Anestezjologia • Ratownictwo • Nauka • Praktyka / Anaesthesiology • Rescue Medicine • Science • Practice

ARTYKUŁ POGLĄDOWY/REVIEW PAPER

Wpłynęło/Submitted: 06.03.2009 • Poprawiono/Corrected: 07.05.2009 • Zaakceptowano/Accepted: 22.05.2009

The diagnosis and management of systemic candidiasis in the Intensive Care Unit

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Summary

Invasive candidiasis has become a major cause of morbidity and mortality in the last few decades, in parallel with the tremendous advances made in medical care. Patients who are critically ill, in medical and surgical ICUs are especially at risk for *Candida* infections. Management of these severe infections has been challenging due to delay in diagnosis and the lack of reliable diagnostic methods. Notable improvements have been made in diagnosis with improved culturing methods, rapid species identification, and detection of fungemia with antigen assays. Additionally, newer classes of antifungals have become available with broader antifungal activity and better tolerability when compared to the older antifungal agents. *Anestezjologia i Ratownictwo 2009; 3: 136-143.*

Keywords: Candidiasis, antifungals, ICU, systemic candidiasis, candidemia

Introduction

Candida species are ubiquitous fungi and are the most common fungal pathogens that affect humans [1]. The growing problem of systemic candidiasis reflects the enormous increase in the pool of patients at risk and the increased opportunity that exists for *Candida* species to invade tissues normally resistant to invasion. *Candida* species are true opportunistic pathogens that exploit recent technological advances to gain access to the circulation and deep tissues. *Candida* species are the most common cause of fungal infection affecting immunocompromised patients and are currently the 4th most common pathogen recovered from blood cultures [2].

Epidemiology

Candida species produce a wide spectrum of diseases, ranging from superficial mucocutaneous disease to invasive illnesses, such as hepatosplenic candidiasis, *Candida* peritonitis, and systemic candidiasis [1]. Management of serious and life-threatening invasive candidiasis remains severely hampered by delays in diagnosis and the lack of reliable diagnostic methods that allow detection of both fungemia and tissue invasion by *Candida* species [3].

Advances in medical technology, chemotherapeutics, cancer therapy, and organ transplantation have had a major impact on reducing the morbidity and mortality of life-threatening disease. Patients who are critically ill and in medical and surgical ICUs have been the prime targets for opportunistic nosocomial fungal infections, primarily due to *Candida* species. Studies suggest that the problem is not under control and, in fact, show it is worsening. On a daily basis, virtually all physicians are confronted with a positive *Candida* isolate obtained from one or more various anatomical sites. High-risk areas for *Candida* infection include neonatal, pediatric, and adult ICUs, both medical and

surgical [4].

Over 165 species of *Candida* exist in nature; only a few species however, are recognized causes of disease in humans (Table 1) [1-3]. *C glabrata* and *C albicans* account for approximately 70-80% of *Candida* species isolated from patients with candidemia and invasive candidiasis. *C glabrata* has recently become important because of its increasing incidence worldwide, and it is intrinsically less susceptible to azoles and amphotericin B [2,5,6]. *C krusei* is also important because of its intrinsic resistance to most azoles including ketoconazole, fluconazole, and itraconazole. In addition, it is also less susceptible to amphotericin B. Another important *Candida* species is *C lusitaniae;* although not as common as some *Candida* species, it is of clinical significance because it is frequently resistant to amphotericin B, although it remains susceptible to azoles and echinocandins. *C parapsilosis* is the 2nd to 3rd most common *Candida* species recovered from blood cultures and has become an important species to consider in hospitalized patients with vascular catheters. Additionally, in vitro susceptibility studies have shown a reduced susceptibility to echinocandins when compared to the other *Candida* species [7]. *C tropicalis* is also considered an important cause of candidemia in patients with cancer (leukemia) and in those who have undergone bone marrow transplantation.

Candida species contain their own set of well-recognized virulence factors. Although not well characterized, several virulence factors may contribute to their ability to cause infection [8]. As with most fungal infections, host defects play a significant role in the development of candidal infections. Numerous host defects have been associated with candidal infections. Risk factors associated with candidemia and/or systemic candidiasis include granulocytopenia, bone marrow transplantation, solid organ transplantation (liver, kidney), parenteral hyperalimentation, solid neoplasms, corticosteroids, broad-spectrum antibiotics, burns, prolonged ICU stay > 3 days, prolonged hospitalization, mechanical ventilation for > 3 days, pancreatitis, severe trauma, recent surgery (especially GI tract), central venous catheters, premature birth weights, and hemodialysis [1,3].

Clinical and autopsy studies have confirmed the marked increase in the incidence of disseminated candidiasis, reflecting a parallel increase in the frequency of candidemia. This increase is multifactorial in origin and reflects increased recognition of the fungus, a growing population of patients at risk. Mortality rates for candidemia and disseminated candidiasis have not improved markedly over the past decade and remain in the range of 30-40%. Systemic candidiasis is the cause of more case fatalities than any other systemic mycosis. More than a decade ago, investigators reported the enormous economic impact of systemic candidiasis in hospitalized patients. Candidemia has been associated with considerable prolongation of length of stay in the hospitals (70 vs. 40 days) and increased costs [9].

Clinical manifestation

Infections due to *Candida* species can manifest in a wide spectrum of clinical syndromes as described below [1,3]. The clinical presentation can vary depending on the type of infection, the organ involved and the degree of immunosuppression. Clinical syndromes associated with *Candida* infection include:

Systemic candidiasis: May be divided into two different categories:

a. candidemia without organ involvement;
b. disseminated candidiasis (organ infection by *Candida* species).

Deep organ infections due to *Candida* species are generally observed as part of the disseminated candidiasis syndromes, which may be associated with

Table 1. *Candida* spp. Why should they be identified?

C. albicans	* 50-60%
C. glabrata - < susceptible to all antifungals	* 15-20%
C. parapsilosis – catheter related	* 10-20%
C. tropicalis	* 6-12%
C. krusei – "neutropenics" – intrinsic azole resistance, also less susceptible to amphotericin B	* 1-3%
C. guillermondi	amphotericin B resistant
C. lusitaniae	
C. dubliniensis – HIV	

either single or multiorgan involvement. Candidemia is generally considered a nosocomially acquired infection. The patient's history commonly reveals the following: several days of fever that is unresponsive to broad-spectrum antimicrobials (frequently the only marker of infection), prolonged intravenous catheterization, several key risk factors, possibly associated with multiorgan infection. Physical examination is remarkable for the following: fever, macronodular skin lesions (approximately 10%), candidal endophthalmitis (approximately ~ 10%), and occasionally septic shock. Common causes of candidemia without invasive disease include the following:

a. intravascular catheter-related candidiasis (usually responds promptly to catheter removal and antifungal treatment),
b. suppurative thrombophlebitis, associated to prolonged central venous catheterization, and manifests as fever and candidemia, which persist despite antifungal therapy and catheter removal,
c. endocarditis.

Disseminated candidiasis is frequently associated with multiple deep organ infections or may involve single organ infection (Table 2). Unfortunately, of patients with disseminated candidiasis, as many as 40-60% may have negative blood culture results for *Candida* species. The history of a patient with presumptive disseminated candidiasis reveals a fever unresponsive to broad-spectrum antimicrobials and negative results from blood culture. Physical examination may only reveal fever, which may be the only symptom, occasionally with sepsis and septic shock of unknown etiology.

Table 2. Manifestations of disseminated candidiasis

Fever unresponsive to broad-spectrum antimicrobials, frequently the only marker of infection
Prolonged intravenous catheterization
A history of several major risk factors
Multi-organ infection
Physical examination is remarkable for the following:
Macronodular skin lesions (~10-20%)
Candidal endophthalmitis (~10 %)
Occasionally, septic shock (hypotension, tachycardia, tachypnea)
Multi-organ dysfunction, depending on the site affected

Candida endophthalmitis can have an exogenous or an endogenous cause. Endogenous endophthalmitis results from hematogenous seeding of the eye. It has beenfound in approximately 10% of patients with candidemia. More recent series have shown a decreasing trend probably due to increasing awareness of this as complication of candidemia and early or empirical antifungal therapy [10]. Hematogenous candidal endophthalmitis is a marker of widespread disseminated candidiasis. The patient's history may reveal a broad range of manifestations from asymptomatic to ocular pain, photophobia, scotomas, blindness and floaters. Upon fundoscopic examination the early lesions are usually the size of a pinhead, tend to be off-white in color, and are found in the posterior vitreous with distinct margins and minimal vitreous haze. Classic lesions are large and off-white, similar to a cotton-ball, with indistinct borders covered by an underlying haze. Lesions are 3-dimensional and extend into the vitreous off the chorioretinal surface. They may be single or multiple.

Diagnosis

Unfortunately, findings from the laboratory studies are often nonspecific [1,4]. Clinicians are required to act definitively and early based on a high index of suspicion. In the past, many patients with life-threatening candidiasis died without receiving antifungal therapy. Patients who remain febrile despite broad-spectrum antibiotic therapy, with either persistent neutropenia or other risk factors and persistent leukocytosis, should be suspected of having systemic candidiasis. To be effective, therapy should be provided early and empirically in such patients [11].

Cultures of nonsterile sites, although not useful for establishing a diagnosis, may demonstrate high degrees of candidal colonization. Gastrointestinal, respiratory, and urinary tract culture results positive for *Candida* may not represent invasive disease; however, they may be considered sites of colonization. Moreover, cultures of nonsterile sites, although not useful for establishing a diagnosis, may be useful for initiating antifungal therapy in patients with fever that is unresponsive to broad-spectrum antimicrobials. Therefore, appropriate interpretation is required. On the other hand, any positive cultures from a sterile site implies the presence of invasive disease. It is important to always consider positive results from these sites significant and definitive evidence of infection. Blood cultures are helpful but are positive in only 50-60%

of cases of disseminated disease. *C. albicans* peptide nucleic acid (PNA) fluorescence in situ hybridization (FISH) test provides a 24-48 hrs faster identification of *C. albicans* when the probe is added to smears made directly from the blood culture bottle followed by the hybridization [13].

Antifungal susceptibility testing although not routinely done may be helpful in guiding difficult therapeutic decisions. In vitro susceptibility testing for *Candida* species is now standardized, using the CLSI microbroth dilution (CLSI M27-A23, 2008) or disk diffusion (CLSI M44-A, 2004) methodologies.

There are several non-culture *Candida* detection assays available. The majority of them do not have significant sensitivity to be relied upon to make a diagnosis of invasive candidiasis. More recently, a newer assay detecting 1-3 β-D-glucan in serum has been approved (Glucatell, Fungitell) [12]. The 1-3 β D-glucan assay measures the level of beta-glucan in serum. β-D-glucan is a major component of the fungal cell wall of a wide variety of fungi and can be detected by its ability to activate factor G of the horseshoe crab coagulation cascade. This test has a sensitivity of 75-100% and a specificity of 88-100%. However, it is a broad-spectrum assay that detects *Aspergillus, Candida, Fusarium, Acremonium,* and *Saccharomyces* species [14]. The Fungitell assay does not detect infections caused by *Cryptococcus neoformans* or Zygomycetes. Molecular assays such as polymerase chain reaction tests and DNA probes are still under development and in the early investigational phases, but they appear promising [12].

Management

The treatment of *Candida* infections varies substantially and is based on the anatomic location of the infection, the patients' underlying disease and immune status, the patients' risk factors for infection, the specific species of *Candida* responsible for infection, and, in some cases, the susceptibility of the strain to the different antifungal drugs [1,15].

In January 2009, the Infectious Disease Society of America and the Mycosis Study Group published updated practice guidelines for the treatment of candidemia and candidiasis [15].

Systemic agents with anti-*Candida* activity currently available include amphotericin B, fluconazole, voriconazole, caspofungin, micafungin, anidulafungin, lipid preparations and flucytosine (Table 3). The activities of these agents against *Candida* are predictable and vary with species. The drug of choice depends on the infecting species and the clinical setting. *C. albicans* is the most susceptible species (Table 4). The pattern for *C. tropicalis* and *C. parapsilosis* express slightly higher MICs for most antifungals. *C. parapsilosis* tends to have higher MICs in-vitro and is less susceptible to echinocandin agents [15-17]. *C. glabrata* is less susceptible to all antifungals and approximately 10-15% are intrinsically resistant to fluconazole. *C. krusei* isolates have the highest fluconazole and flucytosine MICs of any of the species. In addition, it is also resistant to itraconazole, ketoconazole and amphotericin B [2,5,6] (Table 4).

Table 3. Classification of antifungals

• Polyenes Amphotericin B deoxycholate Lipid formulations of amphotericin B
• Flucytosine Adjunct to amphotericin B
• Azoles Fluconazole, itraconazole, voriconazole, posaconazole
• Echinocandins Caspofungin, micafungin, anidulafungin

Until recently, the use of amphotericin B and fluconazole was the standard therapy for all forms of candidiasis. The primary difference between the newer guidelines and the prior guidelines has to do with the up front use of echinocandins in patients with candidemia and suspected candidiasis who have moderate to severe infections, patients with infections due to *C. glabrata* and *C. krusei*, and those who have a history of prior azole exposure [15].

Candidemia and acute disseminated candidiasis

In the non-neutropenic adult patient with candidemia and invasive candidiasis most infections are due to the presence of an intravascular catheter in up to 80% of patients [4,15]. Thus, removal of all intravascular catheters appears to shorten the duration of candidemia and has been associated with reduced mortality [26,27]. Although patients have been cured by catheter removal alone, transient episodes of candidemia have been associated with subsequent hematogenous spread causing endophthalmitis or osteomyelitis. Thus, all episodes of candidemia merit antifungal therapy

Table 4. General Patterns of Susceptibility of *Candida* Species

***Candida* Species**	**Fluconazole**	**Itraconazole**	**Flucytosine**	**Amphotericin B**
C. albicans	S	S	S	S
C. tropicalis	S	S	S	S
C. parapsilosis	S	S	S	S
C. glabrata	S-DD to R	S-DD to R	S	S-I
C. krusei	R	S-DD to R	I-R	S-I
C. lusitaniae	S	S	S	S to R
C. kefyr	S	S	S	S
C. guilliermondii	S	S	S	S-R
C. dubliniensis	S	S	S	S

(Figure 1) [4,15].

Candidemia requires treatment in all patient populations. For most situations, fluconazole is the drug of choice in the management of candidemia and disseminated candidiasis. The options listed below need to be considered depending on history of previous exposure to antifungals, the probability of fluconazole resistance, the presence of comorbid conditions, and the clinical status of the patient. Fluconazole (loading dose of 800 mg, then 400 mg daily) or an echinocandin (caspofungin: loading dose of 70 mg, then 50 mg daily; micafungin: 100 mg daily; anidulafungin: loading dose of 200 mg, then 100 mg daily) are recommended as initial therapy for most adult patients [15]. An echinocandin is preferred for patients with moderate to severe illness and in patients who have had recent azole exposure [18-22]. The patients who are infected with susceptible *Candida* species, and are clinically stable, can be transitioned to oral fluconazole to complete a 14-day course after the blood cultures have been cleared. Initial therapy with an echinocandin is preferred in patients infected with either *C. glabrata* or *C. krusei,* however for patients who have initially received fluconazole and are clinically improving, and whose follow-up culture results are negative, continuing use of an azole is reasonable. For infections due to *C. parapsilosis,* initial treatment with fluconazole is recommended, however if a patient has initially received an echinocandin and is clinically improved, continuing use of an echinocandin is reasonable. If an

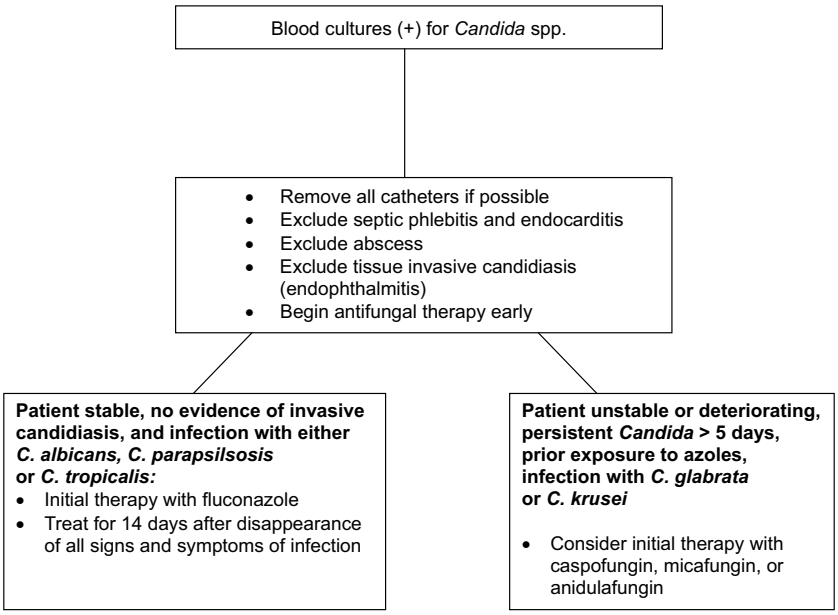

Figure 1. Management of candidemia and disseminated candidiasi

echinocandin is not available and either *C. glabrata* or *C. krusei* are suspected initial therapy with voriconazole 6mg/kg BID, followed by 3mg/kg BID is reasonable [23]. Alternatives may also include amphotericin B deoxycholate (AmB-d) 0.5–1.0 mg/kg daily or a lipid formulation of AmB (LFAmB) 3–5 mg/kg daily in cases of azole or echinocandin intolerance to in areas with limited availability.

Management of invasive candidiasis in neutropenic patients includes LFAmB, echinocandins, or voriconazole (6 mg/kg administered intravenously twice daily for 2 doses, then 3 mg/kg twice daily) are recommended [24]. Fluconazole 400mg/day or itraconazole 200 mg twice daily are also alternative agents. Additionally, posaconazole has been shown to be effective prophylaxis against invasive fungal infections in high-risk neutropenic patients and hematopoietic stem cell transplant recipients, but its role as empirical therapy has not been established.

Urinary tract infections

Treatment of cystitis is recommended only in symptomatic patients, or if they are neutropenic, or prior to urologic procedures. The therapy recommended is fluconazole 200–400 mg daily for two weeks or for several days before and after the procedure [25]. For patients with candidal pyelonephritis and suspected disseminated candidiasis, treatment is similar as for candidemia.

Candida endophthalmitis

Penetration of amphotericin B into the eye is variable, but generally poor. Despite this, published reports are mostly with at least 1 gram of intravenous and/or intravitreal AmB-d with or without oral flucytosine as initial therapy [1,15,26]. However, intravenous therapy is not uniformly successful and intravitreal amphotericin B following vitrectomy has been helpful. Additionally, oral or intravenous fluconazole has also been used successfully as initial, salvage, and transition therapy. LFAmB and voriconazole are also reasonable options. The use of echinocandins is still controversial since little data is currently available and they have poor ocular penetration.

Successful therapy for serious systemic *Candida* infections requires starting antifungal therapy as early as possible. Treatment should be initiated as soon as adequate cultures are obtained. Different groups of antifungals can be used to manage candidal infections. Azoles, in particular fluconazole [27], have become the mainstay of therapy over the past few years.

Antifungal prophylaxis of invasive candidiasis in patients who are in the high-risk group is currently recommended in several situations which include [28-30] patients with chemotherapy-induced neutropenia, fluconazole 400 mg daily, posaconazole 200 mg 3 times per day, or caspofungin 50 mg daily is recommended during induction chemotherapy for the duration of neutropenia; in bone marrow transplant recipients, primarily those with allogeneic transplants fluconazole 400 mg daily, or posaconazole 200 mg three time daily, or micafungin 50 mg daily is recommended during the period of neutropenia; in solid-organ transplant recipients, fluconazole 200–400 mg daily or LFAmB 1–2 mg/kg daily, for at least 7–14 days, is recommended as postoperative prophylaxis for high-risk liver, pancreas, and small bowel transplant recipients.

Empiric therapy

Empiric use of antifungal agents in febrile patients in ICUs is widespread without supporting data [3,31]. A major pitfall may be in establishing a diagnosis of disseminated candidiasis in the setting of negative blood culture results. It appears reasonable to initiate empiric antifungal therapy in selected patients with persistent antibiotic-resistant fever. Echinocandins with their broad spectrum of activity and improved efficacy may be preferable, although less expensive fluconazole may also be an alternative. Some criteria for initiating empiric antifungal therapy includes patients with known risk factors for candidiasis, patients that are febrile and on broad-spectrum antibiotics for > 96 hrs, and patients with multifocal *Candida* colonization. However, the use of empiric antifungals in low-risk patients is currently not justified.

Conclusion

Candidemia and invasive candidiasis is an infection of increasing importance in the ICU setting. Recent advances in antifungal therapy, such as the echinocandins and voriconazole will have a significant impact on the selection of antifungal agents because they are more broad spectrum, they are safer, and they are easier to use in these critically ill patients. In addi-

tion, earlier recognition of the high-risk patient may warrant the use of earlier antifungal therapy despite negative blood cultures in an attempt to decrease the high morbidity and mortality still associated with this infection.

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