

Appropriateness and cost-effectiveness in the treatment of invasive candidiasis in Internal Medicine Wards

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ABSTRACT

Invasive candidiasis (IC), including candidemia, is a major cause of morbidity and mortality among patients and the majority of cases of candidemia are documented in Medical Wards. Early identification of patients at risk, knowledge of local epidemiology and prompt efforts to define etiologic diagnosis are pivotal to ensure appropriateness. Start with an echinocandin and switch to fluconazole when possible, seems to represent a useful strategy for the management of IC. The choice between the three echinocandins should be based on the specific indications, pharmacokinetic/pharmacodynamic profile, clinical experience and cost.

Invasive candidiasis

Invasive candidiasis (IC), including candidemia, is a major cause of morbidity and mortality among patients undergoing to major surgery, receiving broad spectrum antibiotic therapy, having severe clinical conditions, multiple co-morbidities and indwelling devices.^{1,2}

Today the majority of cases of candidemia are documented in Medical Wards.³ In our tertiary-care, 800 beds, University Hospital, 50% of the total 222 episodes of candidemia documented in the period 2012-2013, were observed in Medical Wards. The distribution of the remaining episodes was 27% (60 episodes) in surgical wards, 18% (41) in Intensive Care Unit (ICU), 5% (11) in other wards.

Candida albicans was responsible for 50% (122 episodes) of total cases of candidemia while the non-albicans species were represented by *Candida parapsilosis* 27% (65), *Candida glabrata* 12% (30), *Candida tropicalis* 5% (13) and *Candida krusei* 2.5% (6).

C. glabrata has a dose-dependent susceptibility to

fluconazole while *C. krusei* has an innate resistance to the azoles.⁴ *C. parapsilosis*, often associated with central venous catheter infections, is less susceptible *in vitro* to the echinocandins. Amphotericin B has a good antifungal activity against all isolates of *C. albicans* and virtually all the non-albicans species.

The outcome of candidemia seems to be closely related to *Candida* species: fungemia with a more favorable outcome are those caused by *C. parapsilosis*, followed by those due to *C. albicans*, *C. glabrata*, *C. tropicalis* and *C. krusei*.⁵

Therefore the knowledge of local epidemiology plays a pivotal role in planning an appropriate empirical treatment for *Candida* infections.

Timely and appropriate antifungal therapy is crucial for patient outcome: any delay is associated with an increase of mortality.⁶

Another independent variable associated with mortality is represented by the production of biofilm, the extracellular matrix produced by microorganisms in particular conditions, typically in the presence of foreign bodies such as indwelling devices and prosthesis.⁷ Azoles lack any significant activity against biofilm while echinocandins show variable efficacy; amphotericin B shows *in vitro* a consistent activity.⁸

Treating infections due to biofilm-forming *Candida* with highly active anti-biofilm antifungal agents like caspofungin seems to favorably influence patient survival with respect to fluconazole therapy.⁹

To ensure a timely antifungal treatment, an empirical, fever-driven approach is often used.¹⁰ This strategy, although largely adopted in the setting of patients with hematologic malignancies, did not show consistent efficacy in ICU patients. Schuster *et al.*¹¹ compared high-dose intravenously fluconazole (800 mg) to placebo in persistently febrile ICU patients not responding to antibacterial therapy. Quite unexpectedly, no difference was documented between the two treat-

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Key words: antifungals, invasive candidiasis, Internal Medicine Wards.

Received for publication: 29 July 2014.
Accepted for publication: 30 July 2014.

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Italian Journal of Medicine 2014; 8:221-224
doi:10.4081/ijm.2014.536

ment groups. Two possible explanations for this result were represented by the intrinsic limit of fluconazole antifungal activity and by the patient population unselected for high risk of IC.

Several predictive algorithms and score systems have been proposed to identify patients at higher risk of candidemia and invasive candidiasis. The *Candida score* by León *et al.*¹² is based on total parenteral nutrition (one point), recent surgery (one point), multifocal *Candida* colonization (one point), and severe sepsis (two points). With a score of 3 or greater, the relative risk of developing fungemia and invasive candidiasis is increasing and the start of empirical antifungal therapy is justified. However, this score has been validated in the Surgery and ICU setting and may be less useful for patients cared for in Medical Wards.

Systematic efforts to obtain an etiologic diagnosis have to be made to ensure an appropriate treatment. Culture methods still play a key role in the diagnosis of IC. However, sensitivity of blood culture in case of candidemia is around 50%. Recently Tascini *et al.* showed that cultures taken from arterial blood presented a shorter time to positivity (TTP) with respect to blood cultures drawn from peripheral vein; it is noteworthy that the time sparing was around 12 h. However, no significant difference was documented in TTP for arterial blood and blood drawn from central venous catheter.¹³

Serological methods for the diagnosis of invasive candidiasis include the combined detection of mannan antigen and anti-mannan antibodies and the β -glucan antigen. Mannan is a genus specific antigen produced by *Candida* in the early stages of the infection, but a lytic enzyme clears it rapidly from the serum. Sensitivity may be increased by the concomitant search of the anti-mannan antibodies that, becoming positive at a later stage, are more longer detectable.¹⁴

The β -glucan is a panfungal test useful for the detection of *Candida*, *Aspergillus* and *Pneumocystis jiroveci*. The test has a low specificity due to several causes of false positive results. Trend in the β -glucan levels seems to be useful in predicting the outcome of invasive candidiasis and the response to antifungal therapy.¹⁵

Significant advances have also been made in polymerase chain reaction methods for rapid detection of *Candida* in blood specimens but further evaluation of this approach in different clinical settings is needed.¹⁶

Guidelines for the treatment of IC has been proposed by the Infectious Diseases Society of America (IDSA) in 2009⁴ and by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID)¹⁰ in 2012. Both guidelines emphasize the role of echinocandins; the ESCMID guidelines also suggest a severe downgrading for fluconazole and conventional amphotericin B.

Recently, an Italian consensus for IC management has been issued (ITALIC).¹⁷ The authors focused on patient stratification in terms of risk factors for IC and clinical severity. According to the ITALIC, echinocandins are indicated as first-line treatment of IC because of fungicidal activity, activity against strains producing biofilms, activity against fluconazole-resistant strains, favorable safety profile and low propensity for drug-drug interactions.

The choice between the three echinocandins should be based on the specific indications, pharmacokinetic/pharmacodynamic profile, clinical experience and cost.

Caspofungin, the first echinocandin introduced in the Italian market, is the most widely used echinocandin with a large amount of data related to the efficacy and safety profile; anidulafungin lacks any metabolism (bio-degradation) and may be useful in patients with severe liver disease; micafungin, although limited by the European Medicines Agency warning, is indicated for neonates.

As an alternative, for critically ill patients, the use of liposomal amphotericin B may be considered; voriconazole should be reserved for selected cases.

In stable patients, fluconazole may represent a possible choice.

In case of *Candida* endophthalmitis, pyelonephritis and meningitis, voriconazole is the drug of choice.

Patients should be treated for at least 14 days after the last positive blood culture and even more in deep-seated infections.

De-escalation from an echinocandin to intravenous or oral fluconazole should be encouraged when the patient is clinically stable and the isolated strain is susceptible.

Intravascular non-surgical catheters should be removed in all patients with documented catheter-related fungemia.

Main characteristics of antifungals are summarized in Table 1.

The choice of an antifungal therapeutic strategy has a deep impact on the hospital epidemiology: Lortholary *et al.* reported that the extensive use of caspofungin decrease the isolation of *C. albicans* from 56% to 21% and increase *C. glabrata* from 18% to 35% and *C. parapsilosis* from 13% to 31%.¹⁸ Similar epidemiological modifications were observed using fluconazole. The risk of infection with an isolate with decreased susceptibility to fluconazole or caspofungin is associated with the recent exposure to these drugs.¹⁹

A major concern for the extensive use of echinocandins is represented by cost.

Cost is definitely higher with respect to fluconazole but similar to the cost of true competitors. In particular echinocandins cost more than voriconazole but less than liposomal amphotericin B.

Table 1. Summary of the main characteristics of antifungal agents for treating invasive candidiasis/candidemia.

	Fluconazole	Echinocandins	Amphotericin B
Spectrum of activity	Limited	Wide	Wide
Antifungal activity	Fungistatic	Usually fungicidal	Fungicidal
Anti-biofilm activity	Low	Variable	Consistent
Safety	Good	Very good	Nephrotoxicity
Evidence from RCTs	Inferior to echinocandins	Good	Adequate
Guidelines ECCMID	CI	AI	BI (liposomal)
Cost	Very low	Medium	Very high (liposomal)

RCTs, randomized controlled trials; ECCMID, European Congress of Clinical Microbiology and Infectious Diseases.

Despite a higher cost, echinocandins (aniludafungin, micafungin) have demonstrated to reduce mortality and overall in-hospital costs compared to fluconazole, both in the setting of empirical and definite treatment of IC.²⁰⁻²² Notably, some authors suggest that caspofungin is more cost-effective than fluconazole in the empiric treatment of IC when fluconazole resistance is higher than 25% in hospital, reinforcing the importance of knowing the local epidemiology.²³

No difference between micafungin and caspofungin has been demonstrated in terms of cost-effectiveness in the treatment of candidemia and IC.²⁴

Caspofungin has been proved to be more cost effective than liposomal amphotericin B in the empirical treatment of invasive fungal infections and the treatment of candidemia, not only for a lower cost of drug, but also for a lower incidence of renal failure;^{25,26} similar data have been reported for micafungin.²⁷

De-escalation strategy (initial treatment with echinocandins, followed by fluconazole when possible) has been proved to reduce mortality and improve the outcome of IC with a significant cost saving, compared to escalation strategy (initial treatment with fluconazole).²⁸

However, a timely start of a broad-spectrum antifungal with fungicidal and anti-biofilm activity, switching to a cheaper alternatives according to microbiology results and clinical status is considered to be the main determinant of cost-effectiveness, regardless the antifungal agent.²⁹

In conclusion, IC is a relevant problem also in Medical Wards.

Early identification of patients at risk, knowledge of local epidemiology and prompt efforts to define etiologic diagnosis are pivotal to ensure appropriateness. Start with an echinocandin and switch to fluconazole when possible, seems to represent a useful strategy for the management of IC.

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