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Original article

Predictors of choice of initial antifungal treatment in intraabdominal candidiasis

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ABSTRACT

Intraabdominal candidiasis (IAC) is the second most frequent form of invasive candidiasis, and is associated with high mortality rates. This study aims to identify current practices in initial antifungal treatment (IAT) in a real-world scenario and to define the predictors of the choice of echinocandins or azoles in IAC episodes. Secondary analysis was performed of a multinational retrospective cohort at 13 teaching hospitals in four countries (Italy, Greece, Spain and Brazil), over a 3-year period (2011–2013). IAC was identified in 481 patients, 323 of whom received antifungal therapy (classified as the treatment group). After excluding 13 patients given amphotericin B, the treatment group was further divided into the echinocandin group (209 patients; 64.7%) and the azole group (101 patients; 32.3%). Median APACHE II scores were significantly higher in the echinocandin group (p 0.013), but IAT did not differ significantly with regard to the *Candida* species involved. Logistic multivariate stepwise regression analysis, adjusted for centre effect, identified septic shock (adjusted OR (aOR) 1.54), APACHE II >15 (aOR 1.16) and presence in surgical ward at diagnosis (aOR 1.16) as the top three independent variables associated with an empirical echinocandin regimen. No differences in 30-day mortality were observed between groups. Echinocandin regimen was the first choice for IAT in patients with IAC. No statistical differences in mortality were observed between regimens, but echinocandins were administered to patients with more severe disease. Some disagreements were identified between current clinical guidelines and prescription of antifungals for IAC at the bedside, so further educational measures are required to optimize therapies. **L. Lagunes, CMI 2016;22:719**

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Introduction

Candida is the third most frequently isolated pathogen in critically ill patients [1]. Intraabdominal candidiasis (IAC) is the second most frequent form of invasive candidiasis after bloodstream infection, and it has been associated with high mortality rates of between 25% and 40% [2–6]. The recovery of *Candida* from the abdominal cavity has a worse prognosis in patients with peritonitis [7,8]. The clinical criteria for defining IAC are not specific, although a recent European consensus of experts shortened the definition of an IAC episode [9]. International guidelines focus mostly on candidaemia and make little reference to antifungal therapy for IAC [10–12]. Delay in the initiation of treatment for invasive candidiasis has been associated with increased mortality [13–15]. Recently, in a large multinational multicentre study carried out by our group focusing only on IAC cases [16] the high mortality rate obtained (~27%) underlined the importance of source control in patients with IAC and septic shock. It remains unclear which patients should receive empirical treatment, and which patients are at the highest risk for developing invasive candidiasis. According to current guidelines, appropriate treatment is based on azoles, polyenes or echinocandins; however, the differences between these groups in the treatment of IAC have not been assessed.

The objective of this secondary analysis is to identify current practice in initial antifungal treatment (IAT) of IAC episodes in a 'real-world scenario' and to define the predictors of the choice of one or another antifungal.

Materials and methods

Multinational multicentre retrospective cohort study conducted at 13 teaching hospitals in four countries (Italy, Greece, Spain and Brazil), over a 3-year period (2011–2013). All cases were recorded continuously. Informed consent was waived and approved at each participating centre ethics committee due to the observational characteristics of the study. An episode of IAC was defined according to the 2013 European consensus [9], as follows:

(a) *Candida* detection by direct microscopy examination or growth in culture from purulent or necrotic intraabdominal specimens obtained during surgery or by percutaneous aspiration
(b) *Candida* growth from bile, intra-biliary duct devices and biopsy of intraabdominal organs
(c) *Candida* growth from blood cultures in a clinical setting of secondary and tertiary peritonitis in absence of any other pathogen and
(d) *Candida* growth from drainage tubes only if placed less than 24 h before the cultures.

Patients' demographic characteristics and infection-related variables were collected from hospital medical records, microbiology and pharmacy databases. Demographic data included age, gender, co-morbidities, immunosuppressive agents, Acute Physiology and Chronic Health Evaluation (APACHE II) score measured within the first 24 h of culture positivity, and intra-hospital location at the time of diagnosis. Infection-related variables included source of infection, *Candida* species, prior antibiotic exposure (>7 days in the past 30 days), time to initiation of antifungal therapy, and type of antifungal therapy. Adequate abdominal source control was defined as:

(a) Drainage of infected fluid collections
(b) Debridement of infected tissue and the removal of devices or foreign bodies and
(c) Definitive measures to correct anatomic derangements resulting in ongoing microbial contamination and to restore optimal function within 48 h of IAC diagnosis.

Treatment was considered adequate when the causative organism was ultimately shown to be susceptible. The following antifungal doses were considered adequate: (a) fluconazole 800 mg loading dose (for obese patients body mass index >30 kg/m^2: 1200–1600 mg) followed by a daily dose of at least 400 mg (600–800 mg for patients with body mass index >30 kg/m^2), (b) caspofungin 70 mg loading dose (100 mg in obese) followed by 50 mg/day (80 mg/day), (c) micafungin 100 mg/day, and (d) anidulafungin 200 mg loading dose followed by 100 mg/day. *Candida* species were isolated using the BACTEC 860 system (Becton–Dickinson Inc., Sparks, MD, USA) and BacT/Alert 3D (BioMérieux, Marcy l'Etoile, France). The species were identified using API ID 32C system (BioMérieux) or Vitek 2 system (BioMérieux). If both systems produced inconclusive results, isolates were definitively identified using supplemental tests, e.g. the presence or absence of well-formed pseudohyphae on cornmeal–Tween 80 agar and growth at 42–45°C. The last test was also required to differentiate isolates of *Candida albicans* from those of *Candida dubliniensis*. Antifungal susceptibility testing for caspofungin, anidulafungin, micafungin, fluconazole, itraconazole and voriconazole was performed using the Sensititre YeasOne colorimetric plate (Trek Diagnostics Systems, Cleveland, OH, USA) or by agar diffusion using E-test strips (BioMérieux) and interpreted using CLSI breakpoints.

Population

Patients who received any antifungal were included in the treatment group. Those that did not receive treatment were excluded. Treated patients depending on IAT were further subdivided and assigned to echinocandin and azole groups; those who received amphotericin as IAT were excluded to safeguard the stability of the model due to the low proportion of cases (Fig. 1).

Statistical analysis

All tests of significance were two-tailed and p values $\leq$0.05 were considered statistically significant. Continuous variables were compared by the Student *t* test or analysis of variance for normally distributed variables and the Mann–Whitney *U* test or Kruskal–Wallis test for non-normally distributed variables. The chi-square or Fisher's exact test was used to compare categorical variables. Values were expressed as medians (25–75th centile) (continuous variables) or as a frequency of the group from which they were derived (categorical variables).

Multivariate stepwise analysis was performed, with initial antifungal treatment as the dependent outcome variable, and 0.05 was set as the limit for the acceptance or removal of new terms. All covariates that were statistically significant at 0.05 in the univariate analysis (see Supplementary material, Table S1) were included in the model. The model was adjusted to assess a possible centre influence, by stratification of cases at each centre that ensured a non-different distribution among them. Estimations were carried out at each stratum (centre) [18] and results are expressed as adjusted OR (aOR). Statistics were performed using SPSS, version 21.0 for Windows (SPSS, Inc., Chicago, IL, USA) and R commander (Fox, 2005), version 0.999375-38.

Results

In this 3-year period, 481 cases of IAC were recorded and included in the analysis. In all, 323 patients received antifungal