancreatitis (49). The choice of antimycotic should be guided by the *Candida* species isolated, antifungal susceptibility patterns and local epidemiology. Duration of antifungal therapy depends on response and the adequacy of source control. Source control with adequate drainage and/or debridement is an important part of therapy (32, 49).

***Candida* spp. intravascular infections and endocarditis**

Candida spp. endocarditis was previously considered a rare disease. Its incidence is increasing concurrent with the general increase in *Candida* spp. infections (63). *C. albicans* and non-albicans *Candida* species are the cause of infection with a similar frequency. Risk factors of the disease are: cardiac valvular surgery, but other risk factors include injection drug use, cancer chemotherapy, prolonged presence of CVCs, and prior bacterial endocarditis. Symptoms are similar to those of bacterial endocarditis, but large emboli to major vessels are more frequent. Endocarditis should be suspected when a patient with candidemia has persistent fever despite appropriate treatment, or when a new heart murmur, heart failure, or embolic phenomena occur in the setting of candidemia (11). The preferred treatment is AmBLC 3–5 mg/kg/d (with flucytosine 25 mg/kg every 6 h or without flucytosine) or echinocandin (caspofungin 150 mg/d or micafungin 150 mg/d, or anidulafungin 200 mg/d). Treatment can be continued with fluconazole 400–800 mg (6–12 mg/kg/d), provided the sensitivity is confirmed. In patients who are in stable clinical status after the disappearance of candidiasis, as well as in the case of infection with a fluconazole-resistant strain, voriconazole 200–300 mg (3–4 mg/kg) is recommended every 12 h or posaconazole 300 mg every 24 h after providing confirmed sensitivity. Surgical treatment includes valve replacement and is recommended by Infectious Diseases Society of America. Treatment should be continued for at least 6 weeks after surgery and for a longer duration in patients with perivalvular abscesses and other complications (28, 49). *Candida* spp. endocarditis has a propensity to relapse.

In case of *Candida* spp. infections of pacemakers and cardiac defibrillators, the entire device should be removed. Antifungal therapy is the same as that recommended for native valve endocarditis, given for 4–6 weeks depending on whether the infection involves the wires in addition to the generator pocket. The role of antifungal prophylaxis is controversial (9).

Septic deep venous thrombosis is a major complication associated with central venous catheterization in intensive care units. *Candida* species are one of the most common causative organisms. The incidence of *Candida* spp. infections is increasing, especially in intensive care patients receiving total parenteral nutrition and long-term broad-spectrum antibiotics (6). If it is possible, surgical treatment and catheter removal is recommended. Farmacotherapy includes lipid formulation AmB, 3–5 mg/kg daily, or fluconazole, 400–800 mg (6–12 mg/kg) daily, or an echinocandin (caspofungin 150 mg daily, micafungin 150 mg daily, or anidulafungin 200 mg daily) for at least 2 weeks after candidemia (27, 49). Adjunctive therapy like systemic anticoagulation or thrombolytic therapy can be useful in some cases (7).

Candida spp. osteoarticular infections

Candida spp. osteoarticular infections is usually a chronic disease in patients with comorbidities and risk factors. Hematogenous dissemination is the most common mechanism of infection, but there are some cases of direct inoculation. In adults axial skeleton (spine) is the most common site of inflammation. *C. albicans* is the predominant pathogen. After identification a single focus of infection, there should be a search for other sites of involvement (23, 45). Clinical picture and findings on radiographic imaging are usually not characteristic. *Candida* spp. osteomyelitis should be considered when a patient presents risk factors and pain without previous trauma (29). Diagnosis of *Candida* spp. osteomyelitis required the presence of yeast cells consistent with *Candida* species on histopathological or cytopathological examination of bone specimens, or a positive culture for *Candida* species from a bone sample obtained with a sterile procedure in the setting of concomitant clinical and/or radiographic evidence of infection. First-line treatment is fluconazole, 400 mg (6 mg/kg) daily, for 6–12 months or an echinocandin (caspofungin 50–70 mg daily, micafungin 100 mg daily, or anidulafungin 100 mg daily) for at least 2 weeks followed by fluconazole, 400 mg (6 mg/kg) daily, for 6–12 months. Lipid formulation AmB, 3–5 mg/kg daily, for at least 2 weeks followed by fluconazole, 400 mg (6 mg/kg) daily, for 6–12 months is an alternative recommended treatment. In specific cases (mediastinitis and sternal osteomyelitis) surgical debridement of bone is needed (27, 49).

Candida arthritis is very rare, *C. albicans* is the form that is isolated most frequently from fungus-infected joints. *Candida* spp. arthritis usually affects large joints and particularly involves patients who have risk factors (61). Diagnosis is based on the clinical picture and tests of synovial fluid and blood. Drainage is necessary to successful therapy of *Candida* arthritis, if there is a prosthetic device, it should be removed (64). Infectious Diseases Society of America recommended fluconazole, 400 mg (6 mg/kg) daily, for 6 weeks or an echinocandin (caspofungin 50–70 mg daily, micafungin 100 mg daily, or anidulafungin 100 mg daily) for 2 weeks followed by fluconazole, 400 mg (6 mg/kg) daily, for at least 4 weeks. The alternative drug is Lipid formulation AmB, 3–5 mg/kg daily, for 2 weeks, followed by fluconazole, 400 mg (6 mg/kg) daily, for at least 4 weeks (49).

Candida endophthalmitis

Endophthalmitis is an eye infection that may result in permanent loss of useful vision in the affected eye (17). Inflammation usually involves the posterior chamber. *Candida* species most often cause endogenous infection and are complicated by candidemia. Those infections can be manifested as isolated chorioretinitis or as chorioretinitis with extension into the vitreous, leading to vitritis (36). The most common species is *C. albicans* (58).

Endophthalmitis is a clinical diagnosis supported by culture of the vitreous and/or aqueous and also by blood cultures in endogenous endophthalmitis. Negative cultures do not exclude the diagnosis (36). Early diagnosis and prompt treatment allow to avoid serious complications. Decisions

regarding antifungal treatment and surgical intervention should be made jointly by an ophthalmologist and an infectious diseases physician.

Infectious Diseases Society of America recommends in all patients with candidemia a retinal examination, performed by an ophthalmologist, within the first week of therapy in nonneutropenic patients to establish if endophthalmitis is present. For neutropenic patients, it is recommended to delay the examination until neutrophil recovery (49).

Candida chorioretinitis without vitritis should be treated by fluconazole-/voriconazole-susceptible isolates, fluconazole, loading dose, 800 mg (12 mg/kg), then 400–800 mg (6–12 mg/kg) daily or voriconazole, loading dose 400 mg (6 mg/kg) intravenous twice daily for 2 doses, then 300 mg (4 mg/kg) intravenous or oral twice daily. For fluconazole-/voriconazole-resistant isolates, liposomal AmB, 3–5 mg/kg intravenous daily, with or without oral flucytosine, 25 mg/kg 4 times daily should be given. Inflammatory with macular involvement, should be treated by intravitreal injection of either AmB deoxycholate, 5–10 μg/0.1 ml sterile water, or voriconazole, 100 μg/0.1 ml sterile water or normal saline. Duration of treatment is around 4–6 weeks (49). The treatment *Candida* chorioretinitis with vitritis is similar to that recommended for chorioretinitis without vitreal involvement. Performing a pars plana vitrectomy should be considered, because the risk of retinal detachment is decreased with early vitrectomy (49, 56).

Central nervous system candidiasis

There is an increased incidence of invasive mycoses affecting the CNS, causing important morbimortality. Neurocandidiasis is the most frequent opportunistic entity, with widely clinical presentation like: disseminated candidiasis, as a complication of a neurosurgical procedure, especially when an intracranial device is inserted, or rarely as an isolated chronic infection. *C. albicans* cause most neurocandidiasis. The clinical presentation includes meningitis, microabscesses, macroabscesses, vascular and medullar injury (11, 21, 47). The initial symptoms of acute meningitis by *Candida* spp. are indistinguishable from those produced by bacterial infection (fever, headache, neck stiffness, mental status impairment) (55). Central Nervous System Candidiasis should be suspected in every patient with neurological symptoms and signs presenting with one or more of the following: isolation of *Candida* in cerebrospinal fluid (CSF), blood or in any sterile liquid in patient with pleocytosis in the CSF, lack of response in cases of bacterial or tuberculous meningitis in spite of being under suitable treatment (19, 55). Neuroimaging in meningitis by *Candida* spp. can be useful, CT detect the presence of microabscesses and MRI helps to better evaluate microabscesses. Treatment is based on the antifungal susceptibilities of the infecting species and the ability of the antifungal agent to achieve appropriate concentrations in the CSF and brain. Therapy should be continued until all signs and symptoms and CSF and radiological abnormalities have resolved. Liposomal AmB, 5 mg/kg daily, with or without oral flucytosine, 25 mg/kg 4 times daily, is recommended like an initial treatment. Fluconazole, 400–800 mg (6–12 mg/kg) daily, is recommended as the next step. If it is possible, infected CNS devices should be removed (49).

Urinary tract infections due to *Candida* species

Candiduria is diagnosed on the basis of the presence of *Candida* yeast in 2 cultures and usually indicating colonization, not infection. Risk factors include diabetes, a catheter in the bladder, and antibiotic therapy (60). Asymptomatic candidiasis does not require treatment, except in immunocompromised patients (neutropenic patients, very low-birth-weight infants <1500 g) or those undergoing invasive procedures in the urinary tract. It usually disappears after removing the catheter from the bladder or ending antibiotic therapy (31). Patients few days before and after urologic

procedures should be treated with oral fluconazole, 400 mg (6 mg/kg) daily, or AmB deoxycholate, 0.3–0.6 mg/kg daily. Neutropenic patients and very low-birth-weight infants should be treated like for candidemia (49).

Symptomatic *Candida* spp. cystitis treatment depends on yeast susceptibility. Infectious Diseases Society of America recommends fluconazole, 200 mg (3 mg/kg) daily for 2 weeks. For *C. glabrata* (fluconazol-resistant yeast) there is recommended AmB deoxycholate, 0.3–0.6 mg/kg daily for 1–7 days or oral flucytosine, 25 mg/kg 4 times daily for 7–10 days. In case of *C. krusei*, AmB deoxycholate therapy is shorter (49). If it is possible, bladder catheter should be removed.

Candida spp. pyelonephritis occurs as a consequence of hematogenous spread to the kidneys in a patient who has candidemia. These patients usually are treated for candidemia and have no urinary tract symptoms or signs (21). Symptoms of a pyelonephritis include fever and back pain. Urine diagnostic tests are not helpful in differentiating colonization from infection (30). Radiology imaging of the urinary tract is helpful in defining structural abnormalities like hydronephrosis, abscesses, emphysematous pyelonephritis, and fungus ball formation (33). Pharmacotherapy is similar to that of symptomatic *Candida* spp. cystitis, and the doses used may be slightly higher. Surgical treatment involves removing an obstacle in urine outflow. In the case of stent or nephrostomy catheters, they should be replaced (28, 49).

CONCLUSION

Recent changes in the aetiology and growing incidence of invasive candidiasis have serious implications for current and future diagnosis, treatment and prognosis. There is a progressive shift in the aetiology of invasive candidiasis from *C. albicans* to other species of the *Candida* genus (16). Rise of multiresistant species, such as *C. auris* or *C. glabrata*, is a major problem. Invasive candidiasis is divided into candidemia and deep-seated candidiasis. Mortality rate is extremely high in invasive candidiasis: up to 50% in candidemia and even 97% in patients without having adequate source control and antifungal therapy administered within a short time (32). Intervention as a removal of contaminated central venous catheter or drainage of infected material can affect the increase in the effectiveness of treatment (1, 48). Blood cultures or other samples taken under sterile conditions remain the gold standard in the diagnosis of invasive candidiasis (49). However, microbiological techniques for early culture-independent diagnosis like germ tube antibodies, mannan antigens and antibodies, detection of 1,3-β-D-glucan, MALDI-TOF and PNA-FISH have a shortened time of the diagnosis (10), but interpretation of specificity in these studies can be complicated.

Resistance to antifungal therapy observed in some species (*C. auris, C. glabrata*) is becoming the major problem in the management of *Candida* spp. infections. Resistance to the echinocandins is uncommon (from 0–1.7%) (51). Primary resistance to fluconazole is rare for *C. albicans* (resistance rate of 1.4%), *C. parapsilosis* (3.6%) and *C. tropicalis* (4.1%). *C. krusei* is intrinsically resistant to fluconazole (78.3%), *C. glabrata* displays reduced dose-dependent susceptibility compared with other *Candida* species and has a global resistance rate of 15.7% (20). Voriconazole resistance is generally uncommon (20). In total,

38% of echinocandin-resistant *C. glabrata* isolates is also found to be resistant to fluconazole (51). The majority of *C. albicans*, *C. tropicalis* and *C. parapsilosis* isolates are sensitive to amphotericin B. *C. lusitaniae* strains very often show clinically significant resistance to amphotericin B, but the frequency of this phenomenon has not been precisely determined (20). Flucytosine has a high rate of emergence of resistance during monotherapy, so it is usually given in combination with amphotericin B (3). *C. auris* surpasses all *Candida* species as the most difficult pathogen to identify and treat. It has demonstrated multidrug resistant properties and the high mortality rate (approx. 68%) (44).

The most common side effects of azoles include transient visual disturbances, skin reactions and hepatotoxicity (18). An important side effect of amphotericin B that occurs in almost all patients after prolonged treatment is the impaired renal function. Others include damage to liver function, profound hypokalemia and hypomagnesaemia. The toxicity of amphotericin B significantly limits its use. For this reason, lipid preparations of amphotericin B have been introduced, which have less pronounced side effects (40). One of the most important undesirable effects of flucytosine is myelosuppression and hepatotoxicity, therefore its use in hematological indications requires special care. Side effects during treatment of caspofungin are rare, most commonly it is fever, phlebitis, headache (18).

REFERENCES

1. Andes D.R., Safdar N., Baddley J.W., Playford G., Reboli A.C., Rex J.H., Sobel J.D., Pappas P.G., Kullberg B.J.; Mycoses Study Group. 2012. Mycoses Study Group. Impact of treatment strategy on outcomes in patients with candidemia and other forms of invasive candidiasis: a patient-level quantitative review of randomized trials. Clin. Infect. Dis. 54(8): 1110–1122.
2. Arendrup M.C., Dzajic E., Jensen R.H., Johansen H.K., Kjaeldgaard P., Knudsen J.D., Kristensen L., Leitz C., Lemming L.E., Nielsen L., Olesen B., Rosenvinge F.S., Røder B.L., Schønheyder H.C. 2013. Epidemiological changes with potential implication for antifungal prescription recommendations for fungaemia: data from a nationwide fungaemia surveillance programme. Clin. Microbiol. Infect. 19: E343–353. doi: 10.1111/1469-0691.12212.
3. Barchiesi F., Arzeni D., Caselli F., Scalise G. 2000. Primary resistance to flucytosine among clinical isolates of *Candida* spp. J. Antimicrob. Chemother. 45: 408–409.
4. Barchiesi F., Orsetti E., Gesuita R., Skrami E., Manso E. Candidemia Study Group. 2016. Epidemiology, clinical characteristics, and outcome of candidemia in a tertiary referral center in Italy from 2010 to 2014. Infection 44: 205–213.
5. Bassetti M., Marchetti M., Chakrabarti A., Colizza S., Garnacho-Montero J., Kett D.H., Munoz P., Cristini F., Andoniadou A., Viale P., Rocca G.D., Roilides E., Sganga G., Walsh T.J., Tascini C., Tumbarello M., Menichetti F., Righi E., Eckmann C., Viscoli C., Shorr A.F., Leroy O., Petrikos G., De Rosa F.G. 2013. A research agenda on the management of intra-abdominal candidiasis: results from a consensus of multinational experts. Intensive Care Med. 39(12): 2092–2106.

6. Berdal J.E., Haagensen R., Ranheim T., Bjørnholt J.V. 2014. Nosocomial Candidemia; Risk Factors and Prognosis Revisited; 11 Years Experience from a Norwegian Secondary Hospital. PLoS One. 9(7): e103916.
7. Block A.A., Thursky K.A., Worth L.J., Slavin M.A. 2009. Thrombolytic therapy for management of complicated catheter-related *Candida albicans* thrombophlebitis. Intern. Med. J. 39: 61–63.
8. Boogaerts M., Winston D.J., Bow E.J., Garber G., Reboli A.C., Schwarer A.P., Novitzky N., Boehme A., Chwetzoff E., De Beule K. Itraconazole Neutropenia Study. 2001. Intravenous and oral itraconazole versus intravenous amphotericin B deoxycholate as empirical antifungal therapy for persistent fever in neutropenic patients with cancer who are receiving broad-spectrum antibacterial therapy: a randomized, controlled trial. Ann. Intern. Med. 135: 412–422.
9. Cabrera A.G., Khan M.S., Morales D.L., Chen D.W., Moffett B.S., Price J.F., Dreyer W.J., Denfield S.W., Jeewa A., Fraser C.D. Jr, Vallejo J.G. 2013. Infectious complications and outcomes in children supported with left ventricular assist devices. J. Heart Lung Transplant. 32: 518–524.
10. Candel F.J., Pazos Pacheco C., Ruiz-Camps I., Maseda E., Sánchez-Benito M.R., Montero A., Puig M., Gilsanz F., Aguilar J., Matesanz M. 2017. Update on management of invasive candidiasis. Rev. Esp. Quimioter. 30(6): 397–406.
11. Card L, Lofland D. 2012. Candidal endocarditis presenting with bilateral lower limb ischemia. Clin. Lab. Sci. 25: 130–134.
12. Chen T.L., Chen H.P., Fung C.P., Lin M.Y., Yu K.W., Liu C.Y. 2004. Clinical characteristics, treatment and prognostic factors of candidal meningitis in a teaching hospital in Taiwan. Scand. J. Infect. Dis. 36: 124–130.
13. Clancy C.J., Nguyen M.H. 2013. Finding the "missing 50%" of invasive candidiasis: How nonculture diagnostics will improve understanding of disease spectrum and transform patient care. Clin. Infect. Dis. 56: 1284–1292.
14. Clinical Alert to U.S. Healthcare Facilities – June 2016 – Fungal Diseases | CDC. www.cdc.gov. Retrieved 2017-04-06.
15. De Castro N., Mazoyer E., Porcher R., Raffoux E., Suarez F., Ribaud P., Lortholary O., Molina J.M. 2012. Hepatosplenic candidiasis in the era of new antifungal drugs: a study in Paris 2000–2007. Clin. Microbiol. Infect. 18: E185–187.
16. Diekema D., Arbefeville S., Boyken L., Kroeger J., Pfaller M. 2012. The changing epidemiology of health care-associated candidemia over three decades. Diagn. Microbiol. Infect. Dis. 73: 45–48.
17. Durand M.L. 2017. Bacterial and Fungal Endophthalmitis. Clin. Microbiol. Rev. 30(3): 597–613.
18. Dzierżanowska D. 2006. Leki przeciwgrzybicze stosowane w leczeniu grzybic układowych. In: Zakażenia grzybicze – wybrane zagadnienia. a-Medica Press, Bielsko-Biała: 92–125.
19. Eileen P., Scully L.R., Baden J., Katz T. 2008. Fungal brain infections. Current Opinion in Neurology 21: 347–352.
20. Espinel-Ingroff A., Arendrup M., Cantón E., Cordoba S., Dannaoui E., García-Rodríguez J., Gonzalez G.M., Guarro J., Las-Flord C., Lackhard S.L., Martin-Mazuelos E., Meis J.F., Ostrovsky-Zeichner L., Pelaez T., St-Germain G., Turnidge J. 2016. Multicenter study of method-dependent epidemiological cutoff values for detection of resistance in *Candida* spp. and *Aspergillus* spp. to Amphotericin B and Echinocandins for the Etest agar diffusion method. Antimicrob Agents Chemother. 61(1): e01792-16.
21. Fennelly A.M., Slenker A.K., Murphy L.C., Moussouttas M., DeSimone J.A. 2013. *Candida* cerebral abscesses: a case report and review of the literature. Med. Mycol. 51: 779–784.
22. Fisher J.F., Kavanagh K., Sobel J.D., Kauffman C.A., Newman C.A. 2011.*Candida* urinary tract infection: pathogenesis. Clin. Infect. Dis. 52 (Suppl. 6): S437–351.

23. Gamaletsou M.N., Kontoyiannis D.P., Sipsas N.V., Moriyama B., Alexander E., Roilides E., Brause B., Walsh T.J. 2012. *Candida* osteomyelitis: analysis of 207 pediatric and adult cases (1970–2011). Clin. Infect. Dis. 55: 1338–1351.
24. Garczewska B., Kamińska W., Dzierżanowska D. 2008. Phenotype and genotype characterization of *Candida albicans* strains isolated from patients hospitalized at the Children's Memorial Health Institute. Med. Dośw. Mikrobiol. 60: 231–241.
25. Gedik H., Simsek F., Kanturk A., Yildirmak T., Arica D., Aydin D., Demirel N., Yokuş O. 2014. Bloodstream infections in patients with hematological malignancies: which is more fatal – cancer or resistant pathogens? Ther. Clin. Risk Manag. 10: 743–752.
26. Hirano R., Sakamoto Y., Kudo K., Ohnishi M. 2015. Retrospective analysis of mortality and *Candida* isolates of 75 patients with candidemia: a single hospital experience. Infect. Drug Resist. 8: 199–205.
27. Hot A., Maunoury C., Poiree S., Lanternier F., Viard J.P., Loulergue P., Coignard H., Bougnoux M.E., Suarez F., Rubio M.T., Mahlaoui N., Dupont B., Lecuit M., Faraggi M., Lortholary O. 2011. Diagnostic contribution of positron emission tomography with [18F] fluorodeoxyglucose for invasive fungal infections. Clin. Microbiol. Infect. 17: 409–417.
28. https://www.mp.pl/interna/chapter/B16.II.18.12.
29. Kaldau N.C., Brorson S., Jensen P.E., Schultz C., Arpi M. 2012. Bilateral polymicrobial osteomyelitis with *Candida tropicalis* and *Candida krusei*: a case report and an updated literature review. Int. J. Infect. Dis. 16: 16–22.
30. Kauffman C.A., Fisher J.F., Sobel J.D., Newman C.A. 2011. *Candida* urinary tract infections – diagnosis. Clin. Infect. Dis. 52 (Suppl. 6): S452–456.
31. Kauffman C.A., Vazquez J.A., Sobel J.D., Gallis H.A., McKinsey D.S., Karchmer A.W., Sugar A.M., Sharkey P.K., Wise G.J., Mangi R., Mosher A., Lee J.Y., Dismukes W.E. 2000. Prospective multicenter surveillance study of funguria in hospitalized patients. The National Institute for Allergy and Infectious Diseases (NIAID) Mycoses Study Group. Clin. Infect. Dis. 30: 14–18.
32. Kollef M., Micek S., Hampton N., Doherty J.A., Kumar A. 2012. Septic shock attributed to *Candida* infection: importance of empiric therapy and source control. Clin. Infect. Dis. 54: 1739–1746.
33. Krishnasamy P.V., Liby C. 3rd. 2010. Emphysematous pyelonephritis caused by *Candida tropicalis*. Am. J. Med. 123: e7–8.
34. Kullberg B.J., Arendrup M.C. 2015. Invasive candidiasis. The New England Journal of Medicine 373 (15): 1445–1456. doi: 10.1056/NEJMra1315399. ISSN 1533-4406.
35. Kullberg B.J., Sobel J.D., Ruhnke M., Pappas P.G., Viscoli C., Rex J.H., Cleary J.D., Rubinstein E., Church L.W., Brown J.M., Schlamm H.T., Oborska I.T., Hilton F., Hodges M.R. 2005. Voriconazole versus a regimen of amphotericin B followed by fluconazole for candidaemia in non-neutropenic patients: a randomised non-inferiority trial. Lancet 366: 1435–1442.
36. Lingappan A., Wykoff C.C., Albini T.A., Miller D., Pathengay A., Davis J.L., Flynn H.W. Jr. 2012. Endogenous fungal endophthalmitis: causative organisms, management strategies, and visual acuity outcomes. Am. J. Ophthalmol. 153: 162–166.
37. Lim C.S.Y., Rosli R., Seow H.F., Chong P.P. 2012. *Candida* and invasive candidiasis: back to basis. Eur. J. Clin. Microbiol. Infect. Dis. 31: 21–31.
38. Magill S.S., Edwards J.R., Bamberg W., Beldavs Z.G., Dumyati G., Kainer M.A., Lynfield R., Maloney M., McAllister-Hollod L., Nadle J., Ray S.M., Thompson D.L., Wilson L.E., Fridkin S.K. Emerging Infections Program Health Care-Associated Infections and Antimicrobial Use Prevalence Survey Team. 2014. Multistate point-prevalence survey of health care-associated infections. N. Engl. J. Med. 27; 370(13): 1198–1208.

39. Marchetti O., Bille J., Fluckiger U., Eggimann P., Ruef C., Garbino J., Calandra T., Glauser M.P., Täuber M.G., Pittet D. Fungal Infection Network of Switzerland. 2004. Fungal Infection Network of Switzerland. Epidemiology of candidaemia in Swiss tertiary care hospitals: secular trends 1991–2000. Clin. Infect. Dis.
40. Martino R., Viscoli C. 2005. Empirical antifungal therapy in patients with neutropenia and persistent or recurrent fever of unknown origin. B. J. Haematol. 132: 138–154.
41. Montagna M.T., De Giglio O., Napoli C., Lovero G., Caggiano G., Delia M., Pastore D., Santoro N., Specchia G. 2012. Invasive fungal infections in patients with hematologic malignancies (Aurora project): lights and shadows during 18-months surveillance. Int. J. Mol. Sci. 13: 774–787.
42. Montravers P., Lepape A., Dubreuil L., Gauzit R., Pean Y., Benchimol D., Dupont H. 2009. Clinical and microbiological profiles of community-acquired and nosocomial intra-abdominal infections: results of the French prospective, observational EBIIA study. J. Antimicrob. Chemother. 63: 785–794.
43. Montravers P., Leroy O., Eckmann C. 2015. Intra-abdominal candidiasis: it's still a long way to get unquestionable data. Intensive Care Med. 41(9): 1682–1684.
44. Navalkele B.D., Revankar S., Chandrasekar P. 2017. *Candida auris*: a worrisome, globally emerging pathogen. Expert Review of Anti-Infective Therapy 15(9), 819–827.
45. Neofytos D., Huprikar S., Reboli A., Schuster M., Azie N., Franks B., Horn D. 2014. Treatment and outcomes of *Candida osteomyelitis*: review of 53 cases from the PATH Alliance(R) registry. Eur. J. Clin. Microbiol. Infect. Dis. 33: 135–141.
46. Nosari A.M., Caira M., Pioltelli M.L., Fanci R., Bonini A., Cattaneo C., Castagnola C., Capalbo S.F., De Fabritiis P., Mettivier V., Morselli M., Pastore D., Aversa F., Rossi G., Pagano L. Hema e-Chart Group Hema e-Chart registry of invasive fungal infections in haematological patients. 2013. Improved outcome in recent years in mould infections., Italy. Clin. Microbiol. Infect. 19(8): 757–762.
47. O'Brien D., Cotter M., Lim C.H., Sattar M.T., Smyth E., Fitzpatrick F. 2011. *Candida parapsilosis* meningitis associated with Gliadel (BCNU) wafer implants. Br. J. Neurosurg. 25: 289–291.
48. Ostrosky-Zeichner L., Kullberg B.J., Bow E.J., Hadley S., León C., Nucci M., Patterson T.F., Perfect J.R. 2011. Early treatment of candidemia in adults: a review. Med. Mycol. 49: 113–120.
49. Pappas P.G., Kauffman C.A., Andes D.R., Clancy C.J., Marr K.A., Ostrosky-Zeichner L., Reboli A.C., Schuster M.G., Vazquez J.A., Walsh T.J., Zaoutis T.E., Sobel J.D. 2016. Executive Summary: Clinical practice guideline for the management of candidiasis: 2016 Update by the Infectious Diseases Society of America. Clin. Infect. Dis. 62(4): 409–417.
50. Pappas P.G. Invasive candidiasis. 2006. Infect. Dis. Clin. North Am. 20(3): 485–506.
51. Pfaller M.A., Diekema D.J., Gibbs D.L., Newell V.A., Ellis D., Tullio V., Rodloff A., Fu W., Ling T.A.; Global Antifungal Surveillance Group. 2010. Results from the ARTEMIS DISK Global Antifungal Surveillance Study, 1997 to 2007: a 10.5-year analysis of susceptibilities of *Candida* species to fluconazole and voriconazole as determined by CLSI standardized disk diffusion. J. Clin. Microbiol. 48: 1366–1377.
52. Pfaller M.A., Diekema D.J. 2007. Epidemiology of invasive candidiasis: a persistent public health problem. Clin. Microbiol. Rev. 20: 133–163.
53. Puig-Asensio M.1, Pemán J., Zaragoza R., Garnacho-Montero J., Martín-Mazuelos E., Cuenca-Estrella M., Almirante B. Prospective Population Study on Candidemia in Spain (CANDIPOP) Project; Hospital Infection Study Group (GEIH); Medical Mycology Study Group (GEMICOMED) of the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC); Spanish Network for Research in Infectious Diseases. 2014. Impact of therapeutic strategies on the prognosis of candidemia in the ICU. Crit. Care Med. 42(6): 1423–1432.

54. Rammaert B., Desjardins A., Lortholary O. 2012. New insights into hepatosplenic candidosis, a manifestation of chronic disseminated candidosis. Mycoses 55: e74–84.
55. Richardson M., Lass-Florl C. 2008. Changing epidemiology of systemic fungal infections. Clin. Microbiol. Infect. 14 (Suppl. 4): S5–24.
56. Sallam A., Taylor S.R., Khan A., McCluskey P., Lynn W.A., Manku K., Pacheco P.A., Lightman S. 2012. Factors determining visual outcome in endogenous *Candida endophthalmitis*. Retina 32: 1129–1134.
57. Satoh K., Makimura K., Hasumi Y., Nishiyama Y., Uchida K., Yamaguchi H. 2009. *Candida auris* sp. *nov*., a novel ascomycetous yeast isolated from the external ear canal of an inpatient in a Japanese hospital. Microbiol. Immunol. 53: 41–44. doi: 10.1111/j.1348-0421.2008.00083.x.
58. Shah C.P., McKey J., Spirn M.J., Maguire J. 2008. Ocular candidiasis: a review. Br. J. Ophthalmol. 92: 466–468.
59. Slavin M., van Hal S., Sorrell T.C., Lee A., Marriott D.J., Daveson K., Kennedy K., Hajkowicz K., Halliday C., Athan E., Bak N., Cheong E,. Heath C.H., Orla Morrissey C., Kidd S., Beresford R., Blyth C., Korman T.M., Owen Robinson J., Meyer W., Chen S.C.; Australia and New Zealand Mycoses Interest Group. 2015. Invasive infections due to filamentous fungi other than *Aspergillus*: Epidemiology and determinants of mortality. Clin. Microbiol. Infect. 21: 490 e491–10.
60. Sobel J.D., Fisher J.F., Kauffman C.A., Newman C.A. 2011. *Candida* urinary tract infections – epidemiology. Clin. Infect. Dis. 52 (Suppl. 6): S433–436.
61. Springer J., Chatterjee S. 2012. *Candida albicans* prosthetic shoulder joint infection in a patient with rheumatoid arthritis on multidrug therapy. J. Clin. Rheumatol. 18: 52–53.
62. Staniszewska M., Bondaryk M., Piłat J., Siennicka K., Madga U., Kurzątkowski W. 2012. Czynniki zjadliwości *Candida albicans*. Przegl. Epidemiol. 66: 629–633.
63. Tacke D., Koehler P., Cornely O.A. 2013. Fungal endocarditis. Curr. Opin. Infect. Dis. 26: 501–507.
64. Ueng S.W., Lee C.Y., Hu C.C., Hsieh P.H., Chang Y. 2013. What is the success of treatment of hip and knee candidal periprosthetic joint infection? Clin. Orthop. Relat. Res. 471: 3002–3009.
65. Walsh T.J., Teppler H., Donowitz G.R., Maertens J.A., Baden L.R., Dmoszynska A., Cornely O.A., Bourque M.R., Lupinacci R.J., Sable C.A., dePauw B.E. 2004. Caspofungin versus liposomal amphotericin B for empirical antifungal therapy in patients with persistent fever and neutropenia, N. Engl. J. Med. 351: 1391–1402.
66. Wisplinghoff H., Bischoff T., Tallent S.M., Seifert H., Wenzel R.P., Edmond M.B. 2004. Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. Clin. Infect. Dis. 39: 309–317.
67. Yapar N. 2014. Epidemiology and risk factors for invasive candidiasis. Therapeutics and clinical risk management. 10: 95–105. doi: 10.2147/TCRM.S40160. ISSN 1176-6336. PMC 3928396. PMID 24611015.
68. Yin M., Li C., Wu D., Wang H. 2016. Catheter removal does matter but should be individualized for patients with candidemia. Intern. Med. 55(15): 2133.