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Management of Invasive Candidiasis in Critically Ill Patients

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Abstract

Candida species have become predominant pathogens in critically ill patients. In this population, invasive candidiasis is associated with a poor prognosis but adequate management can limit the attributable mortality. Adequate management, however, is hampered by a problematic diagnosis as the clinical picture of invasive disease is non-specific and blood cultures have a low sensitivity. Moreover, it is often hard to differentiate colonisation from infection and many critically ill patients are heavily colonised with *Candida* species, especially when receiving broad-spectrum antibacterials.

The question of which antifungal agent to choose has become more complex as the development of new drugs raises promising expectations. Until the 1980s therapy for invasive candidiasis was limited to amphotericin B, but with the advent of new antifungal agents, such as azoles and echinocandins, less toxic therapeutic options are possible and doors have opened towards prevention and optimised therapy in the case of documented candidiasis. Through the arrival of these new antifungal agents, a range of therapeutic strategies for the management of invasive candidiasis has been developed: antifungal prophylaxis, pre-emptive therapy, and empirical and definitive antifungal therapy. Each of these strategies has a specific target population, as defined by specific underlying conditions and/or individual risk factors.

Antifungal prophylaxis, in order to prevent candidal infection, is based on the type of underlying diseases with a high risk for invasive candidiasis. Individual risk factors are not taken into account. Potential indications are bone marrow transplantation, liver transplantation, recurrent gastrointestinal perforations or leakages, and surgery for acute necrotising pancreatitis. Pre-emptive therapy is also a preventive strategy. It can be recommended on the basis of an individual risk profile including overt candidal colonisation. Empirical therapy is started in patients with a risk profile for invasive candidiasis. It is recommended in the presence of clinical signs of infection, deteriorating clinical parameters, or a clinical picture of infection not responding to antibacterials but in the absence of a clear causative pathogen. Definitive antifungal therapy is defined as therapy in patients with documented invasive infection.

The main goal is to maintain a balance between optimal prevention and timely initiation of therapy on one hand, and to minimise selection pressure in order to avoid a shift towards less susceptible *Candida* species on the other hand.

Patients in intensive care units (ICUs) have a considerably higher risk of nosocomial infection because of the severity of their disease, and the multiple invasive procedures they undergo along with the high degree of urgency that often is required. Depending on the type of ICU (medical, surgical, burn unit), rates of infection are 2- to 5-fold higher for ICU patients than for those admitted to general hospital wards.[1,2] Over the last few decades *Candida* species have become increasingly important as nosocomial pathogens. In the US, the National Nosocomial Infections Surveillance (NNIS) programme showed an increase in the proportion of nosocomial infections caused by *Candida* species from 2% in 1980 to approximately 5% in the period 1986–9.[3] In this period *Candida* spp. were the fourth most common nosocomial pathogen in patients hospitalised in ICUs in the US.[4] This increased incidence, and its high associated mortality rates as well as considerable costs, has put infections with *Candida* spp. into the forefront of hospital infections. Until the 1980s therapy was limited to amphotericin B, but with the advent of new antifungal agents, such as azoles and echinocandins, less toxic therapeutic options are possible and have opened doors towards prevention and optimised therapy in the case of documented infection with *Candida* spp. The purpose of this paper is to bring insights in the complex nature of invasive candidiasis in adult ICU patients and to provide guidelines for clinical practice.

1. Definitions

Candida species may cause a broad range of infections, from superficial candidiasis of the skin and mucosal surfaces to more severe invasive dis-

ease. Invasive candidiasis indicates invasion of normally sterile body sites. It may occur either with or without documented spread of *Candida* species via the bloodstream. The term invasive candidiasis does not distinguish between haematogenously disseminated candidiasis or infection that is spread from a local source to the surrounding tissue.[5] Candidaemia is the predominant infection type of invasive candidiasis in critically ill patients. It is generally defined as the isolation of *Candida* species from at least one blood culture.[6] Disseminated candidiasis is defined as non-contiguous invasion of multiple organs with *Candida* species secondary to candidaemia.

2. Epidemiology

The increase in incidence of candidiasis seems to have been most marked during the 1980s,[7,8] but rates appeared to have stabilised in the 1990s.[9] This increasing trend of *Candida* infections over the past decades has been noted in all types of hospitals and wards. The NNIS data showed that between 1980 and 1989 the incidence of primary candidaemia increased by 487% in large hospitals and by 219% in smaller hospitals.[7] The overall rate of nosocomial fungal infections increased from 2 to 3.8 per 1000 hospital admissions and the rate of nosocomial fungaemia increased almost 5-fold over the same period. Currently, *Candida* species account for approximately 8–15% of all nosocomial bloodstream infections in the US.[10] However, in some reports a much lower incidence of candidaemia has been observed.[11]

Although ICUs generally account for only 5% or less of the total number of hospital beds, a majority of patients with systemic candidiasis are diagnosed in these units. In a 2-year large-scaled, population-based study of nosocomial candidaemia in England and Wales, 45.5% of cases occurred in ICUs.[12] A European point prevalence study of nosocomial infections in ICUs found 9.3% of all bloodstream infections to be caused by *Candida* species.[13] In a Dutch hospital, an increase in ICU-acquired candidaemia from 4.7 to 7.4 per 10 000 patient days was observed between 1987 and 1990.[14] In a large Spanish prospective multicentre survey, the incidence of ICU-acquired candidaemia was 1 per 500 ICU admissions.[15]

The emergence of *Candida* species as nosocomial pathogens in ICUs can be explained by the changing profile of patients admitted to ICUs. In the past two decades there has been a growing number of patients receiving immunosuppressive therapy. It can be presumed that this implies an increase in the likelihood of infection with opportunistic pathogens like *Candida* spp. Favourable evolutions in emergency medicine and supportive care have led to improved survival rates, enlarging the group of patients with a substantially longer ICU stay.[16] Also, the widespread use of broad-spectrum antibacterials seems to be important as it promotes candidal overgrowth, facilitating systemic infection. However, more recent data from the US showed a decrease in the incidence of primary candidaemia in ICUs over an 11-year period (1989–99).[17] This new trend can be attributed either to the increased use of antifungal prophylaxis in high risk patients or to an overall reduction in the rate of nosocomial bloodstream infection as a result of better infection control practice.[18]

3. Aetiology

Candida species are the most common cause of fungal infection in patients in ICUs, accounting for 85% of all documented mycoses.[19] *C. albicans* is responsible for approximately 60% of all infections.[14,15,20,21] *Candida* non-albicans species have emerged as important pathogens in both immunosuppressed and ICU patients.[14,15,17,22,23] The most frequently isolated species have been *C. tropicalis*, *C. glabrata* and *C. parapsilosis*.[8,20,23] The clinical relevance of this shift is that some *Candida* non-albicans species, particularly *C. glabrata*, are less susceptible or dose-dependently susceptible to azole antifungals. *C. krusei* is intrinsically resistant to fluconazole but an increase in infections with this species has not been reported yet. Some investigators were able to link candidiasis with *Candida* non-albicans species with prior use of antifungals.[23,24] Most of the time this is observed with fluconazole,

the use of which has greatly increased as routine prophylaxis in patients with pronounced risk factors for systemic candidiasis.[17,25,26] In ICUs, *Candida* non-albicans species are isolated from between 25% and 50% of patients with invasive candidiasis.[15,17,20,24,27-30]

4. Risk Factors for Invasive Candidiasis

Candida species belong to the normal flora of gut mucosa and, in small numbers, also on the skin. Disruption of the integrity of these body sites predisposes to infection. Central venous catheters and urinary bladder catheterisation are well known risk factors for candidiasis.[6,31-33] Candidaemia after administration of contaminated infusate is rare.[34] Multilumen catheters are especially associated with increased risk for candidaemia.[33] However, total parenteral nutrition is a much stronger risk factor for candidaemia than central venous catheterisation.[33,35]

General disease severity strongly increases the odds of a patient developing invasive candidiasis. Critically ill patients can be neutropenic as a consequence of their underlying disease but this represents only a minority of the total ICU population. Following an excessive systemic inflammatory response, ICU patients often have prolonged cellular immune dysfunction, with down-regulated monocyte and granulocyte function. This critical illness-induced immunosuppression comes to the fore following major surgery, multiple trauma, extensive burns or corticosteroid administration.[32,33,36,37] Acute or chronic renal failure predispose patients to systemic infection because of their immunocompromised status[38,39] as well as by the presence of the extra catheter needed for renal replacement therapy, which has to be manipulated frequently.[40,41] In animal studies it has been shown that critical illness is associated with decreased intestinal mucosal barrier function facilitating migration of *Candida* species from the gut to the circulation.[42,43] Mucosal atrophy worsens with prolonged total parenteral nutrition and intestinal ischaemia. An experimental study demonstrated fungal translocation through an intact bowel resulting in candiduria and candidaemia.[44]

An important risk factor for invasive candidiasis, and candidaemia in particular, is the use of broad-spectrum antibacterials. Antibacterials promote candidal overgrowth by suppressing the bacterial flora. The risk of candidaemia increases exponentially with every additional antibacterial class administered.[35] Broad-spectrum antibacterials facilitate colonisation by *Candida* species, which in turn represents the strongest predictor of invasive candidiasis.[45,46] Therefore, extensive colonisation with *Candida* species is considered as an indication for early treatment with antifungals in selected patients.[45,47,48]

5. Clinical Consequences of Invasive Candidiasis in Intensive Care Unit Patients

The impact of invasive candidiasis is most frequently studied in patients with systemic candidiasis or candidaemia. In a general patient population, candidaemia carries a high associated and attributable mortality.[49-52] In matched cohort studies Wey et al.[49] and, more recently, Gudlaugsson et al.[52] demonstrated attributable mortality rates of 38% and 49%, respectively. Moreover, in ICU patients candidaemia is associated with high mortality rates ranging from 36% to 63%.[14,15,20,24,27-30,53-55] However, as candidaemia generally occurs in ICU patients with a strongly debilitated physical condition, and an already poor prognosis before the onset of the infection, it is difficult to distinguish mortality due to general disease severity from mortality caused by the candidaemia.[56] Matched cohort studies are better suited for estimating the impact of nosocomial infections.[56,57] In a French multicentre matched cohort study Leleu et al.[54] described a statistically significant attributable mortality of 31% (95% CI 20%, 44%) in ICU patients with systemic candidiasis. However, no mention was made of the appropriateness of antifungal therapy.[58]

A single-centre, matched cohort study by Blot et al.[30] demonstrated a nonsignificant attributable mortality of 5% (95% CI −8%, 19%) in critically ill

patients with nosocomial candidaemia. Mortality for candidaemic patients and matched controls was 48% and 43%, respectively. In this study, 87% of candidaemic patients received appropriate antifungal therapy and with only a short delay in the initiation of the drug (median: 1 day). In a multivariate analysis delaying the initiation of antifungal therapy by more than 2 days was recognised as an independent predictor of mortality. These results indicate that the high mortality in ICU patients with candidaemia is mostly due to the severity of their underlying disease and acute illness, and that in the presence of timely initiated antifungal therapy, the attributable mortality can be limited. In non-ICU populations the lack of antifungal therapy has been repeatedly described as being associated with increased mortality.[59,60]

6. Diagnosis

The diagnosis of systemic candidiasis is problematic as the clinical picture is variable and nonspecific. In one in five patients with candidaemia, it evolves without fever or other overt signs of inflammatory response. Leucocytosis, another key symptom, is present in only 50% of patients with these infections.[31] Moreover, patients may not be immediately seriously ill.[61] The fact that severe invasive candidiasis may evolve with a rather discrete symptomatology increases the changes of missing early diagnosis.[62]

Critically ill patients with a considerable length of ICU stay and prolonged antibacterial therapy are very often colonised with *Candida* species. Multisite colonisation can be considered clinically relevant, as it is a strong predictor of invasive candidiasis, especially when it accompanies other risk factors. Yet its direct impact on patient outcomes remains unclear. It is a most difficult task to distinguish colonisation with *Candida* species from invasive infection. As a consequence, in clinical practice the diagnosis of invasive candidiasis is usually based on inferential data instead of direct evidence of tissue invasion.

In the absence of definite clinical findings, like high-grade candiduria (colony count of $>10^5$ cfu/mL) or tissue histology, diagnosis of invasive candidiasis is mostly based on blood cultures.[16] From within the digestive tract *Candida* spp. might spread via the bloodstream to result in disseminated infection. Candidaemia is a predictor of disseminated disease. A single positive blood culture is considered enough for a definitive diagnosis, and hence definition, of candidaemia. Unfortunately, blood cultures have a low sensitivity for *Candida* species (at most 50–60%).

In the absence of overt haematogenous spread, disseminated candidiasis is even more difficult to diagnose. Ophthalmological examination can be a useful tool for diagnosing disseminated disease in the absence of positive blood cultures. In ICUs, candidal endophthalmitis is the most common type of disseminated infection. Nevertheless, this infection is only found in 9–15% of candidaemic patients.[63] Other types of disseminated candidiasis are even less common.[16]

7. Antifungals Used in the Management of Invasive Candidiasis

Severe invasive candidiasis in critically ill patients requires systemic therapy. Therefore, in this short description of antifungals, only agents that can be administered intravenously are discussed. Nevertheless, oral administration of antifungals can have a role in prophylaxis or maintenance therapy, and can also have an important pharmacoeconomic benefit. Antifungals that are not recommended in current guidelines are not discussed. Because major organ derangements occur at a high rate in critically ill patients with invasive candidiasis (especially renal and hepatic insufficiency), this deserves special attention because dosage adjustments can be necessary. Table I summarises the properties of antifungal agents with intravenous formulations that are recommended for the treatment of invasive candidiasis.

7.1 Amphotericin B

Since the 1960s conventional (deoxycholate) amphotericin B has been the primary treatment option for severe candidal infections (and other mycoses). With the exception of *C. lusitaniae* and

Table I. Selected characteristics of antifungal agents with intravenous (IV) formulation recommended for the treatment of invasive candidiasis

Drug	Characteristics		
	spectrum[a]	general dosage	comments
Amphotericin B	All *Candida* spp.; resistance reported in *C. lusitaniae* and *C. guilliermondii*	Conventional: 0.6–1 mg/kg/day Lipid-associated formulations: 3.0–5 mg/kg/day	In renal insufficiency, including hypokalaemia, azotaemia, increased serum creatinine and hyperchloraemic acidosis, switch to a lipid-associated amphotericin B formulation, voriconazole or caspofungin
Fluconazole	*C. albicans* and *C.* non-albicans spp.; *C.* non-albicans spp. can be less susceptible and so may require higher dosages; *C. krusei* is intrinsically resistant	Loading dosage (first day): 800 mg/day Maintenance dose: 400 mg/day	Dose reduction of 50% when creatinine clearance is between 11 and 50 mL/min
Itraconazole	All *Candida* spp.	Loading dosage (first 2 days): 200 mg/day bid Maintenance dose: 200 mg/day	Monitoring for hypokalaemia, hypomagnesaemia, and elevations in transaminases, bilirubin and alkaline phosphatase is necessary
Voriconazole	All *Candida* spp.	Loading dose (first day): 6 mg/kg/day bid Maintenance dose: 4 mg/kg/day	Switch to oral intake or IV alternative when creatinine clearance is <50 mL/min. Dose adjustment in necessary with hepatic insufficiency
Caspofungin	All *Candida* spp.	First day: 70 mg/day Maintenance dose: 50 mg/day	Dose reduction to 35 mg/day in hepatic insufficiency

a Only with regard to *Candida* species

bid = twice daily.

C. guilliermondii, for which resistance has been reported, the spectrum of amphotericin B covers all *Candida* species. Conventional amphotericin B is an effective antifungal, but its use is limited by substantial toxicity and rather poor tolerability. Nephrotoxicity and acute infusion-related reactions like such as, chills, rigors, headache, nausea and vomiting are the most frequently observed adverse events. Amphotericin B does not penetrate well in cerebrospinal fluid. The typical intravenous dosage of conventional amphotericin B is 0.6–1.0 mg/kg/day. In case of renal insufficiency, including hypokalaemia, azotaemia, increased serum creatinine and hyperchloraemic acidosis, a switch to lipid-associated amphotericin B formulations, voriconazole or caspofungin is recommended.

In an attempt to decrease toxicity and improve drug delivery, three lipid-associated formulations of amphotericin B have been developed: amphotericin B lipid complex, liposomal amphotericin B, and amphotericin B colloidal dispersion. The dosage for lipid-associated amphotericin B is usually 3.0–5.0 mg/kg/day.

With the exception of the reduced rates of adverse events observed, lipid-associated formulations are not superior in efficacy to conventional amphotericin B.[64] It is unknown whether there are situations in which lipid-associated formulations are contraindicated.[65] The only exception to this is for urinary candidiasis where conventional amphotericin B is preferred because the lipid-associated formulations have a reduced delivery as a result of their characteristics protective of the kidney.[66]

7.2 Azole Antifungal Agents

Itraconazole, fluconazole and voriconazole are the only systemically available triazole antifungal agents currently recommended.

Fluconazole has a high water solubility. Oral fluconazole has a bioavailability of 90%, irrespective of food intake and gastric acidity. In plasma the protein-bound fraction is low (12%) and high concentrations can be achieved in the brain, liver, skin, lungs, urine, saliva, cerebrospinal fluid, peritoneal fluid and vaginal fluid. Because of its favourable pharmacokinetic and pharmacodynamic profile,

fluconazole has become widely used for presumptive and definitive antifungal therapy. Its clinical efficacy in non-neutropenic patients with candidaemia is comparable to that of amphotericin B, whereas fewer adverse effects are noted.[67] The typical dosage of fluconazole for invasive candidiasis is a loading dose of 12 mg/kg (~800 mg/day) followed by 6 mg/kg/day (~400 mg/day). Because of its favourable safety profile, dosages as high as 1200–1600 mg/day can be tolerated. It has been presumed that for invasive candidiasis, high-dose fluconazole (800 mg/day) would improve patient outcome but strong evidence is lacking.[16,68,69] Dosage adjustment in renal insufficiency is not necessary as long as the creatinine clearance is >50 mL/min. In patients with a creatinine clearance of 11–50 mL/min, a 50% dosage reduction is recommended. Fluconazole has excellent activity against *C. albicans* and covers most isolates of *C. guilliermondii, C. parapsilosis, C. tropicalis* and *C. glabrata*. However, patients infected with *Candida* non-albicans species might not have a favourable clinical response, and higher dosages may favour a positive outcome. However, some *Candida* species are intrinsically resistant to fluconazole (e.g. *C. krusei*).

Itraconazole has a broader spectrum of antifungal activity against *Candida* species than fluconazole because it has *in vitro* activity against *C. albicans* as well as C. non-albicans species such as *C. guilliermondii*, *C. krusei*, *C. parapsilosis*, *C. tropicalis* and *C. glabrata*. However, in ICU patients its use as a first-line antifungal agent is limited because it is less well tolerated and possible accumulation of cyclodextrin in patients with renal insufficiency. The most frequent adverse effects are infusion-related reactions, thrombophlebitis, vomiting, nausea and diarrhoea.[70] Patients should also be monitored for hypokalaemia, hypomagnesaemia, and elevations in liver transaminases, bilirubin and alkaline phosphatase.[71] In addition, studies investigating the efficacy of itraconazole in invasive candidiasis are lacking. The typical dosage of itraconazole for intravenous administration is 200mg every 12 hours (for 2 days, i.e. four doses), followed by 200 mg/day.

Voriconazole is as active as fluconazole in the treatment of oesophageal candidiasis but it is associated with more adverse events. Because it has a broader spectrum than fluconazole it can be used for the treatment of infections caused by *Candida* non-albicans species. Voriconazole has promise as a salvage agent for the treatment of invasive candidiasis caused by fluconazole-resistant strains or *C. krusei*.[72] However, more data are necessary to confirm this. The dosage for voriconazole is a loading dose of 6 mg/kg every 12 hours during the first 24 hours, followed by 4 mg/kg twice daily administered intravenously. In patients with a poor clinical response, the dose can be increased to up to 300mg twice daily. The same dosages can be used for enteral administration for maintenance therapy. Because of the cyclodextrin in the intravenous formulation, a switch to enteral administration is recommended in patients with renal insufficiency with creatinine clearance of <50 mL/min unless the clinical situation justifies continuing systemic therapy. Haemodialysis does not oblige dosage adjustment. In patients with hepatic insufficiency, a dosage reduction is recommended.

7.3 Echinocandins

Caspofungin is the first agent of this new class of antifungals. For the treatment of oropharyngeal or oesophageal candidiasis, caspofungin is as effective as amphotericin B and fluconazole.[73-75] In patients with invasive candidiasis (83% candidaemia), caspofungin had efficacy that was comparable to amphotericin B but with fewer adverse effects.[76] A better response rate was observed in a predefined secondary analysis of evaluable patients. Caspofungin appears to be active against all *Candida* species but clinical response in *C. parapsilosis* infections might be less likely.[65,76] The typical dosage for caspofungin consists of a loading dose of 70mg followed by 50 mg/day. In patients with discrete hepatic insufficiency, the maintenance dose should be decreased to 35 mg/day. Renal insufficiency does not necessitate dose adjustment. Caspofungin can only be administered intravenously.

7.4 Flucytosine

Flucytosine has a narrower spectrum of activity than the agents discussed so far. It is mostly used in combination with amphotericin B for the treatment of cryptococcal meningitis or disseminated candidiasis. However, because it can induce acute liver failure and myelotoxicity, we do not recommend its use in critically ill patients. Moreover, when used in monotherapy, emergence of resistance has been reported, resulting in clinical failure.[77]

8. Therapeutic Options

Given the high mortality rates in the absence of, or only delayed, antifungal therapy, and the problematic diagnosis of invasive candidiasis, early antifungal therapy, either prophylaxis or pre-emptive therapy, has recommended in the prevention of invasive candidiasis. However, deciding when to initiate antifungal therapy often remains unclear. The complex pathogenesis and difficulties in diagnosis have led to four types of antifungal therapy, each with a specific target population (table II).[78]

8.1 Antifungal Prophylaxis

Prophylaxis is a preventive tool covering a whole patient population at risk for invasive candidiasis. It is based on the primary diagnosis and not on individual risk factors (prolonged antibacterial therapy, *Candida* spp. colonisation, total parenteral nutrition). Patient populations that might benefit from a prophylactic antifungal strategy are patients with allogenic bone marrow transplantation, liver transplant patients and high-risk surgical patients.[79-82]

Table II. Indications for antifungal management in invasive candidiasis

Antifungal prophylaxis

Definition: prevention of invasive candidiasis in the absence of overt candidal colonisation and clinical signs of infection

Recommendation: patients within diagnostic categories with a high risk for invasive candidiasis

Individual risk factors are of minor importance. Potential indications are allogenic bone marrow transplantation,[79] liver transplantation,[80] recurrent gastrointestinal perforations or anastomotic leakages[81] and surgery for acute necrotising pancreatitis[82]

Pre-emptive antifungal therapy

Definition: prevention of invasive candidiasis on basis of an individual risk profile including overt candidal colonisation but in the absence of clinical signs of infection

Recommendation: when a patient has a combination of multisite candidal colonisation (≥2 sites) with ≥2 major risk factors or ≥3 minor risk factors for invasive candidiasis[33,35,45,83]

Major risk factors	*Minor risk factors*
prolonged antibacterial therapy	older age
immunosuppression	renal insufficiency
neutropenia	length of intensive care unit stay >10 days
extensive burns	urinary bladder catheter
intestinal perforation	multilumen central venous catheters
major abdominal surgery	diabetes mellitus
diarrhoea or ileus	candiduria
total parenteral nutrition	
renal replacement therapy	

Empirical antifungal therapy

Definition: antifungal therapy in patients with a risk profile for invasive candidiasis and in the presence of clinical signs of infection

Recommendation: in patients with a risk profile for invasive candidiasis (compared with risk factors for pre-emptive therapy) developing signs of infection or deteriorating clinical parameters (haemodynamic instability, respiratory insufficiency) or a clinical picture of infection not responding to antibacterial therapy

Definitive antifungal therapy

Definition: antifungal therapy in patients with documented invasive candidiasis

Recommendation: see text section 9 and table III: treatment of specified invasive candidiasis

For antifungal prophylaxis, fluconazole 400 mg/day can be used in ICU patients.[47,80,81]

8.2 Pre-emptive Antifungal Therapy

In the absence of clinical signs of infection antifungal therapy can be prescribed on the basis of a pronounced risk profile for the development of invasive candidiasis. Pre-emptive antifungal therapy is justified by the presence of extensive candidal colonisation and several risk factors for invasive candidiasis. Intensity, or the degree of, candidal colonisation can be evaluated with the *Candida* colonisation index as described by Pittet et al.[45] This index was developed to improve the positive predictive value of colonisation to predict invasive candidiasis. It is defined as the ratio of number of non-blood distinct body sites and the semi-quantitative *Candida* load at each site. An index of >0.5 might recommend pre-emptive therapy. However, in daily practice multisite candidal colonisation (≥2 sites) is used in the decision making of initiating pre-emptive therapy. Routine antifungal therapy in patients with multisite candidal colonisation is not recommended. It should be accompanied by at least two major risk factors or three minor risk factors. Major risk factors are prolonged antibacterial therapy, immunosuppression, neutropenia, extensive burns covering more than 50% of the total body surface area, intestinal perforation, major abdominal surgery, diarrhoea or ileus, total parenteral nutrition and renal replacement therapy. Minor risk factors include older age (or neonates), renal insufficiency, length of ICU stay of more than 10 days, the presence of a urinary bladder catheter, multilumen central venous catheters, diabetes mellitus and candiduria (>10^5 cfu/mL).[83,84] Fluconazole 200 or 400 mg/day is the drug of choice for pre-emptive therapy. It can be administered intravenously or, if possible, via the oral route (i.e. if the patient has intact gastrointestinal function).

8.3 Empirical Antifungal Therapy

Empirical therapy is recommended in the patient with a high risk profile, with clinical symptoms of systemic infection but without microbiological evidence of invasive candidiasis. The precise role and duration of empirical therapy in ICUs is unclear but early anticipation of the possibility of invasive candidiasis surely minimises the delay in initiation of therapy.[62] Depending on the clinical status of the patient either fluconazole 400 mg/day in relatively stable patients or amphotericin B in patients with septic shock can be used. However, because of the nephrotoxic characteristics of conventional amphotericin B (lipid-associated formulations are generally not reimbursed for this indication in the US and Europe) its use may lead to acute renal failure, which is associated with high mortality figures, and because the majority of *Candida* species are still susceptible to fluconazole, this agent can also be used in the presence of septic shock.[12,85-88] In this context we recommend higher doses of fluconazole (800 mg/day).

In the setting of neutropenic patients with prolonged fever despite antibacterial therapy, empirical antifungal therapy is well studied. These patients have a likelihood of approximately 20% to develop invasive fungal infection and empirical therapy may reduce the frequency of infection.[89] Amphotericin B is the preferred drug at a dose of 0.5–0.7 mg/kg/day. In comparison with conventional amphotericin B, liposomal amphotericin B is equally effective, better tolerated and associated with less breakthrough fungal infection.[90] Voriconazole has a similar success rate to liposomal amphotericin B.[91]

8.4 Definitive Antifungal Therapy

Definitive antifungal therapy is used in patients with microbiologically and/or histologically documented candidiasis. As already mentioned, in an ICU population, this will mostly be candidaemia or peritonitis. Specific treatment for different types of invasive candidiasis are described in section 9.

9. Treatment of Specified Invasive Candidiasis

The recommended treatment for specified types of invasive candidiasis is summarised in table III.

Table III. Recommended antifungal agents in specified invasive candidiasis (see section 9)

Type of invasive candidiasis	Preferred drug[a]	Antifungal follow-up	Nonpharmacological measures
Candidaemia and haematogenous candidiasis	Fluconazole, amphotericin B or caspofungin for 2 wks	Follow-up therapy is not necessary after careful examination for metastatic septic foci	Catheter removal. *In situ* treatment with amphotericin B lock therapy reported[92-94]
Candidal endocarditis, pericarditis, suppurative phlebitis and thrombophlebitis	Amphotericin B, fluconazole or caspofungin for 6 wks (suppurative phlebitis: 2 wks)	When infected valve can not be replaced: life-long therapy with fluconazole	Surgical intervention in case of left-sided native valve endocarditis
Intra-abdominal candidal infections	Fluconazole or amphotericin B for 2–3 wks	Follow-up therapy is not indicated after control for metastatic septic foci	Removal of any peritoneal devices and surgical source control is essential
Urinary candidiasis	Fluconazole or amphotericin B for 2 wks	Not necessary when candidal load is $<10^5$ cfu/mL and disappearance of infectious signs	Urinary bladder catheter removal. Bladder irrigations in persistent infections caused by fluconazole-resistant strains
Hepatosplenic candidiasis	Fluconazole or amphotericin B for at least 6 wks	Long-term follow up therapy can be indicated in persistent infections. Examination before stopping therapy is necessary	Surgical intervention can be beneficial in selected patients
Candidal pneumonia	Fluconazole or amphotericin B for ≥2 wks depending on respiratory function and medical imaging	Examination before stopping therapy is necessary	
Candidal endophthalmitis	Fluconazole for 2 wks	Examination before stopping therapy is necessary	Vitrectomy warranted
Candidal meningitis	Amphotericin B + flucytosine for at least 4 wks	Examination before stopping therapy is necessary. Fluconazole can be used for follow-up therapy	
Candidal osteomyelitis, mediastinitis and arthritis	Amphotericin B or fluconazole for 6–10 wks	Fluconazole for 6–12mo	Surgical debridement, removal of prosthetic material and adequate drainage is necessary

a Regardless of *Candida* species involved.

9.1 Candidaemia and Haematogenous Disseminated Candidiasis

Every patient with a blood culture positive for *Candida* spp. should be treated. It is generally accepted that a single blood culture is enough to justify antifungal therapy.[16] Fluconazole is to be preferred in most patients as it is as effective as but less toxic than amphotericin B.[67] A dosage of 400 mg/day following a loading dose of 800mg is standard.[95] Higher dosages (600–800 mg/day) during the first 3–5 days are recommended by some authors, although hard evidence for this approach is still lacking.[16,68,69]

In a majority of patients fluconazole will cover the causative *Candida* species as candidaemia in ICU patients is only rarely caused by the intrinsically fluconazole-resistant *Candida* species. In most patients, *C. glabrata* can be treated with higher dosages of fluconazole (800 mg/day). For patients who do not respond to fluconazole, amphotericin B or caspofungin may be used.[76]

Contaminated catheters are an important source of candidaemia. Whenever candidaemia is diagnosed catheters should be removed and replaced. In fact, ICU patients with a pronounced risk profile for candidaemia and who have catheters that have been in place for >5 days, should have their catheters removed at the onset of a clinical picture suggestive for systemic infection. Failure to remove contaminated catheters is likely to result in a worse outcome.[96] It is recommended that catheters are not changed over a guidewire as this may result in reinfection and longer duration of candidaemia.[96]

The objective of treating candidaemia goes beyond the sterilisation of the bloodstream. As candidaemia can be a step to metastatic septic foci, duration of therapy should be 14 days from the last

positive blood culture.[97] In order to avoid a relapse of candidiasis, careful follow-up measures such as the examination of the retina in order to exclude endophthalmitis are warranted.

9.2 Candidal Endocarditis, Pericarditis, Suppurative Phlebitis and Thrombophlebitis

Fungal endocarditis is an uncommon occurrence with an incidence of 1.3–6% of all cases of infective endocarditis. *Candida* species are responsible for approximately two-thirds of fungal endocarditis cases.[98] Mortality generally exceeds 50%. Diagnosis is based on microbiological data and echocardiographic evidence.[99] Persistent candidaemia in the absence of a clear source despite adequate antifungal therapy must also raise suspicion of candidal pericarditis, suppurative phlebitis or thrombophlebitis.[65,98,100,101] Combined medical and surgical therapy can be preferred for all these types of infection.[65,101] Recently, the combination of antimicrobial therapy with surgical intervention resulted in better 6-month survival rates in adults with complicated left-sided native valve endocarditis.[102] However, suppurative phlebitis might respond better to long-term antifungal therapy with amphotericin B.[65] Pharmacological therapy may consist of either intravenous amphotericin B 0.6–1.0 mg/kg/day, fluconazole 6–12 mg/kg/day or caspofungin 50 mg/day.[65] Antifungal therapy should be continued for 6 weeks after surgery, except for suppurative phlebitis where 2 weeks therapy is sufficient. Life-long maintenance therapy with fluconazole can be required for patients in whom the infected valve can not be replaced.[103] Patients with candidal endocarditis are likely to relapse and a 1-year follow-up is warranted.[104]

9.3 Intra-abdominal Candidal Infections

Candidal peritonitis may occur in patients undergoing peritoneal dialysis, or following major abdominal surgery or trauma. The incidence of *Candida* spp. involvement in peritonitis varies depending on the source. Some authors found *Candida* spp. to be the leading or second most frequently isolated pathogen in secondary or tertiary peritonitis.[105-107] In a study of 120 patients with secondary peritonitis, *Candida* spp. were present in only 12%, thus ranking seventh.[108] The incidence of *Candida* spp. involvement probably depends on the presence of predisposing factors such as immunodeficiency or prolonged exposure to antibacterials. Moreover, in pancreatic sepsis, *Candida* spp. are a predominant pathogen and associated with high mortality.[82,109]

The high risk for candidiasis in patients with intra-abdominal contamination has led to an increased use of antifungal prophylaxis after major abdominal surgery or trauma. A placebo-controlled clinical trial demonstrated that fluconazole 400 mg/day reduced the rate of intra-abdominal candidiasis in high risk surgical patients ($p = 0.02$).[81] Although this study solely focused on patients with gastrointestinal perforations and anastomotic leakage, this finding is often generalised to other patients with complicated intraabdominal conditions. Moreover, this study was not able to demonstrate a benefit in outcome for patients receiving antifungal prophylaxis ($p = 0.23$). In addition, in a study evaluating the efficacy of an intra-operative single dose of 400mg fluconazole, no significantly better outcome was observed ($p = 0.059$).[110]

Routine treatment of patients with *Candida* spp. isolated following fast and uncomplicated repair of an intra-abdominal perforation is not recommended if they are otherwise healthy and without clinical signs of sepsis.[65,111] Primary and peritoneal dialysis-related peritonitis can be treated with fluconazole or amphotericin B. In patients with catheter associated peritonitis, removal of the peritoneal catheter is necessary.[5,65] At least 2 weeks of therapy is needed before the catheter can be replaced. Intraperitoneal amphotericin B is not recommended as it may cause chemical peritonitis.

Disease of the biliary tree must be treated by mechanical restoration of functional drainage, and antifungal therapy with fluconazole or amphotericin B. Therapeutic biliary concentrations are achieved with both these drugs.[65,112] Surgical source control, implying repair of perforations and elimination of contaminated peritoneal fluids or infected necrosis, is essential in the treatment of intra-abdominal

candidiasis.[5,65] Prompt surgical intervention should be accompanied by pharmacological therapy, either with fluconazole or amphotericin B. In all types of peritonitis therapy should be for 2–3 weeks.

9.4 Urinary Candidiasis

Urinary candidiasis is mostly found in patients with bladder catheterisation. In ICUs, *Candida* spp. are frequently isolated from urine. However, in most instances this only represents colonisation. Until recently there has been no reliable method to differentiate colonisation from infection. High colony counts ($>10^5$ cfu/mL) have been associated with infection in patients without an indwelling catheter, but in ICUs bladder catheterisation is standard for most patients.[113] Removal of the catheter is the cornerstone of the treatment of candiduria. In the absence of antifungal therapy, candiduria is eliminated in approximately 40% of the patients when the bladder catheter is removed and in 20% of patients when the catheter is removed and replaced.[114] Pyuria normally reflects the diagnosis of infection but it can also be caused either by bacteruria or mucosal trauma by catheterisation.[115] Candidal infection can be ruled out in the absence of pyuria and only low colony counts. Candiduria does not allow distinguishing candidal cystitis from upper urinary tract infections such as candidal pyelonephritis or renal candidiasis.

For candidal cystitis, fluconazole 200 mg/day or amphotericin B ≥0.6 mg/kg/day are sufficient to eliminate infection. Special attention should be given to infection caused by fluconazole-resistant strains such as *C. krusei* or, in some instances, *C. glabrata*. As amphotericin B does not have sufficient concentration in urine, systemic therapy must be combined with bladder irrigations (50 mg/L for 5 days). However, this intervention is only rarely indicated and must be reserved for patients who do not respond to treatment. Persistent candiduria in immunocompromised patients warrants complementary examination (computed tomography or ultrasound of the kidneys).

9.5 Hepatosplenic Candidiasis

This syndrome is also known as chronic disseminated candidiasis and is only described in patients with haematological malignancies and prolonged neutropenia. The patients mostly experience fever not responding to antibacterial therapy and abnormal liver function tests. There may be focal lesions in the liver or spleen.[116] The optimal therapy has yet to be established. Amphotericin B, amphotericin B lipid complex and fluconazole have all been shown to be efficacious in the treatment of this disease.[117-120] Surgical intervention with splenectomy or percutaneous drainage may be beneficial in selected patients.[5,121]

9.6 Candidal Pneumonia

Candidal pneumonia is a rare disease entity. However, colonisation of the respiratory tract with *Candida* spp. is very common in mechanically ventilated patients receiving antibacterials. It is rarely pathogenic and seldom requires antifungal therapy. It is difficult to differentiate colonisation from infection in the respiratory tract. Evidence for candidal pneumonia can be found on histopathological examination of lung biopsy. However, in critically ill patients bonchoscopic or surgical lung biopsy carries significant risks. In patients who are strongly suspected of having candidal pneumonia, antifungal therapy can be initiated in the absence of a definite diagnosis. Amphotericin B 0.6 mg/kg/day or fluconazole 800mg as a loading dose followed by 400 mg/day can be used.[48]

9.7 Candidal Endophthalmitis

Candidal endophthalmitis has been estimated to occur in approximately 15% in patients with candidaemia. Ophthalmological examination is necessary whenever disseminated disease is suspected. Fluconazole should be administered for minimum 2 weeks. Longer therapy may be required, depending clinical evolution. In patients who are not responding to treatment, flucytosine can be combined with fluconazole.

9.8 Candidal Meningitis

Candidal meningitis in adults is rare. It might occur following candidaemia in long-term immunosuppressed patients or after neurosurgical intervention.[122,123] In patients with postsurgical infection any devices such as drainage systems should be removed. Amphotericin B 0.7–1.0 mg/kg/day plus flucytosine 25 mg/kg four times a day has been recommended.[65,123,124] The flucytosine dosage should be monitored and corrected to obtain serum concentrations of 40–60 μg/mL. Because of the high risk of relapse, therapy should be continued for at least 4 weeks after resolution of all symptoms. Limited data are available on the efficacy of fluconazole or other triazoles in the treatment of candidal meningitis. Yet, triazole therapy seems warranted because of the excellent penetration into cerebrospinal fluid.[125,126] Fluconazole can be used for follow-up therapy.

9.9 Candidal Osteomyelitis, Mediastinitis and Arthritis

Candidal osteomyelitis can occur following candidaemia or as a postoperative complication. Candidal mediastinitis can be caused by oesophageal perforation, trauma or occur after cardiac surgery.[127,128] Candidal arthritis occurs postoperatively and is mostly associated with contaminated prosthetic material. Surgical debridement, removal of foreign bodies and extensive drainage are the cornerstones of treatment in all these types of infection. For antifungal therapy either amphotericin B 0.5–1.0 mg/kg/day for 6–10 weeks followed by fluconazole maintenance therapy or fluconazole 400 mg/day for 6–12 months can be used.[5,124]

10. Conclusion

Despite the advances in intensive care medicine and the development of new antifungal agents, the management of invasive candidiasis remains challenging as there is a growing number of patients at risk and diagnosis of invasive disease is still problematic. The arrival of new antifungal agents has led to a re-orientation of the management of invasive candidiasis in critically ill patients. Less toxic drugs have opened doors towards preventive strategies. Patients with a pronounced risk profile may benefit from either prophylaxis or pre-emptive antifungal therapy. However, these strategies should be preserved for patient populations in whom benefits have previously been demonstrated and generalisation of prophylaxis to nearly all critically ill patients should not be encouraged given the potential risk for a shift towards less susceptible *Candida* species. In definitive antifungal therapy, a choice can be made based on host risk factors, clinical status, knowledge of *Candida* species and antifungal susceptibility, relative drug toxicity, and the potential for interactions and organ damage causing diminished drug clearance. In general, infections caused by *C. albicans* can be treated with fluconazole. In patients with infections caused by less susceptible species such as *C. glabrata* higher doses of fluconazole or an antifungal with broader spectrum can be administered (amphotericin B, itraconazole, caspofungin and voriconazole).

Invasive candidiasis represents a wide range of diseases. Yet, with the exception of candidaemia and haematogenous candidiasis, the incidence of invasive disease is rare and so there have been few large randomised trials. Therefore, in rather rare types of invasive candidiasis hard evidence regarding the most optimal treatment option is lacking.

Future research in this field should place special emphasis on more accurate diagnosis of invasive disease to allow antifungal therapy to be initiated in a timely manner. Moreover, the role of combination therapy as well as the usefulness of adjunctive therapy with human recombinant antibody against fungal heat shock protein 90 needs further investigation.[129-132]

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