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Management of invasive fungal infections in non-neutropenic patients

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ABSTRACT

Invasive fungal infections (IFIs) are documented in critically ill, non-neutropenic patients, in intensive care units (ICUs) and surgical wards, but also in non critical patients cared for in medical wards.

Candida spp. infections mainly occur in patients undergone to major abdominal surgery, receiving broad spectrum antibiotic therapy and after a long ICU stay. A more favorable outcome is reported for fungemia due to *C. parapsilosis*; the worse prognosis is associated with *C. tropicalis* infections.

Any delay in starting an appropriate antifungal treatment is associated with an increase in mortality rate of candidemia. When used as empirical therapy, fluconazole did not show any superiority to placebo and was inferior to anidulafungin in the treatment of documented candidemia/invasive candidiasis. ECCMID guidelines emphasize the role of echinocandins and, as a reliable alternative, suggest the use of liposomal Amphotericin B. Although with more nephrotoxicity with respect to echinocandins, Amphotericin B showed a systematic fungicidal and anti-biofilm activity against *C. albicans* and non-*albicans* species.

Invasive Aspergillosis have been also reported in non neutropenic patients with chronic obstructive pulmonary disorders receiving steroid therapy for respiratory failure, in pts with severe liver failure and in solid organ transplant patients. Treatment of choice for Invasive Aspergillosis is represented by Voriconazole, but liposomal Amphotericin B represents a reliable alternative when azole use is contraindicated.

Invasive fungal infections (IFIs) are a well known, life-threatening complication of neutropenia in haematologic patients. However, IFIs also affect various types of non-neutropenic patients, particularly those admitted in the hospital in critical conditions [1].

Candida spp. infections are mainly documented in intensive care units (ICUs), especially in patients undergone to major surgery, receiving broad spectrum antibiotic therapy and having a long ICU stay.

Invasive Aspergillosis have been reported in pts treated with steroid therapy due to chronic obstructive pulmonary disorders with severe respiratory failure, in pts with severe liver failure, in solid organ transplant pts and a few cases have been also documented as a complication of H1N1 influenza virus infection.

The population of patients admitted in ICUs is extremely heterogeneous in terms of age and degree of risk of infection. The range goes from otherwise young and healthy multiple trauma patients to heavily immunocompromised patients.

The EPIC II study provides extensive epidemiological data on the impact of *Candida* infections in ICUs (15,000 patients admitted to 1,250 ICUs in 76 countries). Prevalence of *Candida* is around 7 cases per 1,000 patients with an alarmingly high mortality, namely 40%, higher than the mortality caused by bacterial infections [2].

It is noteworthy that *Candida* infections are not only documented among ICU patients but also in patients admitted in internal medicine and surgery wards.

In the Austrian case series [3] reporting on 250 cases of documented *Candida* infections, over 100 were diagnosed in patients admitted to internal medical wards. The study underlines that in medical wards there are more cases of documented candidemia than in surgical units and ICUs. Candidemia should therefore be considered in the differential diagnosis of sepsis, especially in the elderly and frail patient with multiple co-morbidities.

Candida albicans is responsible of 60% of cases of In-

vative Candidiasis while the non-albicans species are represented by *Candida glabrata* (15-16%), *Candida tropicalis* (7.5%) and *Candida parapsilosis* (7%) [4].

Knowing the local epidemiology is crucial in planning an appropriate empirical treatment for *Candida* infections.

Candida glabrata has a dose-dependent susceptibility to fluconazole while *Candida krusei* has an innate resistance to this compound [5]. *Candida parapsilosis*, often associated with central venous catheter infections is less susceptible in vitro to echinocandins.

Amphotericin B has a good antifungal activity against all isolates of *Candida albicans* and virtually all the non-albicans species.

The outcome of candidemia is closely related to the *Candida* species: fungemias with a more favourable outcome are those caused by *C. parapsilosis*, followed by those due to *C. albicans*, *C. glabrata*, *C. tropicalis* and *C. krusei* [6].

Timely and appropriate antifungal therapy plays a pivotal role in the patient outcome: the later the adoption of an appropriate antifungal treatment, the higher the mortality due to fungemia and invasive candidiasis [7]. Another independent variable associated with high mortality is represented by biofilm-producing *Candida* infection [8]. Echinocandins show variable efficacy in vitro against the *Candida* biofilms while Amphotericin B has a systematic activity [9]. Treating biofilm-producing *Candida* infections with highly active anti-biofilm antifungal agents (echinocandins, amphotericin B) favorably influences the patient survival with respect to fluconazole therapy [10].

To ensure a timely antifungal treatment empirical approach is often used [11]. The empirical strategy has been extensively tested in ICU patients but the evidence of efficacy is well below that obtained in hematological patients. In the Schuster's study [12] fluconazole did not show superiority to placebo when used for empirical therapy in ICU patients unselected for a higher risk of invasive candidiasis.

Several predictive algorithms and score systems have been proposed to identify patients at higher risk of candidemia and invasive candidiasis. The "Candida score" by Leon [13] is based on total parenteral nutrition (one point), recent surgery (one point), multi-focal *Candida* colonization (one point), and severe sepsis (two points). With a score below 3 the risk of developing invasive candidiasis is very low, but 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.

Serology methods for the diagnosis of invasive candidiasis include the combined detection of mannan antigen and anti-mannan antibodies and the beta-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 research of the anti-mannan antibodies that becomes positive

at a later stage. The beta-glucan is a panfungal test that is useful for the detection of *Candida*, *Aspergillus* and *Pneumocystis jirovecii*. The test has a lower specificity due to several causes of false positive results. Trend in the beta-glucan levels seems to be useful in predicting the outcome of invasive candidiasis and the response to antifungal therapy [14]. Significant advances have also been made in nucleic acid-based detection methods for rapid detection of *Candida* in blood specimens but further evaluation of the feasibility and real helpfulness of these approach in different clinical settings is warranted [15].

Guidelines for the treatment of Invasive Candidiasis has been proposed by the Infectious Diseases Society of America (IDSA) in 2009 [5] and by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) [11] in 2012. Both guidelines emphasize the role of echinocandins and the ESCMID Guidelines also suggest a severe downgrading of fluconazole and conventional amphotericin B.

The choice of an antifungal therapeutic strategy has a deep impact on the ecology of the ward and of the whole hospital: with the extensive use of caspofungin, a decrease in the isolation of *C. albicans* from 56% to 21% was observed and, at the same time, *C. glabrata* increased from 18% to 35% and *C. parapsilosis* from 13% to 31%. Similar epidemiological modifications were observed using fluconazole. The risk of infection with an isolate that has decreased susceptibility to fluconazole or caspofungin is associated with the recent exposure to these drugs [16].

In the Microbiology Laboratory of Pisa we evaluated the fungistatic and fungicidal activity of several antifungal agents towards 60 clinical isolates of *Candida* spp. The MIC₅₀ for *C. albicans* and non-albicans species was adequate for Amphotericin B, echinocandins and azoles with the exception of fluconazole. However, the only drug showing a constant fungicidal activity towards *C. albicans* and non-albicans species was Amphotericin B (unpublished data).

Due to broad-spectrum of antifungal activity, fungicidal activity and activity against biofilm-forming *Candida* infections, Amphotericin B should be considered as a possible therapeutic option; the liposomal formulation today represents the most costly but better tolerated formulation.

IDSA Guidelines [5] indicate liposomal Amphotericin B as an alternative to fluconazole and echinocandins for the empirical and targeted treatment of invasive candidiasis both in non-neutropenic and neutropenic patients.

According to the ESCMID Guidelines [11] liposomal Amphotericin B is moderately recommended (B1) for the treatment of invasive candidiasis because of its activity and safety profile. Amphotericin B deoxycholate has a very poor tolerance profile. Liposomal Amphotericin B has been compared to Micafungin [17] showing similar efficacy and lower tolerability. Liposomal Amphotericin B has the best safety profile

among polyenes [18].

The diagnosis of Aspergillosis in ICUs patients is difficult. It's based on culture isolation, serology and clinical suspicion. COPD patients on steroids for a long time, on mechanical ventilation, with malnutrition and impairment of the ciliary function seems to represent a subgroup of high risk patients. The diagnostic radiological criteria are nonspecific and the isolation of *Aspergillus spp* from respiratory samples and the detection of galactomannan in serum and respiratory samples play a pivotal role [19].

Therapy of choice for Invasive Aspergillosis is represented by Voriconazole, but liposomal Amphotericin B is a reliable alternative, becoming the first choice when the azole use is contraindicated [20].

Therapeutic drug monitoring (TDM) is recommended for the optimal use of itraconazole, posaconazole and voriconazole. TDM requires an appropriate laboratory. Voriconazole through levels should be maintained above 1 mg/l for adequate efficacy and less than 5

mg/l for preventing toxicity.

The AmBiLoad study [21] compares 3mg/Kg against 10 mg/Kg of liposomal Amphotericin B and showed comparable results with higher rates of nephrotoxicity in the high-dose regimen.

Nebulized liposomal Amphotericin B may play a role in the treatment of patients with corticosteroid-dependent allergic bronchopulmonary aspergillosis (ABPA) and for prophylaxis and management of pulmonary Aspergillosis [22].

Invasive fungal infections in non-neutropenic patients affect not only ICU patients but also patients admitted to other wards, especially internal medicine. The infections observed in these settings are represented not only by *Candida* but also by molds such as *Aspergillus spp*.

A multidisciplinary approach and systematic cooperation between the microbiology lab and clinicians are recommended to fight successfully the challenge of IFI in non-neutropenic patients.

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