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Review

Fluconazole therapy for treatment of invasive candidiasis in Intensive Care patients. Is it still valid from a pharmacological point of view?

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Abstract

Fluconazole – antimycotic belonging to the first generation azoles – is widely used as treatment for invasive candidiasis and candidemia in numerous clinical settings as Neonatal Intensive Care Unit (NICU) and adult Intensive Care Unit (ICU), as well as oncology, onco-hematology and solid organ transplantation. More recently use of antimycotics has spread to medical divisions, where fungal infections represent an emerging problem due to population's ageing, malnourishment and important comorbidities. Fluconazole is effective against numerous *Candida* species, particularly against *albicans*, *tropicalis* and *parapsilosis* strains. On the other hand, *C. krusei* is intrinsically resistant to fluconazole and *C. glabrata* can be sensitive or resistant in a dose dependent fashion. Epidemiological variability is noteworthy and depends on the geographical location of the institution, the clinical setting, and the frequency and intensity of fluconazole employment for invasive candidiasis. In many ICUs fluconazole sensitive *C. albicans* is cultured in 50% of positive samples, while the remaining 50% show growth of variably sensitive fungal species, often resistant to fluconazole. Due to increasingly frequent emergence of resistant strains of *Candida spp.*, American guidelines (IDSA) in 2009, and European ones (ESCMID) in 2012, recommended substitution of fluconazole with echinocandines as first line therapy in patients with severe disease, as defined by an APACHE II score greater than 15. Thus fluconazole must be limited to low risk cases, treatment of sensitive strains and de-escalation from echinocandin therapy, after microbiological diagnosis and drug resistance profile characterization.

Keywords

Fluconazole, invasive candidiasis, ICU, APACHE II score, sensitivity, resistance.

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Pharmacological profile of Fluconazole

Due to its efficacy and safety for prolonged use – even at high dosages – fluconazole has been extensively used as first line drug in prophylaxis and treatment of invasive candidiasis [1, 2]. It's a fungistatic agent that acts inhibiting selectively fungal cytochrome P450 (CYP)-dependent enzyme lanosterol 14α-demethylase, causing depletion of cell membrane ergosterol, an essential component of fungal cell wall. Inhibition of ergosterol synthesis impairs membrane fluidity, and leads to accumulation of toxic 14α-methylated sterols, resulting in growth arrest and eventual fungal cell death [3, 4]. It is active against 90% of *Candida* species. Nevertheless, increasing drug resistance has been witnessed, especially towards less common species (**Tab. 1**). Among strains most frequently isolated in ICU, *C. krusei* appears to be intrinsically resistant to fluconazole, while *C. glabrata* can be resistant or sensitive in a dose related fashion. Fluconazole exists both in oral and intravenous formulations and shows – as its azoles congeners – an excellent oral availability, linear pharmacokinetics unaffected by gastric pH nor content [6, 7]. It is hydrophilic, with low protein bounded fraction (11-13%) and a volume of distribution (DV) equal to total body water [6]. An important feature of the drug is its capacity to concentrate in cerebrospinal fluid, as much as 50-60% of plasmatic concentration: this makes it useful in treatment of *Candida spp.* infections of the central nervous system [7]. When administered at its standard dosages of 200-400 mg/die, 11% of fluconazole undergoes hepatic metabolism, while 80% is excreted unmodified with urine [8]. Drug's plasmatic half-life ranges from 30 hours in patients with normal renal function to 90 or more hours in patients with creatinine clearance lower than 20 ml/min. It is therefore easy to understand that its posology has to be opportunely reduced in patients affected by renal failure. Generally, in patients with creatinine clearance from 20 to 60 ml/min, a 50% dose reduction – obtained halving the dose or doubling administration intervals – is to be considered adequate. Moderate inhibition of CYP 3A4, CYP 2C8/9 and CYP 2C19 must be taken into account, especially in patients assuming complex therapies (as ICU patients generally are), which could interfere. Clinical efficacy correlates tightly with area under the curve (AUC) of concentration over a 24 hour time span, divided by minimal inhibiting concentration (MIC) for fluconazole. Animal studies enlightened that with azoles, an AUC/MIC ratio of 25 is necessary to obtain 50% of maximal efficacy. An AUC/MIC ratio from 25 to 50 is required to obtain a mean drug concentration equal to twice the MIC [9]. Azoles have a narrow therapeutic range, thus overlooking their pharmacokinetics most likely makes the eventuality of plasmatic levels either below the range of efficacy or oppositely too elevated (possible toxic adverse reactions). Fluconazole posology for an adult with normal renal function, requires a loading dose of 12

Table 1. Candida species sensitivity to antifungal drugs. Modified from Pappas et al., 2009 [5].

Candida species	Fluconazole	Voriconazole	Anphotericine B	Echinocandin
Candida albicans	S	S	S	S
Candida glabrata	From S-DD to R	From S-DD to R	From S to I	S
Candida tropicalis	S	S	S	S
Candida parapsilosis	S	S	S	From S to R
Candida krusei	R	S	From S to I	R
Candida lusitaniae	S	S	From S to R	S
Candida guillermondii	From S to R	From S to R	From S to R	From I to R

S: sensitive; DD: dose dependant; R: resistant; I: intermediate.

mg/kg followed by a daily dose of 6 mg/kg. The dose is halved when creatinine clearance is less than 60 ml/min. Monitoring plasma concentration is usually unnecessary and can be done occasionally when considered useful to improve the therapeutic effect [10]. The empiric use of fluconazole (before microbiological identification of the specific strain and its drug sensitivity is available) is becoming increasingly risky, given the frequent finding of *non albicans* strains in ICU patients biological samples [11, 12].

Invasive candidiasis epidemiology in ICU

Candidemia is the fourth cause of blood stream infection in ICU patients in North America [13]. Similar data are found in Europe. A recent French study observed that 33% of ICU patients presents candidemia, invasive candidiasis or both [14]. A multicenter prospective, observational study conducted in 38 Italian ICUs between 2006-2008 showed a median rate of candidemia of 10.08 per 1,000 admissions, 40% of them were sustained by *non albicans* species [15]. *Candida* species diffusion can be differently distributed among various institutions, as well as their characteristic sensitivity and resistance to fluconazole. In the last two decades many institutions witnessed the progressive reduction in incidence of *C. albicans*, paralleled by the increment of *non albicans* species, which in some ICU represent the 50% of isolated specimens. More frequently isolated *non albicans* species are *C. parapsilosis*, *C. glabrata*, *C. tropicalis* and *C. krusei* [14]. Less frequently *C. lusitaniae*, *C. guillermondii* e *C. rugosa* are the isolated species. *C. glabrata* and *tropicalis* are rare in NICU, while *C. parapsilosis* accounts for as much as 30% in this setting [16, 17]. Numerous studies have been carried out to justify the reasons why there has been a shift in the prevalence from *C. albicans* to *non albicans* species in ICU environment. Extensive fluconazole use is one of the possible causes, for the increased resistance to the drug as well as for the progressive substitution of *albicans* species with *non albicans* drug resistant strains as principal etiologic agent of infection. Furthermore wide use of intravascular devices and parenteral hypernutrition are possible causes for infection by emerging *non albicans* species [18, 19]. Though any hospitalized patient can suffer from *Candida spp.* infection, subjects affected by cancer, hematologic disease or immunodeficiency are more prone to it. Usually infection is endogenous, moving from skin or mucous membranes into the bloodstream then disseminating throughout the organism [20]. Another cause of proliferation and diffusion of fungi in non neutropenic patients, is the wide use of broad-spectrum antibacterial therapy. In ICU patients many risk factors have been identified, such as trauma, parenteral nutrition, intravascular catheters, immunosuppressive drugs and corticosteroids, skin or intestinal barrier damage. The last two in particular, are extremely relevant (**Tab. 2**). Candidemia diagnosis is based on repeated hematic cultures. Culture sensitivity is not optimal and time span to obtain a diagnosis is often prolonged in many institutions. Among new proposed exams, only b-D-glucan is cited as a diagnostic tool for candidemia in IDSA guidelines [5]. Though considered promising, till now no controlled studies have been carried out on its efficacy and elevated costs and false positive rates among ICU patients may limit its utility.

Table 2. Risk factors for candida infection in ICU. Modified from Bassetti et al., 2010 [21].

Patient population	Risk factors
All patients	Abdominal surgery, intravascular catheters, total parenteral nutrition, broad spectrum antibiotics, immunosuppression and corticosteroids, acute kidney injury, diabetes, solid organ trasplantation, hemodialysis, acute pancreatitis
ICU patients	Prolonged stay (> 96 h), candida colonization (expecially if multifocal), high APACHE II score, low birth weight (neonatal intensive care unit)

Therapy of candidiasis

As it takes a long time to have a certain diagnosis, strategies to begin appropriate therapy as soon as possible in patients at high risk for *Candida spp.* infections or probably infected have been developed. These are represented by antimycotic drug prophylaxis in patients at risk for infection, and empiric and preemptive therapy. Antimycotic prophylaxis is well documented in settings such as oncology, oncohematology and neonatology, while guidelines do not recommend it for candidosis and candidemia prevention in ICU [5], although studies reporting a reduction in fungal infections in patients under prophylaxis can be found in literature. No

clear mortality reduction has been proven by these studies. Disadvantages of fluconazole prophylaxis include toxicity from prolonged use, environmental selective pressure on local flora and emergence of resistant strains [22]. Fluconazole prophylaxis is only recommended in specific ICUs, with a rate of infection superior to 1-2% and in patients at high risk for infection [5]. Empiric therapy, defined as administration of antimycotics in presence of persistent fever refractory to therapy, has been proposed in order to anticipate treatment and reduce mortality in neutropenic and non neutropenic patients [5]. This approach can cause a significant and not always necessary increment in the number of treated cases. So preemptive therapy appears till now more promising. It is defined as the introduction of antifungal therapy when specific risk factors are identified: ICU stay > 96 h, broad-spectrum antibiotic therapy, severe sepsis, gastrointestinal surgery, total parenteral nutrition, clinical evidence for multifocal *Candida spp.* colonization or positive b-D-glucan assay. This strategy is meant to permit an early treatment in high risk cases while avoiding many unnecessary treatments [21]. Nevertheless, though promising, its efficacy still needs to be proven by clinically and statistically adequate prospective studies. In cases documented by positive cultures – if an antimycogram is available – treatment is easier. The drug of choice is the one characterized by the highest sensitivity, lowest adverse reaction rate and severity and lowest cost. Unfortunately, even when bloodstream invasion has been documented, exact *Candida spp.* characterization and sensitivity are not always available in short time. For these reasons and according to epidemiological data documenting a constant increase in the incidence rate of *non albicans* species and fluconazole resistant strains, 2009 ISDA and 2012 ESCMID guidelines [23] extend to high risk non neutropenic patients the recommendation of echinocandins as first line drugs for treatment of invasive candidiasis and candidemia. In patients characterized by moderate-severe disease, high APACHE II score, hemodynamic instability and likely cardiac involvement, echinocandins are recommended due to their high fungicidal activity on *Candida spp.* strains. Therapy can be modified later, according to sensitivity demonstrated by cultural exams, shifting to fluconazole in stable sensitive to treatment patients [5, 24, 25]. Echinocandins are contraindicated in *C. parapsilosis* infections, as resistance by this strain has been reported [26]. It is important to remember that after cultures become negative and important clinical improvement is obtained, oral antifungal therapy is recommended for the next 14 days, with single most suitable drug for *Candida* single species (step down therapy). Two more issues must be kept in mind when dealing with treatment of a mycotic infection. Though a clinical trial conducted on 842 adult patients failed to demonstrate any benefit from early removal of intravascular catheters [27], guidelines and expert opinions judge necessary and wise removal of intravascular devices when blood cultures are positive for *Candida spp*. The second problem is represented by the fact that many *Candida* species produce biofilm, significantly contributing to their virulence and persistence of infection [28]. Biofilm producing strains show higher resistance to fluconazole therapy and respond better to treatment with amphotericine B than echinocandins [29].

Conclusions

Candida infections are increasing worldwide and are becoming a frequent cause of disease not only in ICU or oncohematologic settings, but even in medical divisions, among the elder malnourished population and in patients affected by chronic obstructive pulmonary disease. Mycotic infection epidemiology is evolving and *non albicans* fluconazole-resistant strains are emerging. Fluconazole is still useful in treatment of many *Candida spp.* strains and can be used in low risk patients and in institutions where resistant strains have not emerged. In moderate-severe risk patients, or in hospitals where resistant strains are frequently isolated, echinocandins must be considered as first line treatment, and eventually substituted only after patient stabilization and isolation and characterization of the responsible fungus. Oral therapy with fluconazole or other appropriate azoles (step-down) – if active against isolated strain – can be considered when blood cultures become negative. There is still not complete agreement on optimal management for ICU patients with suspect candidemia. Prophylaxis is not recommended, as it exposes to risk of unnecessary treatment and is a likely cause of emergence of resistant strains. Empiric therapy based on local epidemiology and severity of illness is a widely used approach, but implies as well a high number of unnecessary treatments. Preemptive treatment seems to be promising, as it minimizes the risk of late treatment and reduces the number of patients treated unnecessarily. Low sensibility of blood cultures and the long time they require to be performed make

desirable the development of biomarkers of fungal infections. B-D-glucan is promising but no studies have clearly demonstrated its potentialities.

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Declaration of interest

The Authors declare that there is no conflict of interest.

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