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;■:1**

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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 ≤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
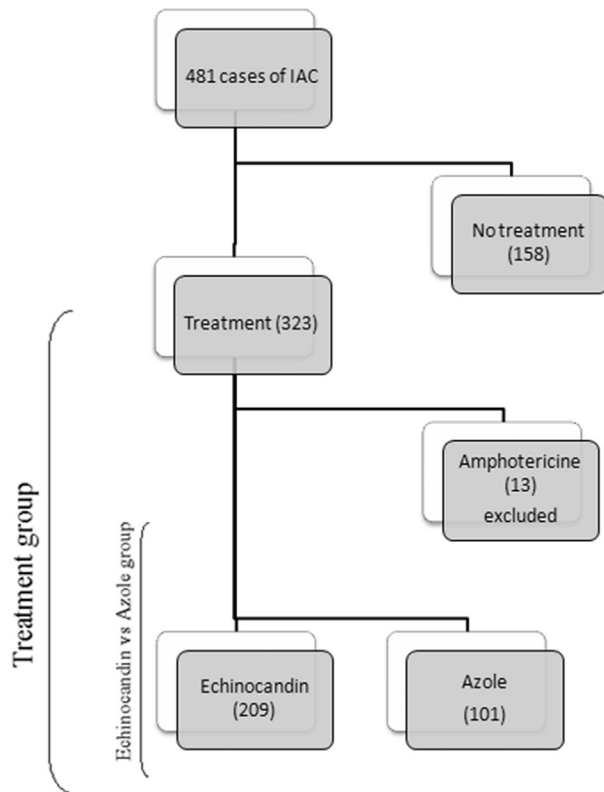
Fig. 1. Total population and treatment group, Echinocandin versus azole group; after exclusion of no treated patients and those who received amphotericin.

treatment and were assigned to the treatment group; 209 of these (64.7%) received an echinocandin as IAT, 101 (32.3%) received an azole and 13 (4%) received amphotericin B. Table 1 summarizes the clinical characteristics of the treatment group. Males more frequently received azoles for IAC than echinocandins (69/101 (68.3%) versus 107/209 (51.2%) respectively, p 0.004). APACHE II score was higher in the echinocandin group (median 17, interquartile range 25%–75% 11–21) than in the azole group (median 16, interquartile range 25%–75% 8–20, p 0.013). Regarding infection types, patients with secondary peritonitis were more likely to receive echinocandins than azoles (44.7% versus 26.8%, p 0.001). Patients in the surgical ward at time of diagnosis more frequently received echinocandins (55% versus 37%, p 0.002); there were no differences associated with other wards. Patients with septic shock at the time of diagnosis more frequently received an echinocandin regimen (52.3% versus 39.6%, p 0.031). In contrast, patients with candidaemia and those with previous *Candida* colonization more frequently received an azole (27.3% versus 13.4%, p 0.003 and 40.4% versus 24.9%, p 0.006; respectively) (Table 2). Adequacy of treatment did not differ significantly (echinocandin group 84.7%, azole group 85.7%, p 0.91). IAT was not affected by the type of *Candida* species, and no difference in 30-day mortality was observed between groups (Table 3).

There was no statistical association between the prescription of antifungal therapy and the year when the IAC episode was recorded. Echinocandins were the most frequent IAT prescribed across the study period, followed by azoles (67.4% versus 32.6%, p 0.64). Differences in IAT according to geographical area zone are shown in the Supplementary material (Table S2).

In adjusted multivariate analysis stratified for the centre effect, the top three risk factors for prescription of an echinocandin were septic shock (aOR 1.54, 95% CI 0.88–2.70), surgical ward (aOR 1.16,

95% CI 0.62–2.19) and APACHE II score >15 (aOR 1.16, 95% CI 0.71–1.90). Azoles were more often prescribed in patients with previous *Candida* colonization (OR for echinocandin 0.57, 95% CI 0.32–1.00 p 0.053) and candidaemia (OR for echinocandin 0.54, 95% CI 0.28–1.04, p 0.068) though the differences were not statistically significant (Table 4).

Discussion

Patients with higher severity scores and septic shock at the time of diagnosis more frequently received an echinocandin as IAT, whereas a trend favouring azoles was identified in the presence of candidaemia or prior azole exposure.

As in a previous study [9] the proportion of patients with both IAC and candidaemia was about 15%, raising concerns on generalization of recommendations to non-candidaemic patients. The time required to have positivity for *Candida* sp. in blood cultures and the fact that only half of the cultures are positive in candidaemia make it difficult to initiate prompt, correct antifungal treatment. The reference standard for IAC diagnosis is the sterile collection of cultures from infected tissues; however, the procedures involved are invasive and may lead to unnecessary risks in unstable patients. In recent years, fungal biomarkers have emerged as promising tools in culture-negative subjects [19] for identifying patients at high risk of developing an IAC episode who are likely to benefit from early initiation and correct treatment [20,21].

The differentiation between contamination and infection when *Candida* is recovered from intraabdominal samples is currently under debate, but in any case the presence of this pathogen has been associated with poor prognosis [7,8]. Recently, an expert European consensus attempted to redefine IAC [9], and a subsequent report showed a high mortality associated with this condition [16]. In this scenario, the selection of a particular antifungal must include a number of factors: the host, the clinical situation at diagnosis, and treatment-related variables such as recent exposure to an antifungal agent, allergies, potential drug interactions, local epidemiology and resistance. Many of these variables were recorded and analysed in the present study. The impact of treatment on the outcome of patients with invasive candidiasis has been widely assessed, and delay and inadequacy of treatment have been associated with poor outcome [13–17]; however, most previous randomized control trials assessed primarily bloodstream infection due to *Candida* spp [22,23].

According to current Infectious Diseases Society of America and ESCMID guidelines, patients with invasive candidiasis must receive prompt, adequate treatment, and the decision should be based on the patient's clinical situation. It is strongly recommended that treatment with an echinocandin be initiated when septic shock, haemodynamic instability or high risk for an azole-resistant causal agent is suspected or present [10,11]. Among our patients with candidaemia, there was a non-significant trend towards the use of an azole regimen as IAT. Our analysis identified septic shock as an independent determinant for receiving an echinocandin-based regimen as IAT for IAC, in accordance with these guidelines, and observed a tendency to use it in patients with higher severity scores at diagnosis, but we did not find in IAC an association of echinocandin with previous azole exposure.

In the light of what is known, some studies have reported an increase in azole-resistant species when azole exposure is documented [24,25] and azole use under these conditions is not recommended. Interestingly, we observed a non-significant trend toward the use of an azole as IAT for IAC in cases of previous azole exposure and its use was safe. However, the incidence of resistance to fluconazole in our population remains relatively low (around 18.3%), whereas susceptibility of therapy in the azole group

Table 1
Clinical characteristics and differences in the treatment group

	ALL (n = 323)	Echinocandin (n = 209)	Azole (n = 101)	Ampho B (n = 13)	p[a]	p[b]
Age median (IQR)	63 (53–75)	63 (53–75)	61 (49–73)	60 (49–67)	<0.001	0.590
Male	182 (56.3)	107 (51.2)	69 (68.3)	9 (69.2)	0.011	0.004
APACHE II score median (IQR)	15 (9–20)	17 (11–21)	16 (8–20)	18 (15–23)	0.003	0.013
Dialysis	23 (7.1)	12 (5.8)	8 (7.9)	3 (23.1)		
SOT	19 (5.8)	8 (3.8)	9 (8.9)	2 (15.4)		
ESRD	24 (7.4)	18 (8.7)	5 (5)	1 (7.7)		
Solid tumour	127 (39.3)	86 (41.1)	36 (35.4)	5 (38.5)		
Haemato-malignancy	10 (3)	6 (2.4)	4 (4)	—		
Immunosuppression	54 (16.7)	33 (15.9)	16 (16)	5 (38.5)		
Steroids	68 (21)	47 (22.6)	15 (15)	6 (46.3)	0.025	0.120
COPD	39 (12)	29 (13.9)	9 (8.9)	1 (7.7)		
Heart disease	59 (18.2)	39 (18.8)	19 (19)	1 (7.7)		
Type					<0.001	0.053
Secondary peritonitis	121 (37.4)	93 (44.7)	26 (26.8)	2 (15.4)	0.001	0.001
Tertiary peritonitis	31 (9.6)	18 (8.7)	13 (13.4)	—		
Abdominal abscess	87 (26.9)	52 (25)	33 (34)	2 (15.4)		
Pancreatitis	37 (11.4)	19 (9.1)	14 (14.4)	4 (30.8)	0.039	0.202
Biliary tract	35 (10.8)	23 (11.1)	9 (9.3)	3 (23.1)		
Other	7 (2.1)	3 (1.4)	2 (2.1)	2 (15.4)	0.004	0.721
WARD					0.004	0.001
Internal medicine	26 (8)	17 (8.1)	7 (7)	2 (15.4)		
Surgery ward	160 (49.5)	116 (55.5)	37 (37)	7 (53.8)	0.007	0.002
ICU	98 (30.3)	61 (29.2)	34 (34)	3 (23.1)	0.611	0.423
Haemato-oncology	6 (1.8)	3 (1.2)	2 (2)	1 (7.4)		
SOT ward	3 (0.1)	2 (1)	1 (1)	—		
Other	29 (8.9)	10 (4.8)	19 (19)	—	<0.001	<0.001
Abdominal surgery	246 (76.1)	152 (72.7)	82 (81.2)	12 (92.3)	0.099	0.105
Reoperation	148 (45.8)	101 (48.3)	44 (43.6)	3 (23.1)		
Gastrointestinal perforation	71 (21.9)	49 (23.6)	20 (19.8)	2 (15.4)		
Anastomotic leak	72 (22.3)	45 (21.5)	25 (24.8)	2 (15.4)		
CVC	251 (77.7)	173 (82.8)	69 (68.3)	9 (69.2)	0.012	0.004
TPN	209 (64.7)	142 (67.9)	58 (58)	9 (69.2)	0.218	0.087
AB >7days	262 (81.1)	166 (79.4)	83 (82.2)	13 (100)	0.175	0.568
Prior azole exposure	54 (16.7)	24 (11.5)	23 (22.8)	7 (53.8)	<0.001	0.009
Prior Candida colonization	95 (29.1)	48 (24.9)	40 (40.4)	4 (30.8)	0.024	0.006
Candidaemia	63 (19.5)	27 (13.4)	27 (27.3)	9 (69.2)	<0.001	0.003
Septic shock	157 (48.6)	110 (52.3)	40 (39.6)	7 (53.8)	0.092	0.031
Vasopressor	154 (47.6)	106 (50.7)	42 (41.6)	6 (46.2)	0.318	0.131
Concomitant bacteria	217 (67.1)	148 (71.2)	64 (64)	5 (38.5)	0.033	0.204
Adequate source control	198 (61.3)	134 (64.1)	64 (64.6)			
CASPO S	280 (86.6)	194 (98)	77 (98.7)	9 (75)	<0.001	0.679
FLUCO S	223 (69)	154 (83.2)	60 (77.9)	9 (75)	0.042	0.012

Abbreviations: IQR, interquartile range; SOT, solid organ transplant; ESRD, end-stage renal disease; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; CVC, central venous catheter; TPN, total parenteral nutrition; CASPO, caspofungin; FLUCO, fluconazole; AB>7days, antibiotics previously received for more than 7 days.
[a] p value for echinocandin versus fluconazole versus amphotericin B.
[b] p value for echinocandin versus fluconazole.

remained high (85.7%). This is consistent with a recent multicentre cohort study of Candida glabrata bloodstream infection in Spain [26] fluconazole use was not associated with unfavourable evolution (aOR for 14-day mortality 1.16, 95% CI 0.22–6.17; aOR for treatment failure 0.83, 95% CI 0.27–2.61) when compared with echinocandins or liposomal amphotericin B regimens, due to the lower incidence of resistance of C. glabrata to azoles in southern Europe when compared with America.

Mortality in patients with inadequate IAT was around 48% [9]. In our cohort, there were no differences between echinocandin and azole regimens on outcomes. Similarly, we could not identify associations between antifungal class and Candida species causing IAC, even in species with lower reported susceptibility to echinocandins such as Candida parapsilosis complex. Recent data show that the echinocandin regimen does not negatively influence outcome in candidaemia due to C. parapsilosis [27]. Echinocandins have been associated with better outcomes in previous reviews [28], but in these cohorts only around 1% of cases were IAC.

Some limitations of our analysis should be acknowledged. First we were only able to analyse the data recorded; for instance, we were unable to record the proportion of patients later transferred to the intensive care unit. Whether certain centres used predictive rules to initiate antifungal therapy remains unknown. Prescription of echinocandin shows a high diversity in different sites, being a limitation and precluding analysis of prognosis. Therefore, the model was adjusted to assess a possible centre effect. Finally there were certain differences according to geographical area, probably due to local ecology, drug interactions, or the fact that either external infectious disease consultants or critical care staff took decisions on antifungal therapy; this may explain the relation between presence in the surgical ward at diagnosis and echinocandin use [29].

Our findings have implications for future research and future practice. This large multinational multicentre analysis represents a real-life scenario and reflects the decision process when choosing one or another antifungal. Indeed, our study suggests that prescription of antifungals for IAC at the bedside does not conform to clinical practice guidelines (e.g. use of fluconazole in the presence of C. glabrata or previous azole exposure); therefore, further dissemination and educational measures are required to use therapies concordant with guidelines.

Table 2
Clinical characteristics and relation between the echinocandin and azole groups

	ALL (n = 310)	Echinocandin (n = 209)	Azole (n = 101)	p
Male	176 (56.8)	107 (51.2)	69 (68.3)	0.004
Age	63 (53–75)	63 (53–75)	61 (49–73)	0.59
APACHE II score diagnosis	15 (9–20)	17 (11–21)	16 (8–20)	0.013
Dialysis	20 (6.5)	12 (5.8)	8 (7.9)	0.471
SOT	17 (5.5)	8 (3.8)	9 (8.9)	0.067
ESRD	23 (7.4)	18 (8.7)	5 (5)	0.245
Solid tumour	122 (39.4)	86 (41.1)	36 (35.4)	0.352
Haemato malignancy	10 (3.2)	6 (2.4)	4 (4)	0.611
Immunosuppressant	49 (15.8)	33 (15.9)	16 (16)	0.976
Steroids	62 (20)	47 (22.6)	15 (15)	0.12
COPD	38 (12.3)	29 (13.9)	9 (8.9)	0.212
Heart disease	58 (18.7)	39 (18.8)	19 (19)	0.958
Type of IAC				0.053
Secondary peritonitis	119 (39)	93 (44.7)	26 (26.8)	0.001
Tertiary peritonitis	31 (10.2)	18 (8.7)	13 (13.4)	0.241
Abdominal abscess	85 (27.9)	52 (25)	33 (34)	0.149
Pancreatitis	33 (10.8)	19 (9.1)	14 (14.4)	0.202
Biliary tract	32 (10.5)	23 (11.1)	9 (9.3)	0.57
Other	5 (1.6)	3 (1.4)	2 (2.1)	0.721
WARD				0.001
Internal medicine	24 (7.7)	17 (8.1)	7 (7)	0.71
Surgery ward	153 (49.4)	116 (55.5)	37 (37)	0.002
ICU	95 (30.6)	61 (29.2)	34 (34)	0.423
Haemato-oncology	5 (1.6)	3 (1.2)	2 (2)	0.721
SOT ward	3 (1.0)	2 (1)	1 (1)	0.97
Previous abdominal surgery	234 (75.5)	152 (72.7)	82 (81.2)	0.105
Reoperation	145 (46.8)	101 (48.3)	44 (43.6)	0.431
Gastrointestinal perforation	69 (22.3)	49 (23.6)	20 (19.8)	0.457
Anastomotic leak	100 (21.4)	45 (21.5)	25 (24.8)	0.528
CVC	242 (78.1)	173 (82.8)	69 (68.3)	0.004
TPN	200 (65.5)	142 (67.9)	58 (58)	0.087
AB >7days	340 (73)	166 (79.4)	83 (82.2)	0.568
Prior azole exposure	47 (15.2)	24 (11.5)	23 (22.8)	0.009
Prior *Candida* colonization	88 (28.4)	48 (24.9)	40 (40.4)	0.006
Candidaemia	54 (17.4)	27 (13.4)	27 (27.3)	0.003
Septic shock	150 (48.4)	110 (52.3)	40 (39.6)	0.031
Concomitant bacteria	212 (68.4)	148 (71.2)	64 (64)	0.204
Adequate source control	284 (61.2)	134 (64.1)	64 (64.6)	0.928
CASPO S	271 (87.4)	194 (98)	77 (98.7)	0.679
FLUCO S	214 (69)	154 (83.2)	60 (77.9)	0.012

Abbreviations: IQR, interquartile range; SOT, solid organ transplant; ESRD, end-stage renal disease; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; GI, gastrointestinal; CVC, central venous catheter; TPN, total parenteral nutrition; CASPO, caspofungin; FLUCO, fluconazole; AB >7 days, antibiotics previously received for more than 7 days.

In an era of personalized medicine, therapeutic decisions should be taken based on scores, phenotypes and biomarkers. Our findings suggest that high severity scores and use of vasopressors are important drivers for therapeutic decisions. Scores and prediction rules have high sensitivity (but low specificity) and should be used to identify patients at low risk [30]. Further epidemiological

Table 3
Adequacy of treatment, microorganism and outcome between echinocandin or azole as initial antifungal therapy, n (%)

	All	Echinocandin	Azole	p
Adequate antifungal	263 (84.8)	177 (84.7)	86 (85.7)	0.91
Candida species				0.37
C. albicans	206 (66.5)	145 (69.2)	61 (60.4)	0.12
C. glabrata	56 (18.1)	33 (15.8)	23 (22.8)	0.15
C. tropicalis	21 (6.8)	15 (7.2)	6 (5.9)	0.68
C. parapsilosis	17 (5.5)	9 (4.3)	8 (7.9)	0.19
C. krusei	7 (2.3)	5 (2.4)	2 (2)	0.81
Death 30 days	79 (25.5)	56 (26.9)	23 (22.8)	0.57

Table 4
Variables selected by multivariate stepwise logistic regression for prediction of choice for echinocandin versus azole therapy

Variable	OR (95% CI)	p value	aOR (95% CI)
Prior *Candida* colonization	0.57 (0.32–1.00)	0.053	1.02 (0.35–2.39)
Septic shock	2.18 (1.25–3.82)	0.006	1.54 (0.88–2.70)
Candidaemia	0.54 (0.28–1.04)	0.068	0.78 (0.38–1.59)
Secondary peritonitis	1.73 (0.97–3.08)	0.062	0.92 (0.57–1.47)
Surgery ward	2.28 (1.30–3.99)	0.004	1.16 (0.62–2.19)
APACHE II score >15	1.54 (0.89–2.68)	0.118	1.16 (0.71–1.90)
Prior azole therapy	0.56 (0.27–1.15)	0.434	0.74 (0.37–1.148)

Included variables: APACHE II score >15, secondary peritonitis, surgery ward, central venous catheter, male gender, previous azole exposure, previous *Candida* colonization, septic shock, candidaemia.
aOR, adjusted OR for centre effect.
Hosmer–Lemeshow goodness-of-fit-test p 0.103.

research should be performed on prognostic factors for IAC with homogeneous prescriptions, differences in IAC between surgical wards and ICU hospitalization, as well as translational research on genomics, proteomics and metabolomics.

Conclusions

Echinocandins were preferred as initial antifungal treatment in patients with IAC and septic shock and in patients in surgical wards at the time of diagnosis. No statistical difference in mortality was observed between the two regimens in IAC episodes, even though echinocandins were administered to patients with more severe disease.

Appendix 1. IAC Study Investigators

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Appendix A. Supplementary materials

Additional Supporting Information may be found in the online version of this article http://dx.doi.org/10.1016/j.cmi.2016.06.005.

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