Clinical Interventions in Aging

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REVIEW

Treatment of invasive candidiasis in the elderly: a review

This article was published in the following Dove Press journal:
Clinical Interventions in Aging
7 September 2013
Number of times this article has been viewed

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Abstract: Fungi are major causes of infections among immunocompromised or hospitalized patients with serious underlying diseases and comorbidities. *Candida* species remain the most important cause of opportunistic infections worldwide, affecting predominantly patients over 65 years old, while they are considered to be the fourth most common cause of nosocomial bloodstream infections. The rapidly growing elderly population has specific physiological characteristics, which makes it susceptible to colonization and subsequent infection due to *Candida* species. Comorbidities and multidrug use should be taken into account any time the therapeutic regimen is under consideration. Different classes of antifungal drugs are available for the treatment of invasive fungal infections but echinocandins, apart from their activity against resistant strains (*Candida glabrata* and *Candida krusei*), seem to be safe, with limited adverse events and minimal drug–drug interactions in comparison to the other regimens. Therefore, these agents are strongly recommended when dealing with elderly patients suffering from an invasive form of *Candida* infection.

Keywords: emerging fungal infections, elderly patients, treatment

Introduction

Candidemia and invasive candidiasis (C/IC) show an increasing incidence in the nosocomial setting. The crude mortality of those infections ranges between 36%–63% depending on patient population.[1–4] Comorbidities, aging and age-associated physiological changes, higher rates of oropharyngeal colonization with *Candida* species, and concomitant drug use make elderly patients (>65years old) more vulnerable to infections. For this reason fungal infections have become a major problem in older adults, since age is a well-documented predisposing factor with increased impact on mortality.[5–7]

The cutoff age for the elderly population cannot be clearly defined because aging is a continuous process. It is also clear that aging is a multifactorial process influenced by both genetic and environmental parameters. Many studies dealing with *Candida* infection in the elderly have used several different arbitrary cutoff points such as over 60, 65, or 70 years old. However, most prospective epidemiological studies define "elderly population" as the age group >65 years.[5–9]

The elderly population is large and is growing in proportion to the general hospitalized population, but available data on epidemiology, clinical impact, and outcome of nosocomial fungal infections are limited.[7–10] The indications for antifungal therapy are the same for older as well as younger individuals, and the initial antifungal therapy

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should be selected on the basis of the infecting organism and the local epidemiology.[9,11] Fluconazole is generally effective against C/IC but its use may be limited by the increasing prevalence of *Candida* species (spp.) with acquired or intrinsic resistance. Echinocandins are recommended as first-line treatment for C/IC in all patients, and more specifically in hemodynamically unstable patients or in those with prior azole exposure, or for invasive infections caused by *C. krusei* or *C. glabrata* because of their activity against azole-resistant strains, while Amphotericin B remains the cornerstone of antifungal treatment.[1,9,11–15]

In this review, we aim to discuss the management and treatment options of fungal infections in the elderly population, considering additionally the specific conditions and the impact of potential comorbidities and drug interactions.

Epidemiology

Invasive candidiasis (IC) (also called systemic), is the invasion of *Candida* spp. in a human organ (invasion via the bloodstream is called candidemia). If multiple organs such as the brain, heart, kidneys, lungs, and liver are affected, the condition is called disseminated candidiasis. *Candida* spp. are ubiquitous (more than 200 species have been described); most consist partly of the human microbiological flora, although only 10% of these species are known to be responsible for infections in humans.[16] Indeed, at least 17 different *Candida* spp. cause IC in humans; *C. albicans* is the most common worldwide, presenting a global average of 66% of all *Candida* spp., with large geographical discrepancies according to the ARTEMIS DISK Global Antifungal Surveillance Study.[17,18] *Candida* spp. account for 8%–10% of all nosocomial infections, next to coagulase-negative *Staphylococci* (31%), *Staphylococcus aureus* (20%), and *Enterococci* (9%) and have become the fourth most common cause of hospital-acquired bloodstream infections (BSIs) in the USA.[19] Other studies in Europe and Canada, with the exception of Denmark, reported a lower incidence of candidemia than that reported in the USA (1.9% in Finland, 4.9% in Iceland and Spain), reflecting probable differences in patient demographics and comorbidities, as well as in medical practices and/or diagnostic methods.[6,20] In all of these studies the highest incidence occurred at the extremities of the age spectrum (infants of less than one year old and in adults >65 years old).[6,21–24]

Candida albicans is the most common pathogen causing IC worldwide, though a shift towards non-*albicans* species has been noted over the years. *C. glabrata* represents an important fungal pathogen, ranking second to *C. albicans* as a cause of bloodstream infection.[6] In the USA, *C. glabrata* accounts for 20%–24% of all *Candida* BSIs but in other geographical regions, including Europe, lower rates have been reported.[6] The origins of these discrepancies are unclear but previous exposure to azoles, increasing patient age, presence of underlying diseases such as malignancies, and different geographic locations or technical methodologies regarding blood cultures could be considered as possible explanations. Older patients (>65 years) have increased risk of candidemia due to *C. glabrata* and increased risk of dying (29%) as well.[25] Systemic broad spectrum antibiotic use, central venous catheters, long stay in the intensive care unit (ICU), renal insufficiency, and total parenteral nutrition were identified as the most important risk factors. It is unclear whether the higher identified rate of oropharyngeal colonization with *C. glabrata* in older, compared to younger, adults, is related to candidemia.[26,27] Blot et al have studied the outcome of critically ill patients with candidemia and found that fungemia from *C.glabrata* was significantly associated with older age. Older age, polymicrobial bloodstream infection and acute renal failure were independent predictors of mortality.[11] A significant epidemiological shift towards *C. glabrata* as a cause of candidemia has been reported in oncology centers, compared to individual hospitals.[6,25,28–30]

C. paraspilosis is an exogenous pathogen, found mostly on skin rather than mucosal surfaces, and is known for its ability to form biofilm on catheters and other implanted devices. It is spread through hand contamination in hospitals and nursing homes. About 38% of *C. paraspilosis* BSIs are acquired outside the hospital, a finding consistent with the fact that older patients often receive home health care with indwelling catheter use due to various chronic diseases.[26,31–33] BSIs due to this species are associated with a lower mortality rate than other *Candida* spp.[2,6] *C. tropicalis* is an important pathogen in neutropenic patients with hematologic malignancies and mucositis. This pathogen is very common in Latin America, responsible for 22% of BSI isolates but, according to the ARTEMIS DISK Global Antifungal Surveillance Study, its incidence worldwide has reached 4%–7% with an increasing trend.[18] *C. krusei* is another important pathogen among patients with hematologic malignancies, and among blood marrow transplant recipients, characterized by intrinsic resistance to fluconazole.[1] *C. krusei* accounts for 2%–5% of all *Candida* infections worldwide, having emerged in oncology patients under prophylaxis with fluconazole.[28,34] Interestingly, it has been reported that exposure to piperacillin-tazobactam and vancomycin leads more often to *C.krusei* infections than does exposure to fluconazole, because the former drugs promote skin and gastrointestinal colonization, rendering the human host more vulnerable to *C. krusei* BSIs.[35]

C. guillermondii and *C. rugosa* are common in Latin America and responsible for clusters of hospital infection, exhibiting low susceptibility to fluconazole, while they are considered as rare causes of catheter-related candidemias in other countries.[36–39] *C. incospicua* and *C. norvegensis* are both phenotypically similar to *C. krusei,* exhibiting intrinsic resistance to fluconazole, causing candidemia in human immunodeficiency virus-infected patients and in patients with hematologic malignancies. *C. norvegensis* has been found mostly in respiratory specimens.[40–42]

Physiological alterations in the elderly

The aging process leads to variable changes in physiological and morphological functions, rendering older patients potentially more vulnerable to infections, particularly from fungal species (Table 1).[7] Aging leads to hyposalivation, which in turn alters the normal microflora of the oral cavity, so that it has fewer anaerobic bacteria, such as enterococci.[43] Less saliva production limits peptide and protein presence in the oral cavity, and the lack of substances with broad antimicrobial activity, such as lysozyme, contributes to oral candidiasis.[43] In the supragingival plaque, which is responsible for caries formation, *Candida* species are the predominant pathogens, especially in adults $>$70 years old.[44] Moreover, in dental prostheses various *Candida* species can be found, with *C. albicans* being the most prevalent, followed by *C. glabrata* and *C. tropicalis.*[44] This colonization is further influenced by (a) poor oral hygiene, (b) drugs that irritate or damage the oral mucosa, such as cytostatics, (c) drugs that alter the oral flora synthesis, such as antibiotics, or (d) by concurrent diseases, such as iron deficiency anemia. Once the oral cavity is colonized, it is easier for the yeasts to reach the respiratory system, and since *Candida* is a commensal of the gut lumen and the cutaneous surfaces, the colonization index is increasing.[43,45] *Candida* spp. are common in the urine of the elderly, especially after treatment with broad spectrum antibiotics. Differentiating asymptomatic candiduria, even in high concentrations ($>10^5$/mL urine), from a true infection which triggers a systematic inflammatory response is difficult, and treatment is influenced by the biofilm formation in the urinary catheter.[43]

Table 1 Normal physiological alterations in the elderly

1. Diminished immunological response expressed by decreased phagocytosis
   - Lack of antigen presenting cells (dendritic, naïve T-cells)
   - Decreased memory capacity of mature T-cells
   - Decreased cytokine production
   - Decreased number of B-cells and immunoglobulin production
2. Decreased hepatic function due to decreased liver mass and blood flow, declining phase I metabolism, and decreased bile secretion
3. Decreased renal function (glomerular filtration rate declines on average 1% per year)
4. Hyposalivation
5. *Candida* colonization of dental prostheses
6. *Candida* colonization of the urinary tract, especially after broad spectrum antibiotic use

Note: Data from.[43,46–48]

The biofilm formation is an aggregate of microorganisms where cells adhere to each other on a surface. It may become a problem in patients with indwelling catheters, such as older people in hospitals or nursing homes. *Candida* colonization is one of the main reasons why older people are so prone to bloodstream infections, but not the only reason. Older age is always accompanied by normal physiological alterations and/or various metabolic disorders or neoplastic diseases, which disrupt the mucosal and cutaneous barrier and make the organism more vulnerable to *Candida* infection (Table 2).[6] Thus, selection of a suitable drug is based not only on the specific microorganism, and on the clinical condition and its severity, but also on all the underlying pathophysiological characteristics of the patient's advanced age.

Aging is characterized by diminished immunological response to infection, especially due to functional insufficiency of monocytes and macrophages, which leads to inadequate phagocytosis.[43] Other antigen presenting cells, such as dendritic cells, are lacking, and so are naive T-cells due to thymus gland involution.[46] Mature T-cells lose their memory capacity and exhibit poor and/or altered cytokine production.[46] Moreover, the number of circulating B-cells is diminished and their response to antigenic challenges through immunoglobulin production is weaker.[47] Animal studies on the aging liver have shown modifications of the hepatic physiology which affect drug metabolism. Possible mechanisms, occurring normally with aging, involve reduction in total liver mass, hepatic blood flow, and protein synthesis. These factors compromise drug metabolism, such as hydroxylation, dealkylation, and reduction; reactions occurring in Phase I drug metabolism, performed by microsomal cytochrome p450.[48,49] Phase I is necessary to prepare the drug or toxin to undergo Phase II metabolism (conjugation, acetylation, and methylation), altering its form and promoting its effective excretion.[49]

Renal function is also impaired with advanced age. Glomerular filtration rate (GFR) decreases by 1% per year of life. This is not reflected in serum creatinine because a 25%

Table 2 Physiological effects of aging and their impact on drug metabolism

Hepatic function	Renal function	Body composition	Comorbidities	Alterations in receptor sensitivity
↓ Liver mass ↓ Hepatic blood flow ↓ Phase I metabolism (oxidation by CYP450 enzymes), further inhibited by Fluconazole ↓ Bile secretion Unaffected phase II metabolism	↓ GFR	↓ Total body water ↑ Body fat	Heart failure Hypertension Diabetes Cancer Pain due to various diseases	↓ β-receptor ↓ CYP450

Abbreviations: GFR, glomerular filtration rate; ↓, decrease; ↑, increase.
Note: Data from.[43,48]

rise in serum creatinine level actually represents a substantial fall in GFR, probably as much as 50%, due to the exponential rise in creatinine level with declining renal function.[50] This decline of renal function is often underestimated, since serum creatinine is dependent on muscle mass, which also attenuates with age and remains almost normal. Therefore, older and very sick patients, with a normal creatinine value, have a GFR of only 30% of that of a young, healthy adult. This is associated with serious clinical problems with drugs dependent on renal excretion.[50]

Polypharmacy in the elderly is another important issue, relevant to both adverse effects and drugs interactions. A recent Dutch study demonstrated that almost 75% of the elderly population was being treated with at least 4 drugs, suggesting that elderly patients are not only prescribed a greater number of medications than younger patients, but they also receive drugs in a more inappropriate manner.[51–53] Analgesics, including nonsteroidal anti-inflammatory drugs (NSAIDs) (eg, acetylsalicylic acid, ibuprofen, indomethacin, naproxen), narcotics (eg, hydrocodone), non-narcotic pain medications (eg, acetaminophen), or drugs with other mechanisms of action that act synergistically on pain relief (benzodiazepines, tricyclic antidepressants), comprise the most popular drug categories.[53] Furthermore, polypharmacy involves, apart from pain relief, treatment of other diseases, such as hypertension, diabetes, chronic obstructive pulmonary disease, heart failure, or cancer. Moreover, alterations in body composition such as decrease in total body water or increase in body fat may result in unexpected toxic effect or duration of action of various drugs. The prevalence of the effect of drug–drug interactions on the liver is >74% in older women of which 63% involve NSAID use.[54] Apart from multiple drug use, the mechanisms of drug-induced liver injury in the elderly include gender, dosage and treatment duration, drug formulations, nutritional status, genetic susceptibility, environmental factors (eg, alcohol abuse), and underlying comorbidities.[53]

Diagnosis

Invasive *Candida* infections include clinical syndromes of different severity where the diagnosis is a challenge, especially in critically ill, immunocompromised, or elderly patients. The signs and symptoms vary from silent or atypical, to that of a bacterial infection. The diagnosis relies on clinical, microbiological, and biochemical evidence. Newer culture methods have raised the sensitivity of *Candida* detection to almost 70%, but it takes a minimum of 24 to 48 hours to become positive and this may come late in the course of the infection.[55] Moreover, patients are often under fluconazole prophylaxis which may render the cultures negative at time of testing.[56] Two antigen based tests are currently available for the early diagnosis of candidemia, relying on detecting components of the fungal cell wall. The first method detects mannan levels, which is a major component of the *Candida* cell wall. In high risk patients, it is recommended to be performed two to three times per week, since its circulation in the bloodstream is intermittent. Sensitivity and specificity of this test, when combined with anti-mannan antibodies detection in critically ill but not immunocompromised patients, are 83% and 86% respectively.[56–59] The second diagnostic tool is based on the detection of 1,3-β-D-glucan. This test has been evaluated mostly in critically ill patients and has demonstrated an overall sensitivity of 77% and specificity of 85% for subjects with proven or probable IC.[58–60] One single positive test is indicative of the infection, but it must be interpreted with caution due to false positive results.[55] A negative 1,3-β-D-glucan test is associated with high negative predictive value (>90%) and can be used to rule out IC, especially in patients with neutropenia.[60–62] Finally, nucleic acid-based detection methods (real-time polymerase chain reaction) have been developed for five different *Candida* spp. of major clinical importance. Although these techniques have shown significant advances in the early and specific diagnosis of IC, further evaluation must be conducted in specific populations such as the elderly, considering the relatively weak immune systems and variable immunological responses among this age group, which render the diagnostic accuracy of the above methods less precise.[55]

Therapeutic targets and drug selection

The management of *Candida* infection includes prophylactic, preemptive, empiric, and targeted treatment (Figure 1). Prophylaxis is used in high risk patients with no symptoms and signs of infection. Preemptive therapy is justified in the presence of positive inflammatory markers – biomarkers in conjunction with certain predisposing risk factors. Empiric therapy is warranted in patients with a currently unknown infection, for whom treatment is justified based on clinical judgment, while targeted treatment is administered when the diagnosis of a certain pathogen is documented. Currently available drugs against IC include amphotericin B (AmB) and its derived lipid formulations (LFAmB), azoles (triazoles) including fluconazole (FLU), voriconazole (VOR), posaconazole (POS), and itraconazole, and echinocandins including caspofungin (CFG), micafungin (MIC), and anidulafungin. 5-fluorocytocine (5FC), a fluorinated pyrimidine analog has also antimycotic properties. Most *Candida* spp. are susceptible to these agents, except for those with intrinsic or acquired resistance after exposure to other drugs.

AmB is a polyene macrolide antifungal regimen with fungicidal action, which was considered in the past to be the "gold standard" for the treatment of invasive fungal infections.[62] Derived from *Streptomyces* spp., it has a high affinity for the sterols of fungal and bacterial membranes, forming small transmembrane channels which lead to monovalent ion leakage and cause fungal cell death. Derivatives of AmB were developed in order to limit toxicity, especially renal failure, which has been rated between 49%–65%.[50,63–65] Three lipid formulations of AmB (LFAmB) are commercially available, all with a good fungicidal activity and no differences in efficacy. Indeed, all *Candida* spp. are susceptible to AmB, along with *Aspergillus* spp., *Cryptococcus* spp., and *Zugomecetes* spp. The formulations include a true liposome structure LFAmB (AmBisome®, Gilead, Cambridge, UK); a ribbon-like structure AmB lipid complex (Abelcet®, Sigma-Tau Pharmaceuticals, Inc, Gaithersburg, MD, USA); and a colloid dispersion, amphotericin B colloidal dispersion (ABCD) (Amphocil/Amphotec®, EvaluatePharma, London, UK) with a disc-like structure. All lipid formulations have less nephrotoxicity than conventional AmB-deoxycholate.[64–66]

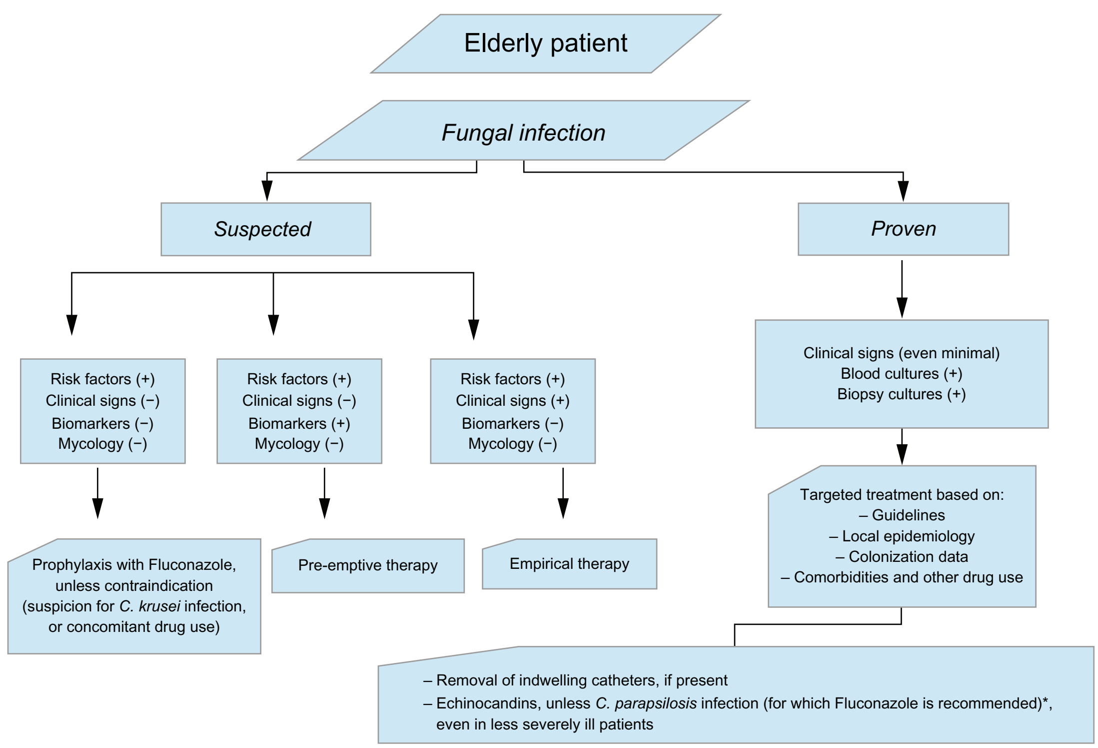

Figure 1 Algorithm for the management of candidiasis in the elderly patient.
Note: *Although there are recent data suggesting that success rates of treating *C. parapsilosis* were similar for the echinocandin group versus other antifungal treatment groups.[81] Adapted from Journal of Critical Care, Dimopoulos G, Antonopoulou A, Armaganidis A, Vincent JL. How to select an antifungal agent in critically-ill patients. In press. Copyright 2013, with permission from Elsevier.[62]

Among these, the liposome structure of AmB seems to have lower nephrotoxicity rates (15%) than the ribbon-like structure (>40%).[67] LFAmB is used in a dose of 3 to 5 mg/kg daily in life-threatening mycoses, as well as for empirical treatment of suspected IC, or in situations where an antifungal agent with rapid time-kill rate and high post-antifungal effect is needed.[11,68] However, in older patients it should be used with caution, especially if parameters such as dehydration, large cumulative dosage, abnormal baseline renal function, and concomitant nephrotoxic drug use exist.

The azoles FLU, itraconazole, VOR, and POS inhibit the fungal cytochrome P450 enzyme 14α-demethylase and prevent the conversion of lanosterol to ergosterol, which is essential for the fungal cell membrane integrity. All the above azoles demonstrate activity against *Candida* spp. but reduce activity against *C. glabrata* and *C. krusei*.

FLU, with primarily fungistatic effect (800 mg or 12 mg/kg loading dose, followed by 400 mg or 6 mg/kg daily), has comparable efficacy to AmB for the treatment of candidemia, while it is indicated as empirical and curative treatment in non-neutropenic patients.[69–70] FLU is recommended for the treatment of *C. parapsilosis* BSI, while among all the triazoles, it possesses the greatest penetration to the cerebrospinal fluid and it is therefore indicated for the treatment of central nervous system and intraocular infections. Prophylactic use of FLU led to a shift to resistant *Candida* species, and its use alters (and may even increase) the frequency of infection due to molds. Prophylaxis (6 mg/kg daily) is recommended in solid organ transplant recipients (liver, pancreas, and small bowel), during induction chemotherapy and in stem cell transplant recipients during the period of neutropenia.[11] FLU is an inhibitor of the human cytochrome P450 system and therefore it decreases the metabolism or increases the concentration of any drug metabolized by these enzymes. This should be kept in mind, considering the high number of concomitant drugs that older people take, which also undergo hepatic metabolism, in order to avoid serious and life-threatening drug–drug interactions. Serum levels of warfarin, phenyntoin, or oral hypoglycemic agents are increased by the azoles, whereas serum digoxin levels may increase. Another rare adverse event is the potential effect on electrocardiographic QT interval, whose elongation increases the risk of ventricular arrhythmias, especially if drugs are used concurrently, which also prolong its duration (eg, macrolides, fluoroquinolones, anticholinergic, antihistamines, diuretics, and the gastroprokinetic agent cisapride). Itraconazole has a broader spectrum of activity than FLU (in vitro activity against *Candida* spp., *Aspergillus* spp., and dimorphic fungi, but not as broad as VOR or POS), but is not able to penetrate cerebrospinal fluid. VOR is active against *Candida* spp., *Mucor* spp., and *Aspergillus* spp. in severely immunocompromised patients, while it is active against *C. krusei, C. guillermondii,* and *C. lusitaniae.*[71] Intravenous VOR is complexed to a cyclodextrin molecule and after two loading doses of 6 mg/kg every 12 hours, a lower maintenance dosage of 3–4 mg/kg twice daily is recommended. Due to cyclodextrin accumulation, VOR is not indicated in patients with renal dysfunction and creatinine clearance of <50 mL/min.[72] VOR is effective in candidemia, but it offers little advantage over FLU and is therefore recommended as a step-down oral therapy for *C. krusei* infection and for FLU-resistant, VOR-sensitive *C. glabrata* infection. Oral VOR does not require dosage adjustment in renal insufficiency, but is the only triazole that requires dosage reduction in patients with mild-to-moderate hepatic insufficiency. In a randomized, international, multicenter trial comparing VOR with LFAmB as empirical antifungal treatment, the authors suggested that VOR could be a suitable alternative to LFAmB in patients with neutropenia and persistent fever.[73] POS is available only as an oral suspension with high oral availability and seems to be more active than the other triazoles. POS exhibits a broad spectrum activity against yeasts, molds, or rare fungal strains.

Echinocandins (ECs) are a new class of antifungal agents that target the fungal cell wall by inhibiting 1,3-β-D-glucan synthetase, leading to osmotic instability and cell death. ECs are considered to be safe drugs, with few reported side effects. The three members of the group, CFG (loading dose of 70 mg, then 50 mg daily), MIC (100 mg daily), and anidulafungin (loading dose of 200 mg, then 100 mg daily), are all available only for parenteral use. Each of these agents has been studied for the treatment of IC in comparative and noncomparative clinical trials.[74–77] The MICs of the echinocandins are low for a broad spectrum of *Candida* spp., including *C. krusei* and *C. glabrata. C. parapsilosis* demonstrates less in vitro susceptibility (higher MICs) than most other *Candida* spp., and that has raised the concern of its being less responsive.[71,78,79] Similarly, there have been reports of increased clinical failure and persistence of infection with this species, claiming that *C. parapsilosis* infection may indeed require higher echinocandin dosage.[1,80] Therefore, in the recent clinical practice guidelines for the management of candidiasis, FLU is the treatment recommendation for *C. parapsilosis* infection, unless the patient has already received an echinocandin, is clinically improved, and has negative follow-up cultures.[11] Until now, this matter was still under debate, since a recent meta-analysis showed that ECs are effective for the treatment of candidemia or invasive candidiasis due to *C. parapsilosis*.[81]

Another important issue, unique for the ECs, is the "eagle effect", a term used to describe the paradoxical in vitro and in vivo growth of *Candida* and *Aspergillus* isolates when the dose of the drug gets over the MIC level.[82] This phenomenon has similarities to the "eagle effect" observed in other cell wall active antimicrobial agents, such as penicillins. Although the clinical impact of this phenomenon has not been elucidated, it might be of some importance in biofilm tretment.[62] None of the ECs require dosage adjustment for renal insufficiency or dialysis. Both CFG and MIC undergo minimal hepatic metabolism, but neither is a major substrate for cytochrome P450 and therefore they have minimal drug-drug interactions. Anidulafungin has not hepatic metabolism; it undergoes slow chemical degradation to a ring opened peptide with no antifungal activity. Though concerns have been raised about the potential hepatotoxicity of MIC due to tumor formation in rodents, CFG is the only EC for which dosage adjustment is recommended for patients with moderate to severe hepatic dysfunction. The clinical practice guidelines favor the use of an EC as initial therapy for candidemia in non-neutropenic as well as neutropenic adult patients, with moderate to severe illness.[11] Alternatively, FLU and LFAmB may be used, but for infection due to *C. glabrata* an EC is preferred, since the triazoles have diminished activity against this species.

Moreover, very little is known about the pharmacological/pharmacokinetic properties of antifungal drugs in the elderly. The diminished drug clearance that occurs naturally with aging, along with the presence of other comorbidities and drug use, make the pharmacodynamic and pharmacokinetic issues very intriguing. Drug interactions and comorbidities are the main reasons why we would not recommend azoles or amphotericin B as our first therapeutic choice in this specific population. Dose modification is not warranted unless indicated for other reasons (eg, hepatic or renal dysfunction).[83] Monitoring of plasma levels could be an option, but it is time and resource consuming, even in health care facilities where the method is available. Monitoring drug levels in plasma cannot be indicated for routine use unless future studies provide us with more data.

Flucytocine (or 5-fluorocytosine, 5FC) is an antimetabolite that acts as an antifungal against *Candida* spp., *Cryptococcus* spp., and other fungi. 5FC enters the fungal cell via cytosine permease, and is metabolized to 5-fluorouracil, which is incorporated extremely closely into the fungal RNA, inhibiting both DNA and RNA synthesis. Most of the drug is excreted unchanged in the urine, so that dose adjustment is necessary for patients with renal dysfunction. Considering the fact that 5FC is rarely administered as a single agent but in combination with other antifungal drugs (mainly LFAmB) for patients with IC, it is not suggested as a combination in elderly patients due to the accumulative nephrotoxicity risk.

Table 3 Risk factors for fungal infections in the elderly

- Multifocal (including oropharyngeal) colonization
- Presence of intravascular catheters (biofilm formation)
- Residence in health care facilities
- Admission and prolonged intensive care unit stay
- Renal failure
- Systemic administration of broad spectrum antibiotics
- Parenteral nutrition
- Recent abdominal surgery
- Neutropenia
- Use of corticosteroids or immunosuppressant drugs

Note: Data from.[2,6,25,35,88–91]

Nosocomial candidemia is associated with increased mortality and this seems to be further aggravated in case of delay in antifungal drug initiation.[84–86] Morrell et al have shown that initiating empiric antifungal treatment more than 12 hours after the first blood culture sample is associated with a greater risk of hospital mortality than when patients are started on antifungal therapy within the first 12 hours.[84] In a 5-year study, Parkins et al studied 207 patients with IC; 64 patients (32%) received empirical therapy, in 51 (26%) of which was deemed appropriate.[86] Similarly, Kumar et al demonstrated a 12% decreased survival probability for every hour's delay in patients with fungal septic shock.[87] Therefore, prompt initiation of early empiric therapy is warranted in high risk patients.

Knowledge of risk factors for IC may help to identify those patients who could benefit from early antifungal therapy (Table 3). The *Candida* score was first introduced by León et al and the EPCAN study group, from data available from the surveillance study of fungal infection and colonization in critically ill patients.[88] Clinical sepsis (2 points), multifocal colonization (1 point), surgery (1 point), and total parenteral nutrition (1 point) are the risk factors that must be evaluated by the physician in order to identify patients who are candidates for empirical treatment. A score of >2.5 showed 81% sensitivity and 74% specificity for the early administration of empirical treatment in ICU patients.[88,89]

Conclusion

In summary, the increase in invasive candidiasis in older adults has become an important clinical problem, since the older population is growing and is nowadays more likely to take aggressive chemotherapeutic regimens for cancer, or immunosuppressive drugs for nonmalignant diseases. Moreover, aging leads to variable physiological changes, rendering older patients potentially more vulnerable to fungal infections. Elderly patients are more easily colonized by pathogenic fungi and have an increased incidence of *C. glabrata* fungemia, which has higher mortality rates as well as higher rates of resistance to fluconazole, especially after exposure to the drug. Therefore, although clinical manifestations in older and younger adults may be similar, for the treatment of the former the use of an echinocandin is safer, since treatment with amphotericin B is associated with increased nephrotoxicity risk. Azoles are less toxic but they must be used with caution, since older adults are usually under a number of medications and the risk of serious drug–drug interactions is more likely to appear.

Disclosure

The authors have no conflicts of interest to declare.

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