Universitat Autònoma de Barcelona

Intraabdominal Candidiasis: epidemiology, predictors of choice for treatment and factors associated with mortality

Leonel Lagunes Luna

Doctoral Thesis

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To obtain the Doctor Degree

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Success is not final; failure is not fatal: it is the courage to continue that counts.

— Sir Winston S. Churchill

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ABREVIATIONS

ICU: Intensive Care Unit

IAC: Intraabdominal Candidiasis

APACHE: Acute Physiology and Chronic Health Evaluation

CASPO: Caspofungin

FLUCO: Fluconazol

IQR 25-75: interquartile range 25-75

INTRODUCTION

Candida spp. are commonly found in humans. They colonize the skin and mucosal surfaces of most healthy individuals [1]. *Candida* spp. are highly prevalent fungi and have been well studied in the context of human microbiota [2-3]. Only in certain circumstances becomes pathogenic and cause life-threatening infections. The composition of the mycobiome differs according to body region and therefore its local role in the development of disease may vary. Gut microbiota form part of the first line of anti-microbial defense, along with the mucosal barrier, antibodies, antibiotic peptides and the intestinal epithelium. Members of the intestinal microbiota secrete bacteriocins - toxins produced by bacteria to inhibit growth of similar or closely related bacterial strains- and compete with pathogens for nutrients, surfaces and substrates. [3,4]

A crucial step in the process in which *Candida* spp. become invasive is their ability to form hyphae and become virulent, adhering to and invading into deeper tissues. It is clear that the morphogenesis of *Candida* is regulated by a complex network which depends on micro-environmental status and host innate-immunity and can lead to a range of clinical scenarios. Any variable that alters the commensal relation between *Candida* spp. and the host could be interpreted as a risk factor for invasive candidiasis. Its clinical manifestations may differ, depending on the clinical conditions at which the invasion takes place [5,6].

These opportunistic fungal pathogens can cause either local or systemic infection; in recent years, the prevalence of sepsis due to fungal organisms has risen by more than 200% [4] and they have become the third most common pathogen isolated from blood samples in large epidemiological studies in critically ill patients [7]. Patients with systemic fungal infection by *Candida* can be subdivided into three groups: those who present with bloodstream infection (can-

didemia), those who develop deep-seated candidiasis (most frequently intra-abdominal candidiasis), and those who develop a combination of the two. High mortality rates, ranging from 27% to 55%, have recently been correlated with these infection [8,9]

The clinical criteria for defining intraabdominal candidiasis (IAC) are not specific, although a recent European consensus of experts shortened the definition of an IAC episode [10]. International guidelines focus mostly on candidemia and make little reference to antifungal therapy for IAC [11,12]. Patients in the intensive care unit (ICU) are at the highest risk for invasive candidiasis, mostly due to the severity of their disease, immune-suppressive states, prolonged length of stay, septic shock and *Candida* colonization. Colonization occurs in the ICU population during the first week in up to 80% of cases [7,13], but few develop an ensuing severe infection [14]. The pathophysiology route of infection will determine the clinical scenario [15]; indeed, during a large recent study [9] focusing on intra-abdominal candidiasis, only 14% patients also developed candidemia

Delay in the initiation of treatment for invasive candidiasis has been associated with increased mortality [16-18]. It remains unclear which patients should receive empirical treatment or which not. According to current guidelines, appropriate treatment is based on azoles, polyenes or echinocandins; however, the differences between these groups according to the treatment of IAC have not been assessed, neither the differences between those more severe than those in regular wards.

JUSTIFICATION

Considerations made above have justifies our beliefs about patients with IAC being different from those that presents with candidemia in the ICU. Information regarding candidemia is extense however that one related to IAC is still scarce considering it as a different entity that requires a different clinical approach.

There have been a lot of efforts trying to establish or predict which patient will benefit the most from one or another antifungal treatment. Recent recommendations made emphasis on treating the most severe patients with an echinocandin and leave azoles for those with no previous exposure or less severe patients. No considerations have been made on local susceptibilities.

The publications in this matter comes from the largest international cohort of IAC cases and constitutes the base for the present doctoral thesis:

- First article “Predictors of choice of initial antifungal treatment of intraabdominal candidiasis” gives a global pattern of epidemiology on this matter and the implication regarding the decision of which antifungal to prescribe when facing an IAC patient.
- Second article “Association between source control and mortality in 258 patients with intra-abdominal candidiasis: A retrospective multicentric analysis comparing intensive care versus surgical wards in Spain” is centered in Spain cohort in order to reduce the possible bias of admission to an ICU according to bed availability or treatment policies in different countries regarding where the patient has been diagnosed of an IAC episode.

HYPOTHESIS

Every article included in this work follows the same direction based on the following hypothesis.

1. IAC may be a frequent entity in Europe and not always followed by candidemia.
2. Current antifungal therapy in IAC not homogenous and it may differ from current recommendations.
3. Some specific risk factors may be associated with mortality according to ward of infection.

OBJECTIVES:

General objective: To contribute to current understanding on epidemiology of IAC in Europe, its treatment and outcome in different clinical scenarios.

Specific objective

Study 1:

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

Study 2:

Primary objective is to improve understanding of the interaction between source control, early antifungal therapy, and outcome in patients with IAC. The secondary objective is to identify possible differences according to pathophysiology of *Candida* invasion, species, and risk factors when compared to those that developed an IAC episode in surgical wards.

METHODS

Multinational multicenter retrospective cohort study conducted at 13 teaching hospitals in four countries (Italy, Greece, Spain, and Brazil), over a three-year period (2011-2013). All cases were recorded continuously. Informed consent was waived and approved at each participating center ethical committee due to the observational characteristics of the study. An episode of IAC was defined according to the 2013 European consensus [10], as follows:

- Candida detection by direct microscopy examination or growth in culture from purulent or necrotic intraabdominal specimens obtained during surgery or by percutaneous aspiration.
- Candida growth from bile, intra-biliary duct devices, and biopsy of intraabdominal organs.
- Candida growth from blood cultures in a clinical setting of secondary and tertiary peritonitis in absence of any other pathogen.
- 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, comorbidities, immunosuppressive agents, Acute Physiology and Chronic Health Evaluation (APACHE II) score measured within the first 24 hours of culture positivity, and intra-hospital location at the time of diagnosis. Infection-related variables included source of infection, Candida species, prior antibiotic exposure (> than 7 days in the past 30 days), time to initiation of antifungal therapy, and type of antifungal therapy. Adequate abdominal source control was defined according to previous reports [34] and always performed within the 48h after diagnosis of IAC to be considered adequate:

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 48h of IAC diagnosis.

Treatment was considered adequate when the causative organism was ultimately shown to be susceptible. The following antifungal doses were considered adequate: 1) fluconazole 800mg loading dose (for obese patients BMI >30: 1200-1600mg) followed by a daily dose of at least 400mg (600-800mg for patients with BMI >30), 2) Caspofungin 70mg loading dose (100mg in obese) followed by 50mg/day (80mg/day), 3) micafungin 100 mg/day, and 4) anidulafungin 200mg loading dose followed by 100mg/day. Candida species were isolated using the BACTEC 860 system (Becton–Dickinson, Inc., Sparks, MD) 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 ºC. 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) or by agar diffusion using E-test strips (BioMérieux, France) and interpreted using Clinical Laboratory Standards Institute (CLSI) breakpoints.

Specific methods:

Study 1

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 in order to safeguard the stability of the model due to the low proportion of cases. Fig 1.

Statistical analysis

Continuous variables were compared by the Student t test or ANOVA for normally distributed variables and the Mann-Whitney U 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 (25-75 percentile) (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 (Table 6) were included in the model. The model was adjusted to assess a possible center influence, by stratification of cases at each center that ensured a non-different distribution among them. Estimations were carried out at each stratum (center) and results are expressed as Adjusted OR. All tests of significance were two-tailed and P values of 0.05 or less were considered statistically significant. Statistics were performed using SPSS, version 21.0 for Windows (SPSS, Inc., Chicago, IL) and R commander (Fox, 2005), version 0.999375-38.

Study 2

Population:

Only patients enrolled in Spain were included in this analysis, because ICU ratios per hospital bed are different in each country, possibly associated with differences in ICU admission criteria. The current retrospective multicenter analysis included patients from three large general referral university hospitals (>1,000 beds), with active liver transplant programs, over a 4-year period.

Statistical analysis

Continuous variables were compared by the Student's t-test or ANOVA for normally distributed variables and the

Mann–Whitney U or Kruskal–Wallis test for nonnormally distributed variables. The chi-square or Fisher's exact test was used to compare categorical variables. Values were expressed as medians (25–75 percentile) (continuous variables) or as a frequency of the group

from which they were derived (categorical variables). Multivariable stepwise logistic regression was performed, where mortality at day 30 was 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 were included into the model. All comparisons were unpaired. All tests of significance were two-tailed, and P values of 0.05 or less were considered to indicate statistical significance. All statistical analysis were performed using SPSS, version 21.0 for Windows (SPSS, Inc., Chicago, IL, USA).

RESULTS

Epidemiology

481 cases of IAC were recorded in four countries in 13 hospitals across Europe and South America. (Italy, Spain, Greece, Brazil). Distribution across the study period and country is shown in table 1. Most patients were male 276 (57,3%), median age 65 (Interquartile range 25-75 (IQR25-75): 53-75), with a median APACHE II score at diagnosis of 15 (IQR25-75: 9-20). First type of IAC was peritonitis in 223 patients (46,3%) mostly secondary peritonitis in 189 patients (39,2%) followed by abdominal abscess in 138 (28,6%). Patients were mostly at surgery ward at diagnosis 252 (52,3%) followed by Intensive care unit in 132 (27,4). *Candida albicans* was the most common species recovered from intraabdominal cavity in this population accounting for 314 (65,1%) followed by *Candida glabrata* in 88 (18,3%) and *Candida tropicalis* in 37 (7,7%), *Candida parapsillosis* in 23 (4,8%) and finally *Candida Kruseii* in 13 (2,7%). Mortality in whole study population at day 30 was of 129 (26,8%).

STUDY 1. PREDICTORS OF CHOICE OF INITIAL ANTIFUNGAL TREATMENT OF INTRAABDOMINAL CANDIDIASIS

In this 3-year period, 481 cases of IAC were recorded and included in the analysis. Three hundred and twenty-three patients received antifungal treatment and were assigned to the treatment group; 209 of these patients (64.7%) received an echinocandin as IAT, 101 (32.3%) received an azole and 13 (4%) received amphotericin B. Table 2 summarizes the clinical characteristics of the treatment group. Males more frequently received azoles and ampho B for IAC than echinocandins (69/101 (68.3%) vs. 107/209 (51.2%) respectively, p=0.004). APACHE II score was higher in the echinocandin group ((median 17 (IQR: 25-75% 11-21) compared to the azole group, median 16 (IQR: 25-75% 8-20 p=0.013). Regarding infection types, patients with secondary peritonitis were more likely to receive echinocandins than azoles (44.7% vs. 26.8% p=0.001). Patients in the surgical ward at time of diagnosis more frequently received echinocandins (55% vs. 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% vs. 39.6% p=0.031). In contrast, patients with candidemia and those

with prior *Candida* colonization more frequently received an azole (27.3% vs. 13.4%, p =0.003) and 40.4% vs. 24.9% respectively; p=0.006). (Table 3) 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 4)

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 Figure 2.

In adjusted multivariate analysis stratified for the center effect, the top three risk factors for prescription of an echinocandin (EC) 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 prior *Candida* colonization (OR for EC 0.57, 95%CI: 0.32-1.00 p=0.053) and candidemia (OR for EC: 0.54 95%CI 0.28-1.04, p=0.068) though the differences were not statistically significant (Table 5).

STUDY 2

ASSOCIATION BETWEEN SOURCE CONTROL AND MORTALITY IN 258 PATIENTS WITH INTRA.ABDOMINAL CANIDIASIS: A RETROSPECTIVE MULTI-CENTRIC ANALYSIS COMPARING INTENSIVE CARE VERSUS SURGICAL WARDS IN SPAIN.

Two hundred and fifty-eight cases of intra-abdominal candidiasis (IAC) were documented in this period of time. 166 patients (64.3%) had an abdominal surgery, and 109 (42.2%) had to be re-operated. 61 patients (23.6%) were at the ICU at diagnosis. Candidemia was present only in 12 patients (4,7%). Mortality was 22.9% in the overall group general population. When comparing ICU episodes versus those at surgical wards, age was different between groups (ICU 68 years' median (60.5-74.5) vs Non-ICU (64 years median (48,5-73,5) p= 0,013), however no differences in sex, comorbidities or days from admission to IAC between groups were observed. Peritonitis was the most common cause of IAC in both groups (ICU 26 cases (42,6%) vs Non-ICU 71 cases (36%), p=0,353) followed by intra-abdominal abscess, and biliary tract infection, with no differences between groups. More severe patients with higher APACHE II score were at ICU group (median:15 IQR 25-75: 11,75-20,25) *versus* non-ICU group (median 11, IQR 25-75: 7-17) (p=0,001). No differences in Candida species were observed between groups. *Candida albicans* was the most common species isolated in 128 (65%) non-ICU patients and in 33 (54,1%) ICU patients (p=0,133), followed by *Candida glabrata*. Classical risk factor for candidemia, such as having a central venous catheter (CVC), parenteral nutrition, septic shock, and candida colonization were higher in the ICU group as shown in table 7. Echinocandins were more commonly prescribed as initial antifungal treatment (IAT) in the ICU group (33 patients; 55%) vs 77 (39,5%) in non-ICU, p=0,038 (Univariate OR: 1,87 95%IC: 1,87-3,35)). Mortality in ICU patients was higher (21 (35%) vs 38 (19,5%), p=0,011 Univariate OR: 2,25, 95%IC: 1,19-4,26). Table 8 summarizes differences between survivors and non-survivors in the ICU group. Differences between survivors and non-survivors in the Non-ICU group are shown in Table 9. Results of the multivariate logistic regression analysis including age>65y, APACHE II score>15 at diagnosis, peritonitis, use of vasopressors or septic shock, echinocandin, treatment after 24h of diagnosis, no treatment, recur-

rent GI perforation, inadequate antifungal treatment and inadequate source control are shown in Table 10. Inadequate source control was identified as the only independent risk factor for 30-day mortality in both groups (ICU group OR: 13.78 (95%CI: 2.60-72.9, p=0,002) and Non-ICU group OR: 6,53 (95%CI: 2,56-16.61, p=<0,001)). The population having both adequate source control and adequate antifungal treatment was the one associated with higher survival rate, in both groups, as shown in Figure 1 and Figure 2.

TABLES AND FIGURES

Table1. Distribution across years and countries of IAC cases in the study period.

Country	2011 144	2012 163	2013 175
ITALY	44 (30)	74 (45)	75 (43)
SPAIN	92 (64)	79 (49)	87 (49)
BRAZIL	4 (3)	2 (1)	5 (3)
GREECE	4 (3)	8 (5)	8 (5)

Numbers are expressed as total (proportions)

Table 2. Clinical characteristics and differences in the treatment group.

	ALL 323	Echinocandin 209	Azole 101	Ampho B 13	P[a]	P[b]
Age median (IQR 25-75)	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 25-75)	15 (9-20)	17 (11-21)	16 (8-20)	18 (15-23)	0,003	0,013
Dyalisis	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 tumor	127 (39,3)	86 (41,1)	36 (35,4)	5 (38,5)		
Hemato malignancy	10 (3)	6 (2,4)	4 (4)	--		
Immunosupression	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 of IAC					<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)	--		
Adbominal 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
Hemato-onco	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)		
GI 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
Candidemia	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

P^a = echinocandin vs fluconazole vs amphotericin B.
P^b =echinocandin vs fluconazole.
Abbreviations: AB>7days= antibiotics previously received for more than 7 days, CVC=central venous catheter, TPN= total parenteral nutrition, COPD= chronic obstructive pulmonary disease, SOT= solid organ transplant, ESRD= end stage renal disease ICU= intensive care unit.

Table 3. Clinical characteristics and relation between the Echinocandin vs Azole group

	ALL 310	Echinocandin 209	Azole 101	P value
Age median (IQR 25-75)	63 (53-75)	63 (53-75)	61(49-73)	0,59
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 median (IQR 25-75)	15 (9-20)	17 (11-21)	16 (8-20)	0,013
Dyalisis	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 tumor	122 (39,4)	86 (41,1)	36 (35,4)	0,352
Hemato malignancy	10 (3,2)	6 (2,4)	4 (4)	0,611
Immunosupressant	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
Hemato-onco	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
GI 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
Candidemia	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: AB>7days= antibiotics previously received for more than 7 days, CVC=central venous catheter, TPN= total parenteral nutrition, COPD= chronic obstructive pulmonary disease, SOT= solid organ transplant, ESRD= end stage renal disease, ICU= intensive care unit.

Table 4. Adequacy of treatment, microorganism and outcome between echinocandin or azole as initial antifungal therapy.

	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 5. Variables selected by multivariate stepwise logistic regression for prediction of choice for echinocandin versus azole therapy.

Variable	OR (IC 95%)	P value	OR[a] (CI95%)
Prior candida colonization	0.57 (0,32 - 1,00)	0,053	1.02 (0.35-1.77)
Septic Shock	2,18 (1,25 – 3,82)	0,006	1.54 (0.88-2.70)
Candidemia	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 (0.37-1.48)

Included variables: APACHE II score >15, Secondary peritonitis, Surgery ward, CVC, Prior azole exposure, Prior Candida colonization, Septic shock, Candidemia. OR[a]= Adjusted OR for center effect.

Table 6 Univariate analysis for echinocandin vs azole group

Variable	OR (IC 95%)
Prior candida colonization	0.48 (0,29 – 0.81)
Septic Shock	1.69 (1.04 – 2.74)
Candidemia	0.41 (0.22 - 0.75)
Secondary peritonitis	2.31 (1.37- 3.90)
Surgery Ward	2,15 (1,32 – 3,51)
APACHE II score >15	1,49 (0,92 – 2.41)
CVC	2.22 (1.28-3.87)
Prior azole therapy	0.49 (0.23-0.82)
Male	2.13 (1.37-3.90)

Table 7. Demographical and clinical characteristics of ICU and Non ICU patients

	All 258	ICU 61	NON ICU 197	p
Age (median, IQR 25-75)	62,5 (50-74)	68 (60,5-74,5)	64 (48,5-73,5)	0,013
Age >65 y	115 (44,5)	36 (59)	79 (40,1)	0,009
Male	140 (54,3)	33 (54.1)	107 (54,3)	0,978
Immunocompromised	135 (52,7)	32 (52,5)	103 (52,8)	0,961
ERSD	14 (5,4)	6 (9,8)	8 (4,1)	0,084
COPD	30 (11,6)	5 (8,2)	25 (12,8)	0,333
Hearth disease	33 (12,8)	9 (14,8)	24 (12,3)	0,619
Trauma	2 (0,8)	1 (1,6)	1 (0,7)	0,383
Dyalisis	6 (2,3)	2 (3,2)	4 (2,0)	0,576
DM	56 (21,7)	15 (24,6)	41 (21,4)	0,546
Days from admission to IAC median (IQR25-75)	11 (4-21)	11 (5-29)	11 (3-20)	0,402
Number of surgical interventions median (IQR25-75)	1 (1-2)	2,05 (1-2)	1 (1-2)	<0,001
Antifungal after 24h	178 (69,3)	39 (63,9)	139 (70,6)	0,328
APACHE II score <15	143 (55,4)	27 (44,3)	116 (58,9)	
APACHE II score >15	115 (44,6)	34 (55,7)	81 (41,1)	0,045
Type of IAC				0,421
Peritonitis	97 (37,6)	26 (42,6)	71 (36)	0,354
Abdominal abscess	92 (35,7)	16 (27,1)	76 (39,6)	
Pancreatitis	29 (11,2)	6 (10,2)	23 (12,0)	
Biliary tract infection	30 (11)	10 (16,9)	20 (10,4)	
Other	3 (1,2)	2 (1,7)	1 (1,0)	
Previous abdominal surgery	166 (64,3)	42 (68,9)	124 (62,9)	0,40
Recurrent GI perforation	52 (20,2)	9 (14,8)	43 (22,1)	0,216
Reoperation	109 (42,2)	36 (59)	73 (37,8)	0,004
Anastomotic leakage	52 (20,2)	16 (26,2)	36 (16,4)	0,182
CVC	193 (74,8)	60 (98,4)	133 (67,9)	<0,001
Parenteral nutrition	123(47,7	43 (70,5)	80 (41,2)	<0,001
Prolonged use of AB	183 (70,9	48 (78,7)	135 (68,9)	0,139
Prior azol exposure	23 (8,9)	8 (13,1)	15 (7,7)	0,192
Candida colonization	42 (16,3)	15 (25)	27 (13,8)	0,042
Septic shock	116 (45)	43 (70,5)	73 (37,2)	<0,001
Use of vasopressors	115 (44,6)	44 (73,3)	71 (36,2)	<0,001
Candidemia	12 (4,7)	3 (5,0)	9 (4,6)	0,896
Candida species				0,576
C albicans	161 (62,4)	33 (54,1)	128 (65,0)	
C glabrata	54 (20,9)	15 (24,6)	39 (19,8)	
C tropicalis	20 /7,8)	7 (11,5)	13 (6,6)	
C parapsilosis	10 /3,9)	3 (4,9)	7 (3,6)	
C krusei	9 (3,5)	3 (4,9)	6 (3,0)	
Concomitant isolation of bacteria	203 (78,7)	45 (75)	158 (80,6)	0,348
Initial antifungic				0,030
Echinocandin	116 (42,6)	33 (55)	77 (39,5)	0.038
Azole	41 (15,9)	4 (6,7)	37 (19)	0.026
None	104 (40,3)	14 (66,7)	81 (23,7)	0.768
Caspo S	199 (77,1)	55 (90)	144 (73)	0,286
Fluco S	134 (51,4)	34 (70,8)	100 (79,4)	0,234
Inadequate antifungal	131 (51)	29 (47,5)	102 (52)	0,539
Inadequate source control	100 (39,1)	27 (44,3)	73 (37,4)	0,340
Exitus day 30	59 (22,9)	21 (35)	38 (19,3)	0,011

DM= diabetes mellitus, ESRD= end stage renal disease, COPD= chronic obstructive pulmonary disease, IAC= intraabdominal candidiasis, GI= gastrointestinal, CVC= central venous catheter, AB=antibiotics.

Table 8 Variables associated with survival in ICU patients .

	ALL ICU 61	Non Survivors 21	Survivors 39	P	OR 95%CI
Age >65y	115 (44,5)	16 (76,2)	20 (51,3)	0,060	3,04 (0,93-9,93
Male	31 (52,5)	13 (61,9)	20 (51,3)	0,587	
APACHE II <15	27 (44,3)	4 (19)	23 (59,8)		
APACHE II >15	34 (55,7)	17 (81)	16 (41)	0,003	6,10 (1,72-21,58)
Immunocompromised	32 (52,5)	8 (38,1)	23 (59)	0,123	
ERSD	6 (9,8)	3 (14,3)	3 (7,7)	0,417	
COPD	5 (8,2)	1 (4,8)	4 (10,3)	0,463	
Hearth disease	9 (14,8)	5 (23,8)	4 (10,3)	0,161	
DM	15 (24,6)	4 (19)	11 (28,2)	0,541	
Days from admission to IAC median (IQR25-75)	21,26 (5-29)	10 (4,5-22.5)	12 (6-32)	0,399	
Number of surgical procedures. median (IQR25-75)	2,05 (1-2)	2 (1-3)	2 (1-2)	0,118	
Antifungal after 24h	39 (65)	18 (85,7)	21 (53,8)	0,014	5,14 (1,30 -20,33)
Type of IAC				0,490	
Peritonitis	26 (42,6)	11 (52,4)	15 (38,6)	0,299	1,76 (0,60-5,14)
Abdominal abscess	16 (27,1)	4 (19)	12 (32,4)	0,327	0,52 (0,14-1,91)
Pancreatitis	6 (10,2)	3 (14,3)	3 (7.7)	0,417	
Biliary tract infection	9 (15)	2 (9,5)	7 (18,9)	0,383	
Other	2 (1,7)	1 (4,8)	1 (2.5)	0.169	
Previous abdominal surgery	41 (68,3)	13 (61,9)	28 (71,8)	0,562	
Recurrent GI perforation	9 (14,8)	3 (14,3)	6 (15,4)	0,909	
Reoperation	36 (59)	13 (61,9)	23 (59)	0,825	
Anastomotic leakage	16 (26,2)	6 (28,6)	10 (25,6)	0,807	
CVC	60 (98,4)	21 (100)	38 (97,4)	0,987	
Parenteral nutrition	43 (70,5)	13 (61,9)	30 (76,9)	0,243	
Prolonged use of AB	48 (78,7)	16 (76,2)	32 (82,1)	0,737	
Prior azol exposure	8 (13,1)	2 (9,5)	61(15,4)	0,524	
Candida colonization	15 (25)	6 (30,0)	9 (23,1)	0,563	
Septic shock	43 (70,5)	17 (81)	25 (64,1)	0,174	
Use of vasopressors	43 (72.9)	18 (90)	25 (64,1)	0,034	5.04(1.01-24.98)
Candidemia	3 (5,0)	1(5)	2 (5,1)	0,98	
Candida species				0,730	
C albicans	33 (54,1)	13 (61,9)	20 (51,3)		
C glabrata	15 (24,6)	5 (23,8)	9 (23,1)		
C tropicalis	7 (11,5)	2 (9,5)	5 (12,8)		
C parapsilosis	3 (4,9)	1 (4,8)	2 (5,1)		
C krusei	3 (4,9)		3 (7,7)		
Concomitant isolation of bacteria	45 (75)	17 (85)	27 (69,2)	0,188	
Initial antifungal					
Echinocandin	33 (55)	6 (18,8)	26 (68,4)	0,005	0.18 (0,005-0,59)
Azole	4 (6,7)	1 (4,8)	3 (7,9)	0,647	
None	24 (39.3)	14 (66,7)	10 (25,7)	0.002	5,8 (1,8 2- 18,45)
Caspo S	55 (90,2)	20 (97)	34 (87)		
Fluco S	34 (70,8)	13 (76,5)	21 (70)	0,634	
Inadequate antifungal	28 (46,7)	15 (71,4)	13 (33,3)	0,005	5,00 (1,57 – 15,90)
Inadequate source control	27 (45)	15 (71,4)	12 (30,8)	0,003	5,62 (1,75 – 18,04)

DM= diabetes mellitus, ESRD= end stage renal disease, COPD= chronic obstructive pulmonary disease, IAC= intraabdominal candidiasis, GI= gastrointestinal, CVC= central venous catheter, AB=antibiotics.

Table 9 Variables associated with survival in surgical wards

	All 197	Non survivors 38	Survivors 159	p	OR 95% CI
AGE >65 y	79 (40,1)	23 (60,5)	56 (35,2)	0.004	2.82 (1.36- 5.83)
Male	107 (54,3)	18 (47,4)	89 (56)	0.339	
Female	90 (45,7)	20 (52,6)	70 (44)		
Immunocompromised	103 (52,8)	20 (52,6)	83 (52,9)	0.979	
ERSD	8 (4,1)	2 (5.3)	6 (3.8)	0.682	
COPD	25 (12,8)	10 (26.3)	15 (9.5)	0,005	3.40 (1.38-8.34)
Hearth disease	24 (12,3)	8 (21.1)	16 (10.2)	0.067	
Dyalisis	4 (2,0)	1 (2.6)	3 (1.9)	0.774	
DM	41 (21,4)	9 (23,7)	32 (20.8)	0.696	
Days from admission to IAC median (IQR25-75)	11 (3-20)	12.5 (7-21.2)	10 (3-20)	0.273	
Number of surgical interventions median (IQR25-75)	1 (1-2)	1 (1-3)	1 (1-2)	0.017	
Antifungal after 24h	139 (70,6)	112 (70,4)	27 (71,1)	0,941	
APACHE II score <15	116 (58,9)				
APACHE II score >15	81 (41,1)	24 (63.2)	57 (35.8)	0.002	3.06 (1.47-6.39)
Type of IAC					
Peritonitis	71 (36)	24 (63.2)	47 (29.2)	<0,001	4.08 (1.94-8.57)
Abdominal abscess	76 (39,6)	9 (23.7)	67 (42.1)	0.036	0.42 (0.18-0.95)
Pancreatitis	23 (12,0)	2 (5.3)	21 (13.2)	0.171	
Biliary tract infection	20 (10,4)	2 (5.3)	18 (11.3)	0.267	
Other	1 (1,0)				
Previous abdominal surgery	124 (62,9)	22 (57,9)	102 (64,2)	0,473	
Recurrent GI perforation	43 (22,1)	17 (44,7)	26 (16,6)	<0,001	4,07 (1,89-8,76)
Reoperation	73 (37,8)	17 (45,9)	56 (35,9)	0,257	
Anastomotic leakage	36 (16,4)	10 (26,3)	26 (16,5)	0,159	
CVC	133 (67,9)				
Parenteral nutrition	80 (41,2)	22 (57,9)	58 (37,2)	0,020	2,32 (1,13 -4,77)
Prolonged use of AB	135 (68,9)	29 (76,3)	106 (67,1)	0,270	
Prior azol exposure	15 (7,7)	1(2,6)	14 (8,9)	0,196	
Candida colonization	27 (13.8)	9 (23.7)	18 (11.5)	0.050	2.39 (0.98-5.83)
Septic shock	73 (37.2)	28 (73.7)	45 (28.5)	<0,001	7.03 (3.15-15.65)
Use of vasopressors	71 (36,2)	28 (73.7)	43 (27.2)	<0,001	7.48 (3.35-16.70)
Candidemia	9 (4,6)	2 (5.3)	7 (4.4)	0.826	
Candida species				0.257	
C albicans	128 (65,0)	25 (65,8)	103 (64.8)		
C glabrata	39 (19,8)	6 (15.8)	33 (20.8)		
C tropicalis	13 (6,6)	4 (10.5)	9 (5.7)		
C parapsilosis	7 (3,6)	-	7 (4.4)		
C krusei	6 (3,0)	1 (2.6)	5 (3.1)		
Concomitant isolation of bacteria	158 (80,6)	31 (81.6)	127 (80.4)	0.867	
Initial antifungic treatment				0.007	
Echinocandin	77 (39,5)	21 (56.8)	56 (35.4)		
Azole	37 (19)	1 (2.7)	36 (22.8)		
None	81 (23,7)	15 (40.5)	66 (41.8)		
Caspo S	144 (73)	34 (100)	110 (97.3)	0.337	
Fluco S	100 (79,4)	23 (82.1)	77 (78.6)	0.680	
Inadequate antifungal	102 (52)	22 (57.9)	80 (50.6)	0.421	1.34 (0.65-2.74)
Inadequate source control	73 (37,4)	27 (71.1)	46 (29.3)	<0.001	5.92 (2.71- 12.93)

DM= diabetes mellitus, ESRD= end stage renal disease, COPD= chronic obstructive pulmonary disease, IAC= intraabdominal candidiasis, GI= gastrointestinal, CVC= central venous catheter, AB=antibiotics.

Table 10 Independent risk factors for 30 day mortality in ICU and surgical wards patients (multivariate analysis).

Variable	ICU		Regular wards	
	OR 95% CI	P value	OR 95% CI	P value
Age >65y			2.23 (0.91-5.48)	0.078
Peritonitis			2.46 (0.99-6.13)	0.052
APACHE >15	10.18 (1.86-55.7)	0.007		
Vasopressors	4.80 (0,6734.31)	0.118	10.63 (3.8-29.72)	<0.001
None treatment	5.94 (1.35-26.11)	0.018		
Inadequate source control	13.78 (2.60-72.9)	0,002	6.53 (2.56-16.61)	<0,001
Inadequate antifungal			2.38 (0.91-6.21)	0.076

Variable(s) entered in the model : Peritonitis, Inadequate antifungal, inadequate source control, Treatment after 24h, Use of vasopressor, Echinocandin, None treatmentl, More than 65, APACHE higher than 15, recurrent gastrointestinal perforation. Hosmer-Lemeshow Goodness-of- fit-test, p:0.880

FIGURES

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

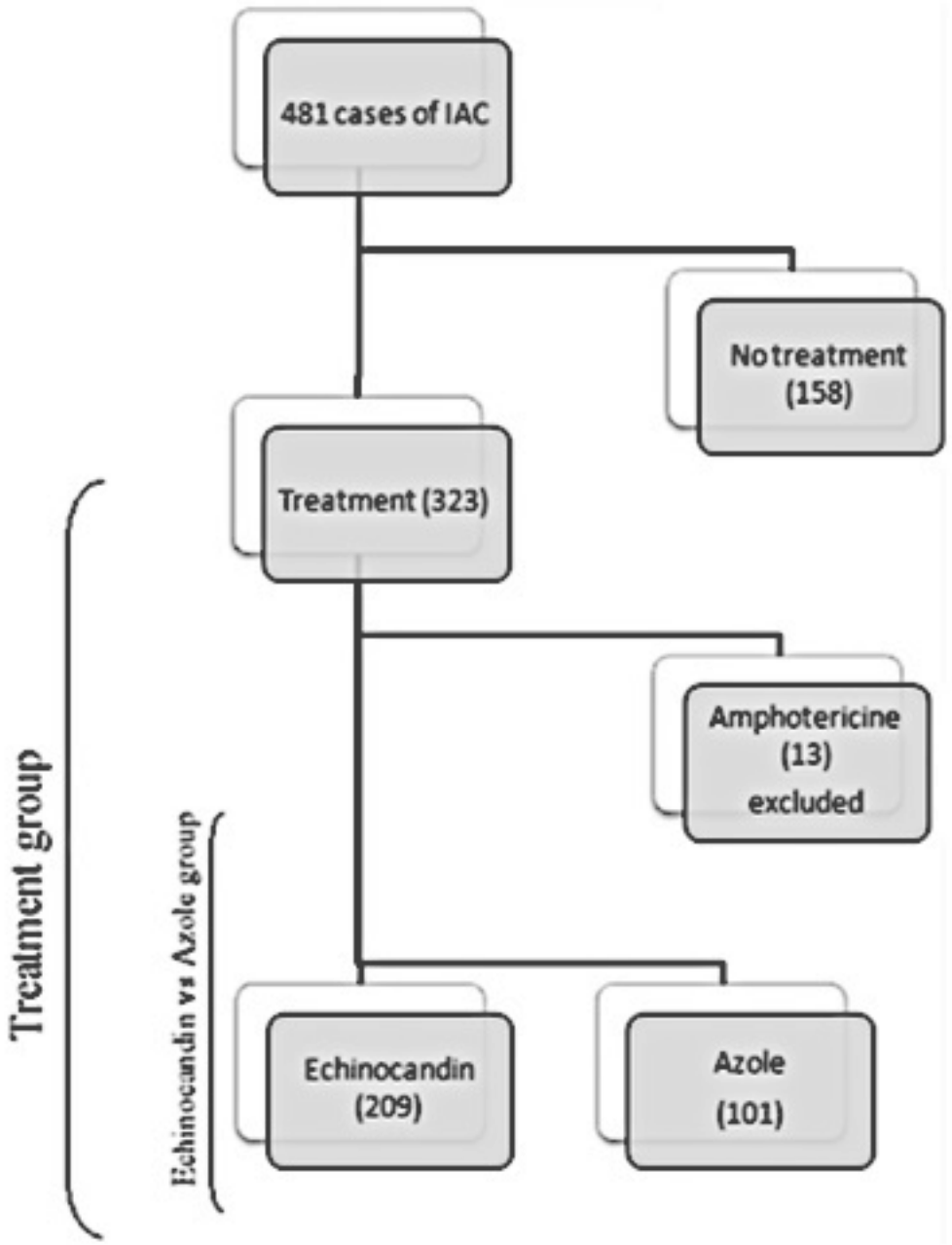


Figure 2. Differences in IAT according to geographical area during the study period.

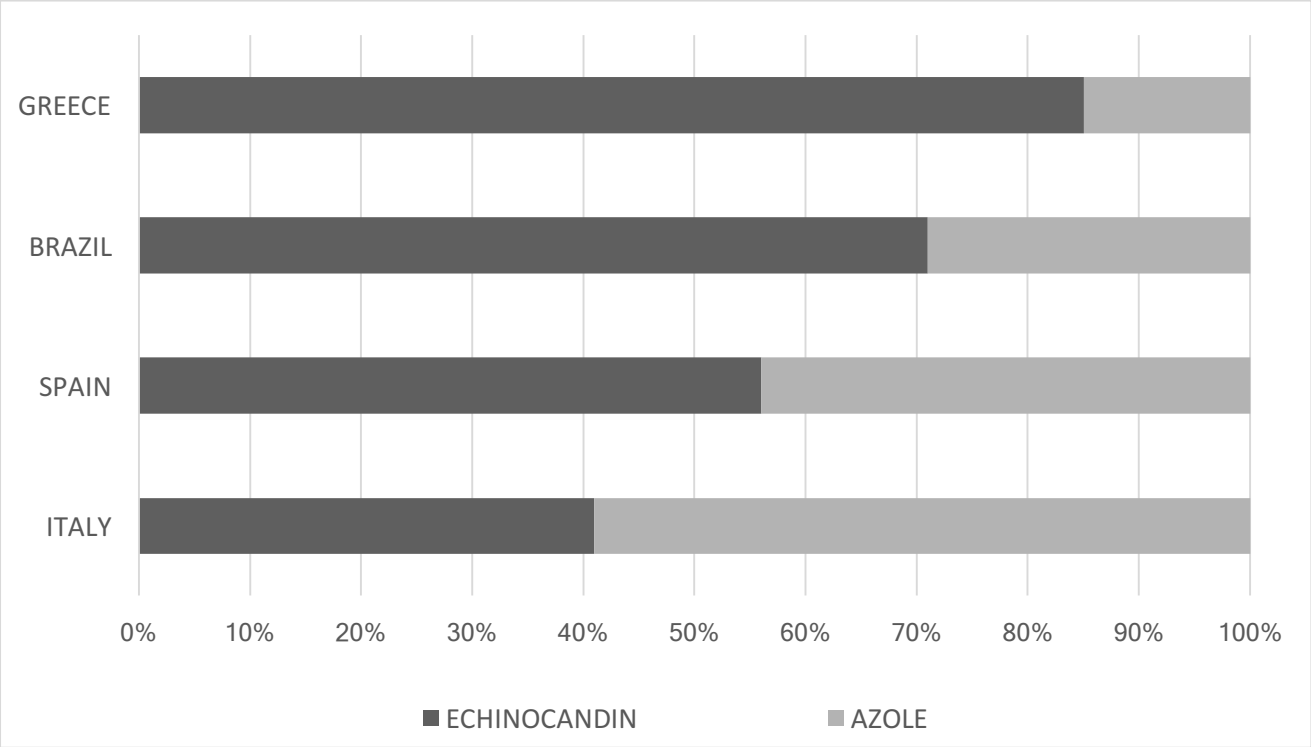
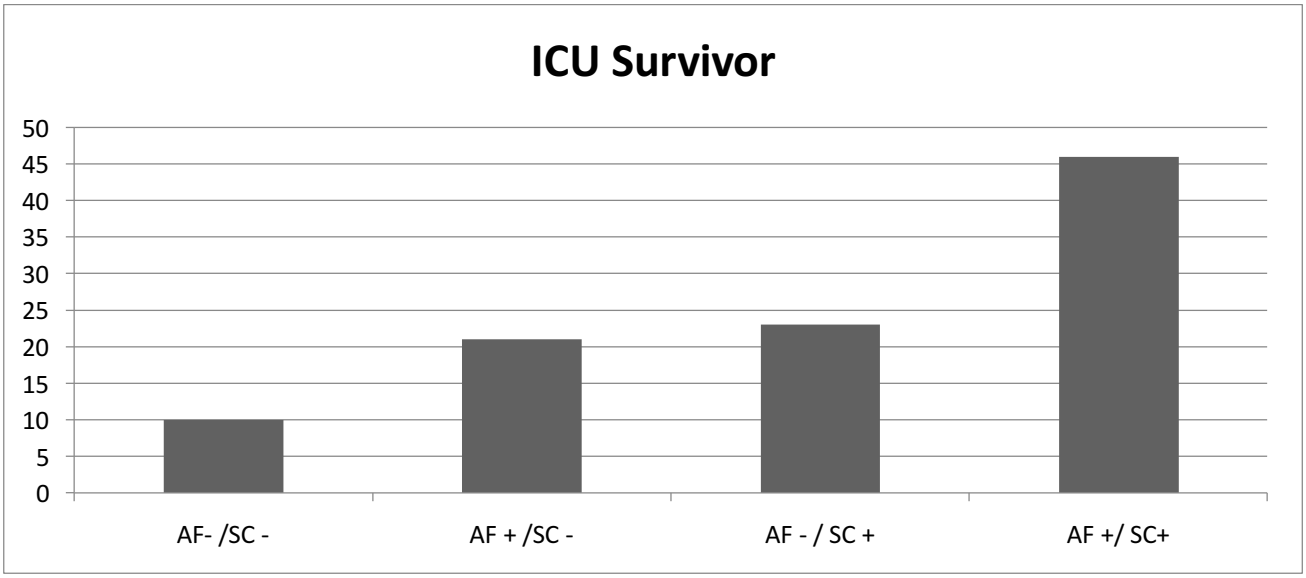
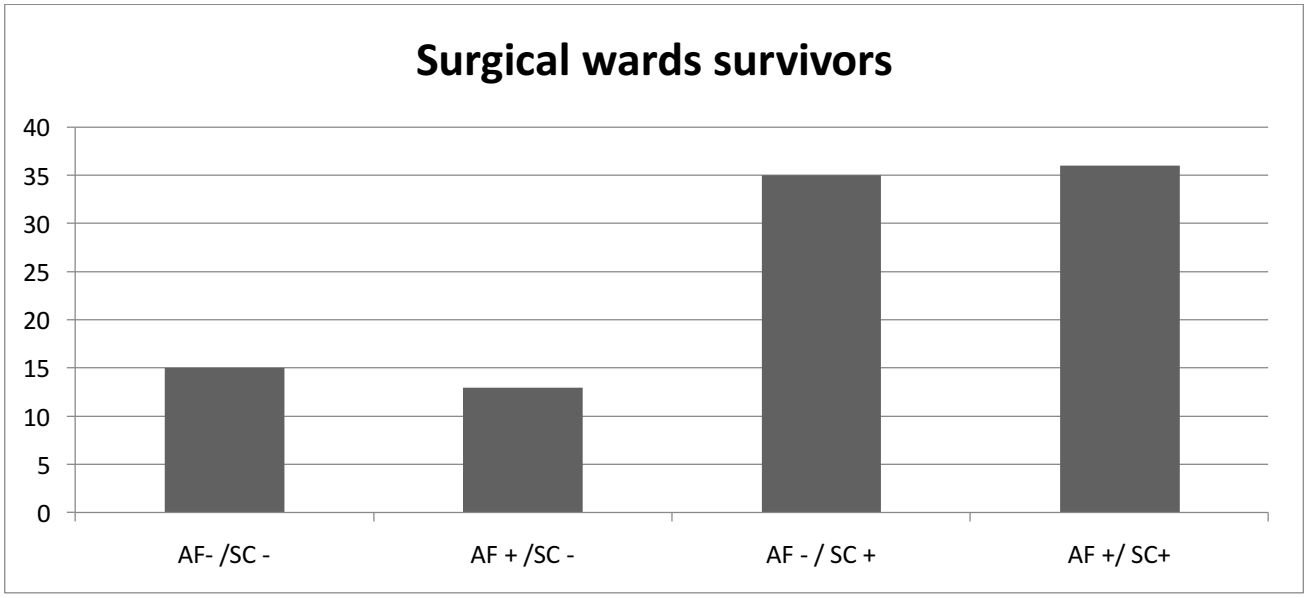


Figure 3 Survival in patients with and without adequate source control or adequate antifungal therapy in ICU.



AF + = adequate antifungal therapy, SC += adequate source control in 48h.

Figure 4 Survival in patients with and without adequate source control or adequate antifungal therapy in surgical wards.



AF + = adequate antifungal therapy, SC += adequate source control in 48h.

DISCUSSION

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 [19,20]. Recently, an expert European consensus attempted to redefine IAC [10], and a subsequent report showed a high mortality associated with this condition [9]. 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 analyzed 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 [16-18]; however, most previous randomized control trials assessed primarily bloodstream infection due to *Candida* spp. [21, 22].

Patients with higher severity scores and septic shock at the time of diagnosis more frequently received an echinocandin as IAT, whereas a trend favoring azoles was identified in presence of candidemia or prior azole exposure. As in a previous study [9] the proportion of patients with both IAC and candidemia was about 15%, raising concerns on generalization of recommendations to non-candidemic 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 candidemia make it difficult to initiate prompt, correct antifungal treatment. The gold 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 [23] for identifying patients at high risk of developing an IAC episode who are likely to benefit from early initiation and correct treatment [24,25].

According to current IDSA and ESCMID guidelines, invasive candidiasis patients 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, hemodynamic instability or high risk for an azole-resistant causal agent is suspected or present [11,12]. Among our

patients with candidemia, 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 EC with prior azole exposure.

In the light of what is known, some studies have reported an increase in azole-resistant species when azole exposure is documented [26,27] 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 remained high (85.7%). This is consistent with a recent multicenter cohort study of *Candida glabrata* bloodstream infection in Spain [28] fluconazole use was not associated with unfavorable evolution (adjusted OR for 14-day mortality: 1.16, 95%CI: 0.22-6.17; adjusted OR for treatment failure: 0.83, 95%CI: 0.27-2.61) when compared to 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 candidemia due to *C. parapsilosis*. [29]. Echinocandins have been associated with better outcomes in previous reviews [30], but in these cohorts, only around 1% of cases were IAC.

On the other hand, this is the first study to the best of our knowledge assessing differences between IAC episodes in surgical wards *versus* those observed at the ICU. Inadequate source control was identified as the only common prognostic factor in both ICU group (OR: 13.78) and surgical ward (OR: 6.53), an observation with important clinical implications. In contrast, empiric adequate antifungal ther-

apy only influenced survival in patients at the ICU. The importance of source control has been retaken with the surviving sepsis campaign [31]; intra-abdominal infection seems to be the main anatomical site where source control becomes more feasible besides soft tissues [32-34]. Although the quality of source control is difficult to evaluate [35], without it mortality can reach up to 100%. In recent studies the time between admission and source control in intra-abdominal infection has been assessed as a critical determinant of survival in patients with GI perforation with associated septic shock [36], however the majority of episodes are focused in bacterial peritonitis.

Candida albicans was the most prevalent species isolated in our analysis in both groups, with no differences between them, in correspondence to previous reports in European ICUs [37,38]. Most published reports of *Candida* infection are based on ICU mixed populations, and mostly on candidemia. However, information on *Candida* peritonitis outside the ICU is scarce.

Other studies have compared IAC versus non-peritonitic invasive *Candida* disease [30] with only 93 patients in the IAC group, and a high proportion of patients with candidemia in this group (28%). When assessed non-survivors had a higher ratio of underlying disease and a higher severity score at diagnosis. However, this comparison may have some bias, as previously reported IAC pathogenesis in surgical patients is different from those that present with only bloodstream infection or a combination of both, since the anatomical barrier is persistently damaged [15]. In our analysis, we found the lowest proportion of patients with candidemia and IAC ~ 5% so far reported; and around 22% of cases with exclusively this isolation in concordance with previous reports 4 - 27% [37,38].

In our analysis, up to 68% of the patients at the ICU had a recent abdominal surgery and up to 59% had to be re-operated, making this group a high-risk population for the development of IAC. Interestingly our data demonstrate that patients with IAC in the ICU show little differences compared to those in surgical wards, mostly due to severity of disease, septic shock, and in concordance a higher mortality rate in the ICU group. This is the first report where a delay of more than 24 hours of initiation of an antifungal therapy in IAC episodes in the ICU group was associated with an increase of ∽5 fold in mortality in the univariate analysis but not in the Non-ICU group. In our series around 40% of patients did not receive an initial, immediate antifungal treatment. To left untreated *Candida i*solation in the

peritoneum may lead to spread to distant organs or the formation of abscesses, multiple organ failure and death [39,40]. Whereas 2003 guidelines [41] for complicated intra-abdominal infections suggested that antifungal therapy was necessary only when recurrent intra-abdominal infection or immunosuppressive therapy were present, 2016 IDSA guidelines [11] suggests to consider empiric antifungal therapy in patients with clinical evidence of intra-abdominal infections and significant risk factors for *Candida* infection, such as recent abdominal surgery, anastomotic leaks or necrotizing peritonitis (strong recommendation; moderate-quality evidence), in our analysis patients that do not receive antifungal therapy for an IAC episode had a ∽6 fold increase in mortality in the ICU group, however this finding was not observed in the Non ICU group.

In recent reports mortality in *Candida* peritonitis varied from 25-60% [9,19,40]. Some risk factors for mortality in ICU-IAC related to underlying disease and severity of infection have been reported [37,38]. However, no differences were assessed between ICU and non ICU patients to identify specific risk factors for mortality in this population. In comparison to highly selected post chirurgical ICU patients [37,38], our analysis has the strength that ICU and Non-ICU IAC episodes could be compared. APACHE II score was the second most strong risk factor for mortality in the ICU group, a cutoff similar of our group was selected in previous reports [37] with similar results.

Due to the retrospective design of the study we cannot assessed some other variables and should be taken into account as study limitations. First of all, some centers used predictive rules to initiate antifungal therapy remains unknown. Prescription of EC shows a high diversity in different sites, being a limitation and precluding an analysis of prognosis. Therefore, the model was adjusted to assess a possible center effect. Certain differences according to geographical area, probably due to local ecology, drug interactions, or the fact that ether external ID consultants or critical care staff took decisions on antifungal therapy; this may probably explain the relation between presence in the surgical ward at diagnosis and echinocandin use. [42] We cannot assess if an earlier source control can result in a better outcome and this issue should be explored in further studies. Furthermore, no data regarding the influence of concomitant antibiotic therapy on outcomes could be assessed.

Our findings have implications for future research and future practice. This large multinational multicenter analysis represents a real-life scenario and reflects the decision process when choosing one or another antifungal and decisions taken into account regarding source control. In recent years, fungal biomarkers had become one of the promising tools in post-operative critically ill patients [24] to identify patients at higher risk for developing an IAC episode. Recent recommendations make emphasis on utilizing predictive rules in combination with other biomarkers, and severity of disease to initiate empirical treatment in high risk patients and to its potential role in reducing duration of treatment or withdrawal of it [25,43,44] but not so much emphasis in source control is made. Any empirical or preemptive antifungal therapy has demonstrated to decrease mortality in a specific population of patients with peritonitis, nevertheless an overuse of antifungals agents can contribute to a high financial burden and promotion of resistant strains even in the sickest patients [44-48].

Indeed, our study suggests that prescription of antifungals for IAC at the bedside does not conform to clinical practice guidelines (.eg. use of fluconazole in presence of *Candida glabrata* or prior azole exposure); neither the source control measures suggested by guidelines. Therefore, until this new approach becomes routine practice, educational efforts should be directed to achieve a prompt and adequate source control in IAC episodes in and outside the ICU and educational measures are required in order to use therapies concordant with guidelines.

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 [43]. Further epidemiological research should be done 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

STUDY 1

Echinocandins were the first choice 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 more severe patients.

STUDY 2

Our findings suggest no differences in source of infection or Candida species at ICU or surgical wards were observed.

Adequate initial treatment was higher in the ICU population and has stronger impact on outcome particularly in the subset with higher severity.

Source control remains the main goal for decreasing mortality of IAC episodes in and outside the ICU, emphasizing the contribution of the surgeon in intra-abdominal infections.

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ANEX 1

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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;▪: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 $\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

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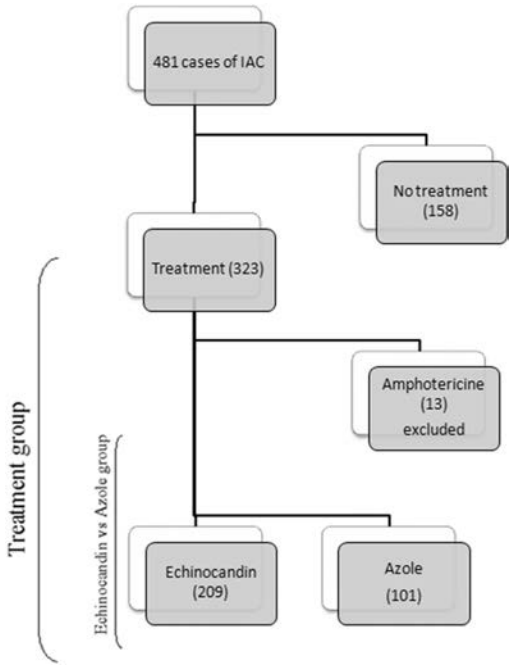

Fig. 1. Total population and treatment group, Echinocandin versus azole group; after exclusion of no treated patients and those who received amphotericin.

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

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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.

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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 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.

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.

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.

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Transparency declaration

MB serves on scientific advisory boards for Pfizer Inc, Merck Serono and Astellas Pharma Inc.; has received funding for travel or speaker honoraria from Pfizer Inc., Merck Serono, Gilead Sciences, Teva Inc. and Astellas Pharma Inc. ALC serves on scientific advisory boards for MSD and has received funding for continuing education programmes from Pfizer Inc., Gilead Sciences, United Medical, MSD and Astellas Pharma Inc. CT has been paid for lectures on behalf of Pfizer, Novartis, MSD, AstraZeneca, Zambon and Astellas. The rest of the authors declare no conflict of interest.

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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ORIGINAL ARTICLE

Association between source control and mortality in 258 patients with intra-abdominal candidiasis: a retrospective multi-centric analysis comparing intensive care versus surgical wards in Spain

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Abstract Early empiric therapy and adequate resuscitation have been identified as main predictors of outcome in patients with candidemia or bacteremia. Moreover, source control is a major determinant in infectious sites when feasible, as a main technique to reduce microbiological burden. A retrospective, multicenter, cohort study was performed at surgical wards and intensive care units (ICU) of three University Hospitals in Spain between 2010 and 2014, with the aim of improving understanding of the interaction between source control, early antifungal therapy, and use of vasoactives in patients with intra-abdominal candidiasis (IAC). Source control was defined as all physical actions taken to control a focus of infection and reduce the favorable conditions that promote microorganism growth or that maintain the impairment of host defenses. Two hundred and fifty-eight patients with IAC were identified. Sixty-one patients were at ICU for diagnosis. Mortality was higher in the ICU group compared to what was documented for the non-ICU group (35 % vs 19.5 %, $p = 0011$). Adequate source control within 48 h of diagnosis was achieved in 60 % of the cohort. In multivariate analysis, inadequate source control was identified as the only common risk factor for 30-day mortality in both groups (ICU group OR: 13.78 (95% CI: 2.60–72.9, $p = 0.002$) and non-ICU group OR: 6.53 (95% CI: 2.56–16.61, $p = <0.001$). The population receiving both adequate source control and adequate antifungal treatment was the one associated with a higher survival rate, in both the ICU and surgical groups. Source control remains a key element in IAC, inside and outside the intensive care unit. Early antifungal treatment among ICU patients was associated with lower mortality.

Introduction

Fungi are responsible for around 20 % of all microbiologically documented infections in the intensive care unit (ICU) [1]. The isolation of *Candida spp* from the peritoneum of critically ill patients is correlated with higher mortality [2]. Patients are frequently admitted to ICU because of multi-organ failure due to intra-abdominal infection. Mortality due to severe intra-abdominal infection remains high despite improvement in intensive care [3]. There is an current controversy concerning

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the role of Candida in peritonitis, since up to 80 % of patients with peritonitis are colonized with Candida but only 5–30 % develop an intra-abdominal candidiasis requiring antifungal treatment [4–6]. Patients in the ICU after abdominal surgery have been identified as being at higher risk for developing invasive candidiasis [7]. The loss of integrity of the first line of defense in a natural reservoir of *Candida spp.* such as the gut, in addition to many other risk factors identified for invasive candidiasis in critically ill patients, make this population a high-risk population [2, 6–9]. Nevertheless, data concerning this type of infection are scarce outside the ICU setting. Therefore, our primary objective was to improve understanding of the interaction between source control, early antifungal therapy, and outcome in patients with IAC. The secondary objective was to identify possible differences according to pathophysiology of *Candida* invasion, species, and risk factors when compared to those that developed an IAC episode in surgical wards.

Methods

This is a secondary analysis using the largest database of intra-abdominal candidiasis cases reported elsewhere [10]. Only patients enrolled in Spain were included in this analysis, because ICU ratios per hospital bed are different in each country, possibly associated with differences in ICU admission criteria. The current retrospective multicenter analysis included patients from three large general referral university hospitals (>1,000 beds), with active liver transplant programs, over a 4-year period (2010–2014). Informed consent was waived in every participating centre due to the observational characteristics of the study. All cases were monitored continuously. An episode of IAC was defined according to the 2013 European consensus [6]:

- Candida detection by direct microscopy or growth in culture from purulent or necrotic intra-abdominal specimens obtained during surgery or by percutaneous aspiration.
- Candida growth from bile, intra-biliary duct devices, and biopsy of intra-abdominal organs.
- Candida growth from blood during secondary and tertiary peritonitis in the absence of any other pathogen.
- Candida growth from drainage tubes only if placed less than 24 h before the cultures become positive.

Patient demographic characteristics and infection-related variables were collected from hospital medical records, microbiology, and pharmacy databases. Demographic data included age, gender, comorbidities, immunosuppressive agents, acute physiology and chronic health evaluation (APACHE II) measured within the first 24 h from the culture positivity, and intrahospital 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 according to previous reports [11] and always performed within the 48 h after diagnosis of IAC to be considered adequate:

A) Drainage of infected fluid collections.
B) Debridement of infected tissue and removal of devices or foreign bodies.
C) Definitive measures to correct anatomic derangements resulting in ongoing microbial contamination and to restore optimal function.

Adequacy of treatment was considered correct when the causative organism was ultimately shown to be susceptible and the dosage of the antifungal used was adequate within the first 24 h from culture positivity. Adequate dosage was considered as follows: 1) fluconazole 800 mg loading dose (for patients with BMI >30: 1,200–1,600 mg), followed by a daily dose of at least 400 mg (600–800 mg for those with BMI >30), caspofungin 70 mg loading dose (100 mg in obese) followed by 50 mg/day (70 mg/day), micafungin 100 mg/day, anidulafungin 200 mg loading dose followed by 100 mg/day. Yeasts were isolated by inoculating abdominal fluids in blood culture bottles incubated in automated systems until flagged as positive (Becton or BioMerieux) or by conventional culture in selective mycological media. The species were identified using the API ID 32C system (bioMérieux, Marcy l'Etoile, France) or the Vitek 2 system (bioMérieux). Additional supplementary test included the use of Cornmeal-Tween 80 to show the presence or absence of pseudohyphae and chlamydospores, and the performance of a thermotolerance test at 45° to discriminate between *Candida albicans* and *Candida dubliniensis* Antifungal susceptibility testing to amphotericin B, caspofungin, anidulafungin, micafungin, fluconazole, itraconazole, and voriconazole was performed using the Sensititre YeastOne colorimetric plate (Trek Diagnostics Systems, Cleveland, OH, USA) or by agar diffusion using E-test strips (BioMerieux, France) and interpreted by the Clinical Laboratory Standards Institute (CLSI) breakpoints.

Patients were considered immunosuppressed if they had received long-term treatment (>14 days) with corticosteroids or other immunosuppressive drugs, had cancer or hematologic disease, or had received a solid organ transplant [12].

Statistical analysis

All comparisons were unpaired. All tests of significance were two-tailed, and P values of 0.05 or less were

considered to indicate statistical significance. Continuous variables were compared by the Student's *t*-test or ANOVA for normally distributed variables and the Mann–Whitney U 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 (25–75 percentile) (continuous variables) or as a frequency of the group from which they were derived (categorical variables).

Multivariable stepwise logistic regression was performed, where mortality at day 30 was 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 were included into the model. All statistical analysis were performed using SPSS, version 21.0 for Windows (SPSS, Inc., Chicago, IL, USA).

Results

Two hundred and fifty-eight cases of intra-abdominal candidiasis (IAC) were documented in this period of time. One hundred and sixty-six patients (64.3 %) had an abdominal surgery, and 109 (42.2 %) had to be re-operated. Sixty-one patients (23.6 %) were at the ICU at diagnosis. Candidemia was present only in 12 patients (4.7 %). Mortality was 22.9 % in the overall group general population. When comparing ICU episodes versus those at surgical wards, age was different between groups (ICU 68 years median (60.5–74.5) vs non-ICU (64 years median (48.5–73.5) $p = 0013$); however, no differences in sex, comorbidities, or days from admission to IAC between groups were observed. Peritonitis was the most common cause of IAC in both groups [ICU 26 cases (42.6 %) vs non-ICU 71 cases (36 %), $p = 0353$] followed by intra-abdominal abscess, and biliary tract infection, with no differences between groups. More severe patients with higher APACHE II score were at ICU group (median:15 IQR 25–75: 11.75–20.25) versus non-ICU group (median 11, IQR 25–75: 7–17), $p = 0001$. to differences in *Candida* species were observed between groups. *Candida albicans* was the most common species isolated in 128 non-ICU patients (65 %) and in 33 ICU patients (54.1 %) ($p = 0133$), followed by *Candida glabrata*. Classical risk factor for candidemia, such as having a central venous catheter (CVC), parenteral nutrition, septic shock, and candida colonization were higher in the ICU group as shown in Table 1. Echinocandins were more commonly prescribed as initial antifungal treatment (IAT) in the ICU group [33 patients (55 %) vs 77 (39.5 %) in non-ICU), $p = 0038$ (Univariate OR: 1.87, 95% IC: 1.87–3.35)]. Mortality in ICU patients was higher [21 (35 %) vs 38 (19.5 %), $p = 0.011$ (Univariate OR: 2.25, 95% IC: 1.19–4.26)]. Table 2 summarizes differences between survivors and non-survivors in the ICU group. Differences between survivors and non-survivors in the Non-ICU group are shown in Table 3. Results of the multivariate logistic regression analysis including age > 65 years, APACHE II score > 15 at diagnosis, peritonitis, use of vasopressors or septic shock, echinocandin, treatment after 24 h of diagnosis, no treatment, recurrent GI perforation, inadequate antifungal treatment, and inadequate source control are shown in Table 4. Inadequate source control was identified as the only independent risk factor for 30-day mortality in both groups [ICU group OR: 13.78 (95% CI: 2.60–72.9, $p = 0002$) and non-ICU group OR: 6.53 (95% CI: 2.56–16.61, $p = <0.001$)). The population having both adequate source control and adequate antifungal treatment was the one associated with higher survival rate, in both groups, as shown in Figs. 1 and 2.

Discussion

This is the first study to the best of our knowledge assessing differences between IAC episodes in surgical wards versus those observed at the ICU. Inadequate source control was identified as the only common prognostic factor in both the ICU group (OR: 13.78) and the surgical ward group (OR: 6.53), an observation with important clinical implications. In contrast, empiric adequate antifungal therapy only influenced survival in patients at the ICU. The importance of source control has been retaken with the surviving sepsis campaign [13]; intra-abdominal infection seems to be the main anatomical site where source control becomes more feasible besides soft tissues [11, 14–16]. Although the quality of source control is difficult to evaluate [17], without it mortality can reach up to 100 %. In recent studies, the time between admission and source control in intra-abdominal infection has been assessed as a critical determinant of survival in patients with GI perforation with associated septic shock [18]; however, the majority of episodes are focused in bacterial peritonitis.

Candida albicans was the most prevalent species isolated in our analysis in both groups, with no differences between them, in agreement with previous reports in European ICUs [19, 20].

Candida peritonitis has been widely studied in critically ill patients [2, 19, 20], and it has been associated with high mortality. Up to 40 % of patients with secondary and tertiary peritonitis may develop IAC, mainly represented by peritonitis or an intra-abdominal abscess [6]. Most published reports of *Candida* infection are based on ICU mixed populations, and mostly on candidemia. However information on *Candida* peritonitis outside the ICU is scarce.

Table 1 Demographical and clinical characteristics of ICU and non-ICU patients

	All: 258	ICU: 61	Non-ICU: 197	*P*
Age (median, IQR 25–75)	62.5 (50–74)	68 (605–745)	64 (485–735)	0.013
Age >65 years	115 (44.5)	36 (59)	79 (40.1)	0.009
Male	140 (54.3)	33 (54.1)	107 (54.3)	0.978
Immunocompromised	135 (52.7)	32 (52.5)	103 (52.8)	0.961
ERSD	14 (5.4)	6 (9.8)	8 (4.1)	0.084
COPD	30 (11.6)	5 (8.2)	25 (12.8)	0.333
Heart disease	33 (12.8)	9 (14.8)	24 (12.3)	0.619
Trauma	2 (0.8)	1 (1.6)	1 (0.7)	0.383
Dialysis	6 (2.3)	2 (3.2)	4 (2.0)	0.576
DM	56 (21.7)	15 (24.6)	41 (21.4)	0.546
Days from admission to IAC	11 (4–21)	11 (5–29)	11 (3–20)	0.402
Number of surgical interventions	1 (1–2)	2.05 (1–2)	1 (1–2)	<0.001
Antifungal after 24 h	178 (69.3)	39 (63.9)	139 (70.6)	0.328
APACHE II score <15	143 (55.4)	27 (44.3)	116 (58.9)	
APACHE II score >15	115 (44.6)	34 (55.7)	81 (41.1)	0.045
Type of IAC				0.421
Peritonitis	97 (37.6)	26 (42.6)	71 (36)	0.354
Abdominal abscess	92 (35.7)	16 (27.1)	76 (39.6)	
Pancreatitis	29 (11.2)	6 (10.2)	23 (12.0)	
Biliary tract infection	30 (11)	10 (16.9)	20 (10.4)	
Other	3 (1.2)	2 (1.7)	1 (1.0)	
Previous abdominal surgery	166 (64.3)	42 (68.9)	124 (62.9)	0.40
Recurrent GI perforation	52 (20.2)	9 (14.8)	43 (22.1)	0.216
Reoperation	109 (42.2)	36 (59)	73 (37.8)	0.004
Anastomotic leakage	52 (20.2)	16 (26.2)	36 (16.4)	0.182
CVC	193 (74.8)	60 (98.4)	133 (67.9)	<0.001
Parenteral nutrition	123 (47.7	43 (70.5)	80 (41.2)	<0.001
Prolonged use of AB	183 (70.9	48 (78.7)	135 (68.9)	0.139
Prior azol exposure	23 (8.9)	8 (13.1)	15 (7.7)	0.192
Candida colonization	42 (16.3)	15 (25)	27 (13.8)	0.042
Septic shock	116 (45)	43 (70.5)	73 (37.2)	<0.001
Use of vasopressors	115 (44.6)	44 (73.3)	71 (36.2)	<0.001
Candidemia	12 (4.7)	3 (5.0)	9 (4.6)	0.896
Candida species				0.576
C albicans	161 (62.4)	33 (54.1)	128 (65.0)	
C glabrata	54 (20.9)	15 (24.6)	39 (19.8)	
C tropicalis	20 /7.8)	7 (11.5)	13 (6.6)	
C parapsilosis	10 /3.9)	3 (4.9)	7 (3.6)	
C krusei	9 (3.5)	3 (4.9)	6 (3.0)	
Concomitant isolation of bacteria	203 (78.7)	45 (75)	158 (80.6)	0.348
Initial antifungic				0.030
Echinocandin	116 (42.6)	33 (55)	77 (39.5)	0.038
Azole	41 (15.9)	4 (6.7)	37 (19)	0.026
None	104 (40.3)	14 (66.7)	81 (23.7)	0.768
Caspo S	199 (77.1)	55 (90)	144 (73)	0.286
Fluco S	134 (51.4)	34 (70.8)	100 (79.4)	0.234
Inadequate antifungal	131 (51)	29 (47.5)	102 (52)	0.539
Inadequate source control	100 (39.1)	27 (44.3)	73 (37.4)	0.340
Exitus day 30	59 (22.9)	21 (35)	38 (19.3)	0.011

DM diabetes mellitus, *ESRD* end-stage renal disease, *COPD* chronic obstructive pulmonary disease, *IAC* intraabdominal candidiasis, *GI* gastrointestinal, *CVC* central venous catheter, *AB* antibiotics

Table 2 Variables associated with survival in ICU patients

	All ICU: 61	Non-survivors: 21	Survivors: 39	*P*	OR 95%CI
Age (median, IQR)	68 (60.5–74.5)	72 (64.5–78.5)	66 (56–72)	0.009	
Age >65 years	115 (44.5)	16 (76.2)	20 (51.3)	0.060	3.04 (0.93–9.93)
Male	31 (52.5)	13 (61.9)	20 (51.3)	0.587	
APACHE II <15	27 (44.3)	4 (19)	23 (59.8)		
APACHE II >15	34 (55.7)	17 (81)	16 (41)	0.003	6.10 (1.72–21.58)
Immunocompromised	32 (52.5)	8 (38.1)	23 (59)	0.123	
ERSD	6 (9.8)	3 (14.3)	3 (7.7)	0.417	
COPD	5 (8.2)	1 (4.8)	4 (10.3)	0.463	
Heart disease	9 (14.8)	5 (23.8)	4 (10.3)	0.161	
DM	15 (24.6)	4 (19)	11 (28.2)	0.541	
Days from admission to IAC	21.26 (5–29)	10 (4.5–22.5)	12 (6–32)	0.399	
Number of surgical procedures	2.05 (1–2)	2 (1–3)	2 (1–2)	0.118	
Antifungal after 24 h	39 (65)	18 (85.7)	21 (53.8)	0.014	5.14 (1.30–20.33)
Type of IAC				0.490	
Peritonitis	26 (42.6)	11 (52.4)	15 (38.6)	0.299	1.76 (0.60–5.14)
Abdominal abscess	16 (27.1)	4 (19)	12 (32.4)	0.327	0.52 (0.14–1.91)
Pancreatitis	6 (10.2)	3 (14.3)	3 (7.7)	0.417	
Biliary tract infection	9 (15)	2 (9.5)	7 (18.9)	0.383	
Other	2 (1.7)	1 (4.8)	1 (2.5)	0.169	
Previous abdominal surgery	41 (68.3)	13 (61.9)	28 (71.8)	0.562	
Recurrent GI perforation	9 (14.8)	3 (14.3)	6 (15.4)	0.909	
Reoperation	36 (59)	13 (61.9)	23 (59)	0.825	
Anastomotic leakage	16 (26.2)	6 (28.6)	10 (25.6)	0.807	
CVC	60 (98.4)	21 (100)	38 (97.4)	0.987	
Parenteral nutrition	43 (70.5)	13 (61.9)	30 (76.9)	0.243	
Prolonged use of AB	48 (78.7)	16 (76.2)	32 (82.1)	0.737	
Prior azol exposure	8 (13.1)	2 (9.5)	61 (15.4)	0.524	
Candida colonization	15 (25)	6 (30.0)	9 (23.1)	0.563	
Septic shock	43 (70.5)	17 (81)	25 (64.1)	0.174	
Use of vasopressors	43 (72.9)	18 (90)	25 (64.1)	0.034	5.04 (1.01–24.98)
Candidemia	3 (5.0)	1 (5)	2 (5.1)	0.98	
Candida species				0.730	
C albicans	33 (54.1)	13 (61.9)	20 (51.3)		
C glabrata	15 (24.6)	5 (23.8)	9 (23.1)		
C tropicalis	7 (11.5)	2 (9.5)	5 (12.8)		
C parapsilosis	3 (4.9)	1 (4.8)	2 (5.1)		
C krusei	3 (4.9)		3 (7.7)		
Concomitant isolation of bacteria	45 (75)	17 (85)	27 (69.2)	0.188	
Initial antifungal					
Echinocandin	33 (55)	6 (18.8)	26 (68.4)	0.005	0.18 (0.005–0.59)
Azole	4 (6.7)	1 (4.8)	3 (7.9)	0.647	
None	24 (39.3)	14 (66.7)	10 (25.7)	0.002	5.8 (1.8 2–18.45)
Caspo S	55 (90.2)	20 (97)	34 (87)		
Fluco S	34 (70.8)	13 (76.5)	21 (70)	0.634	
Inadequate antifungal	28 (46.7)	15 (71.4)	13 (33.3)	0.005	5.00 (1.57–15.90)
Inadequate source control	27 (45)	15 (71.4)	12 (30.8)	0.003	5.62 (1.75–18.04)

DM diabetes mellitus, *ESRD* end-stage renal disease, *COPD* chronic obstructive pulmonary disease, *IAC* intraabdominal candidiasis, *GI* gastrointestinal, *CVC* central venous catheter, *AB* antibiotics

Table 3 Variables associated with survival in surgical wards

	All: 197	Non-survivors: 38	Survivors: 159	*P*	OR 95 % CI
Age >65 years	79 (40.1)	23 (60.5)	56 (35.2)	0.004	2.82 (1.36–5.83)
Male	107 (54.3)	18 (47.4)	89 (56)	0.339	
Female	90 (45.7)	20 (52.6)	70 (44)		
Immunocompromised	103 (52.8)	20 (52.6)	83 (52.9)	0.979	
ERSD	8 (4.1)	2 (5.3)	6 (3.8)	0.682	
COPD	25 (12.8)	10 (26.3)	15 (9.5)	0.005	3.40 (1.38–8.34)
Hearth disease	24 (12.3)	8 (21.1)	16 (10.2)	0.067	
Dialysis	4 (2.0)	1 (2.6)	3 (1.9)	0.774	
DM	41 (21.4)	9 (23.7)	32 (20.8)	0.696	
Days from admission to IAC	11 (3–20)	12.5 (7–21.2)	10 (3–20)	0.273	
Number of surgical interventions	1 (1–2)	1 (1–3)	1 (1–2)	0.017	
Antifungal after 24 h	139 (70.6)	112 (70.4)	27 (71.1)	0.941	
APACHE II score <15	116 (58.9)				
APACHE II score >15	81 (41.1)	24 (63.2)	57 (35.8)	0.002	3.06 (1.47–6.39)
Type of IAC					
Peritonitis	71 (36)	24 (63.2)	47 (29.2)	<0.001	4.08 (1.94–8.57)
Abdominal abscess	76 (39.6)	9 (23.7)	67 (42.1)	0.036	0.42 (0.18–0.95)
Pancreatitis	23 (12.0)	2 (5.3)	21 (13.2)	0.171	
Biliary tract infection	20 (10.4)	2 (5.3)	18 (11.3)	0.267	
Other	1 (1.0)				
Previous abdominal surgery	124 (62.9)	22 (57.9)	102 (64.2)	0.473	
Recurrent GI perforation	43 (22.1)	17 (44.7)	26 (16.6)	<0.001	4.07 (1.89–8.76)
Reoperation	73 (37.8)	17 (45.9)	56 (35.9)	0.257	
Anastomotic leakage	36 (16.4)	10 (26.3)	26 (16.5)	0.159	
CVC	133 (67.9)				
Parenteral nutrition	80 (41.2)	22 (57.9)	58 (37.2)	0.020	2.32 (1.13–4.77)
Prolonged use of AB	135 (68.9)	29 (76.3)	106 (67.1)	0.270	
Prior azol exposure	15 (7.7)	1 (2.6)	14 (8.9)	0.196	
Candida colonization	27 (13.8)	9 (23.7)	18 (11.5)	0.050	2.39 (0.98–5.83)
Septic shock	73 (37.2)	28 (73.7)	45 (28.5)	<0.001	7.03 (3.15–15.65)
Use of vasopressors	71 (36.2)	28 (73.7)	43 (27.2)	<0.001	7.48 (3.35–16.70)
Candidemia	9 (4.6)	2 (5.3)	7 (4.4)	0.826	
Candida species				0.257	
C albicans	128 (65.0)	25 (65.8)	103 (64.8)		
C glabrata	39 (19.8)	6 (15.8)	33 (20.8)		
C tropicalis	13 (6.6)	4 (10.5)	9 (5.7)		
C parapsilosis	7 (3.6)	–	7 (4.4)		
C krusei	6 (3.0)	1 (2.6)	5 (3.1)		
Concomitant isolation of bacteria	158 (80.6)	31 (81.6)	127 (80.4)	0.867	
Initial antifungic treatment				0.007	
Echinocandin	77 (39.5)	21 (56.8)	56 (35.4)		
Azole	37 (19)	1 (2.7)	36 (22.8)		
None	81 (23.7)	15 (40.5)	66 (41.8)		
Caspo S	144 (73)	34 (100)	110 (97.3)	0.337	
Fluco S	100 (79.4)	23 (82.1)	77 (78.6)	0.680	
Inadequate antifungal	102 (52)	22 (57.9)	80 (50.6)	0.421	1.34 (0.65–2.74)
Inadequate source control	73 (37.4)	27 (71.1)	46 (29.3)	<0.001	5.92 (2.71–12.93)

DM diabetes mellitus, *ESRD* end stage renal disease, *COPD* chronic obstructive pulmonary disease, *IAC* intraabdominal candidiasis, *GI* gastrointestinal, *CVC* central venous catheter, *AB* antibiotics

Table 4 Independent risk factors for 30-day mortality in ICU and surgical ward patients (multivariate analysis)

Variable	ICU		Regular wards	
	OR 95 % CI	*P* value	OR 95 % CI	*P* value
Age >65 years			2.23 (0.91–5.48)	0.078
Peritonitis			2.46 (0.99–6.13)	0.052
APACHE >15	10.18 (1.86–55.7)	0.007		
Vasopressors	4.80 (0.67–34.31)	0.118	10.63 (3.8–29.72)	<0.001
No treatment	5.94 (1.35–26.11)	0.018		
Inadequate source control	13.78 (2.60–72.9)	0.002	6.53 (2.56–16.61)	<0.001
Inadequate antifungal			2.38 (0.91–6.21)	0.076

Variable(s) entered in the model : peritonitis, inadequate antifungal, inadequate source control, treatment after 24 h, use of vasopressor, echinocandin, no treatmentl, more than 65, APACHE higher than 15, recurrent gastrointestinal perforation,

Hosmer–Lemeshow goodness-of-fit-test, $p = 0.880$

Other studies have compared IAC versus non-peritonitic invasive *Candida* disease [21] with only 93 patients in the IAC group, and a high proportion of patients with candidemia in this group (28 %). When assessed, non-survivors had a higher ratio of underlying disease and a higher severity score at diagnosis. However, this comparison may have some bias, as previously reported IAC pathogenesis in surgical patients is different from those that present with only bloodstream infection or a combination of both, since the anatomical barrier is persistently damaged [6]. In our analysis, we found the lowest proportion of patients with candidemia and IAC ~ 5 % so far reported; and around 22 % of cases with exclusively this isolation, in concordance with previous reports reporting 4–27 % [2, 20].

In our analysis, up to 68 % of the patients at the ICU had a recent abdominal surgery and up to 59 % had to be re-operated, making this group a high-risk population for the development of IAC. Interestingly, our data demonstrate that patients with IAC in the ICU show little difference compared to those in surgical wards, mostly due to severity of disease, septic shock, and in agreement with a higher mortality rate in the ICU group.

Current international guidelines [4, 22] are focused mostly on treatment and characteristics of candidemia, and minimal recommendations are identified for IAC. Echinocandins are the first-line therapy recommended for current guidelines for critically ill patients, and have been associated with better outcomes in previous review analysis [23]. However, in these reports the numbers of intra-abdominal candidiasis cases were only around 1 %. Delayed initiation of antifungal therapy has been associated with death, mostly in candidemia [24–26]. This is the first report where a delay of more than 24 h in initiating an antifungal therapy in IAC episodes in the ICU group was associated with an increase of ~5-fold in mortality in the univariate analysis but not in the non-ICU group.

In our series, around 40 % of patients did not receive an initial, immediate antifungal treatment. If left untreated, *Candida* isolation in the peritoneum may lead to spread to distant organs or the formation of abscesses, multiple organ failure, and death [27, 28]. Whereas 2003 guidelines [29] for complicated intra-abdominal infections suggested that antifungal therapy was necessary only when recurrent intra-abdominal infection or immunosuppressive therapy

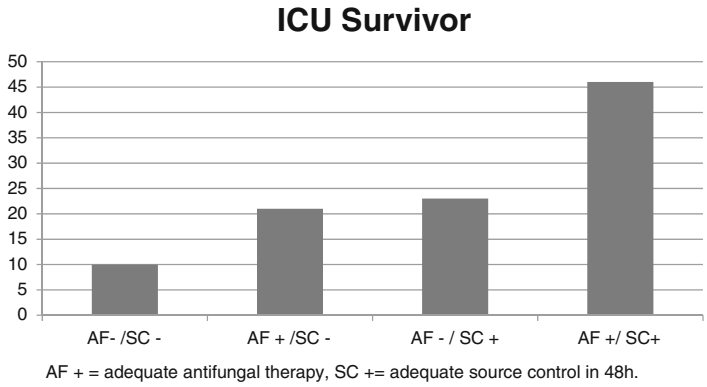

Fig. 1 Survival in patients with and without adequate source control or adequate antifungal therapy in ICU

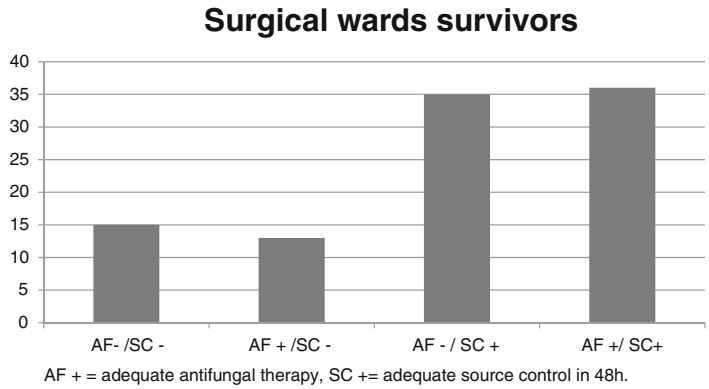

Fig. 2 Survival in patients with and without adequate source control or adequate antifungal therapy in surgical wards

were present, 2016 IDSA guidelines [22] suggest that empiric antifungal therapy should be considered in patients with clinical evidence of intra-abdominal infections and significant risk factors for *Candida* infection, such as recent abdominal surgery, anastomotic leaks, or necrotizing peritonitis (strong recommendation; moderate-quality evidence). In our analysis, patients that did not receive antifungal therapy for an IAC episode had a ∼6-fold increase in mortality in the ICU group; however, this finding was not observed in the non-ICU group.

In recent reports, mortality in Candida peritonitis varied from 25 to 60 % [2, 10, 28]. Some risk factors for mortality in ICU-IAC related to underlying disease and severity of infection have been reported [20, 21]. However, no differences were assessed between ICU and non-ICU patients to identify specific risk factors for mortality in this population. In comparison to highly selected post-chirurgical ICU patients [20, 21], our analyses have the strength that ICU and non-ICU IAC episodes could be compared. APACHE II score was the second most strong risk factor for mortality in the ICU group; a cutoff similar to our group was selected in previous reports [20] with similar results.

Differentiation between contamination, colonization, and infection in Candida peritonitis remains the main diagnostic goal [30]. In recent years, fungal biomarkers have become one of the promising tools in postoperative critically ill patients [31] to identify patients at higher risk for developing an IAC episode. Recent recommendations make emphasis on utilizing predictive rules in combination with other biomarkers, and severity of disease, to initiate empirical treatment in high-risk patients and on its potential role in reducing duration of treatment or withdrawal of it [3, 32–34] but not so much emphasis on source control is made. Any empirical or pre-emptive antifungal therapy has been demonstrated to decrease mortality in a specific population of patients with peritonitis; nevertheless, an overuse of antifungal agents can contribute to a high financial burden and promotion of resistant strains even in the sickest patients [35–38]. Until this new approach becomes routine practice, educational efforts should be directed towards achieving a prompt and adequate source control in IAC episodes in and outside the ICU.

Due to the retrospective design of the study, we cannot assess some other variables, and this should be taken into account as a study limitation. First, we cannot assess if earlier source control can result in a better outcome, and this issue should be explored in further studies. Furthermore, no data regarding the influence of concomitant antibiotic therapy on outcomes could be assessed.

Conclusion

Our findings suggest no differences in source of infection or *Candida* species in ICU or surgical wards were observed. Adequate initial treatment was higher in the ICU population and has a stronger impact on outcome, particularly in the subset with higher severity. Source control remains the main goal for decreasing mortality of IAC episodes inside and outside the ICU, emphasizing the contribution of the surgeon in intra-abdominal infections.

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ANNEX 2

Other manuscripts published and related to this work.

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REVIEW

Invasive candidiasis: from mycobiome to infection, therapy, and prevention

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Abstract *Candida* spp. are commonly found in humans, colonizing most healthy individuals. A high prevalence of invasive candidiasis has been reported in recent years. Here, we assess the relation between *Candida* spp. as part of the human mycobiome, the host defense mechanisms, and the pathophysiology of invasive disease in critically ill patients. Many hypotheses have been proposed to explain the different immune responses to the process where *Candida* goes through healthy mycobiome to colonization to invasion; the involvement of other microbiota inhabitants, changes in temperature, low nitrogen levels, and the caspase system activation have been described. Patients admitted to an intensive care unit (ICU) are at the highest risk for invasive candidiasis, mostly due to the severity of their disease, immune-suppressive states, prolonged length of stay, broad-spectrum antibiotics, septic shock, and *Candida* colonization. The first approach should be using predictive scores as screening, followed by the determination of biomarkers (when available), and, in the near future, probably immune-genomics and analysis of the clinical background in order to initiate prompt and correct treatment. Regarding treatment, the initiation with an echinocandin is strongly recommended in critically ill patients. In conclusion, prompt treatment and adequate source control in the more severe patients remains the ultimate goal, as well as restoration of a healthy microbiota.

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Introduction

Candida spp. are commonly found in humans. They colonize the skin and mucosal surfaces of most healthy individuals [1], being part of what is fashionably termed microbiota or what others named the "mycobiome". *Candida* spp. are highly prevalent fungi and have been well studied in the context of human microbiota [2, 3] (Table 1). These opportunistic fungal pathogens can cause either local or systemic infection; in recent years, the prevalence of sepsis due to fungal organisms has risen by more than 200 % [4] and they have become the third most common pathogen isolated from blood samples in large epidemiological studies in critically ill patients [5]. Patients with systemic fungal infection by *Candida* can be subdivided into three groups: those who present with bloodstream infection (candidemia), those who develop deep-seated candidiasis (most frequently intra-abdominal candidiasis), and those who develop a combination of the two. High mortality rates, ranging from 27 to 55 %, have recently been correlated with these infections [6, 7].

In the present study, we assess the relation between *Candida* spp. as part of the human mycobiome, host defense mechanisms, and the pathophysiology of invasive disease in critically ill patients, and consider future directions for their diagnosis and therapeutic management.

Normal immune response to *Candida* and pathophysiology

As mentioned above, *Candida* spp. are opportunistic pathogens which are resident members of the healthy mycobiome.

Table 1 Major components of the mycobiome in different body sites

Site	Fungal composition
Oral cavity	*Candida* spp., *Cladosporium*, *Aspergillus* spp., *Fusarium*
Nasal cavity	*Cladosporium*, *Penicillium*, *Alternaria*, *Aspergillus* spp.
Gut	*Wallemia*, Trichocomaceae, *Saccharomyces*, *Rhodotorula* *Candida* spp., uncultured fungi, *Aspergillus*, *Simplicillium* *Rhodotorula*, *Galactomyces*, *Trametes*, *Pleospora*
Vagina	*Candida*, *Pichia*, *Eurotium*, *Alternaria*
Conjunctiva (leprosy)	*Candida*, *Aspergillus*, *Geotrichum*, *Acremonium*
Skin	*Candida*, *Malassezia*, *Cladosporium*, *Cryptococcus*

Modified from [2]

Only in certain circumstances do they become pathogenic and cause life-threatening infections. The composition of the mycobiome differs according to body region and, therefore, its local role in the development of disease may vary.

Gut microbiota form part of the first line of antimicrobial defense, along with the mucosal barrier, antibodies, antibiotic peptides, and the intestinal epithelium. Members of the intestinal microbiota secrete bacteriocins—toxins produced by bacteria to inhibit the growth of similar or closely related bacterial strains—and compete with pathogens for nutrients, surfaces, and substrates [8, 9].

A crucial step in the process in which *Candida* spp. become invasive is their ability to form hyphae and become virulent, adhering to and invading into deeper tissues (Fig. 1). When loss of integrity occurs in a normal ecosystem such as the gut, other microbiota inhabitants such as *Pseudomonas aeruginosa* and *Enterococcus faecalis* have been shown to inhibit hyphal morphogenesis [10]. Other environmental factors such as temperature below 35 °C inhibit hyphal development through the action of the heat shock protein 90 (HSP90). Low nitrogen levels due to starvation have been associated with activation of hyphal development through mitogen-activated protein kinase (MAPK) [11]. These morphogenic changes are associated with proteins localized in the cell wall that act as adhesins and invasins, and these simultaneously modulate immune responses [12].

Increased activity of peritoneal macrophages, more efficient neutrophil activity, and a re-balanced cytokine response have all been noted after lactobacilli supplementation. All of these mechanisms have been found to be altered during *Candida* infection. In a recent randomized controlled trial (RCT) in a pediatric population, probiotics were shown to decrease the rate of fungal colonization by more than 30 % and as early as day 7 [13, 14]. It is clear that the morphogenesis of *Candida* is regulated by a complex network which depends on the microenvironmental status and host innate immunity, and can lead to a range of clinical scenarios. The recognition of *Candida* by innate immune cells is mediated by at least three families of pattern recognition receptors (PRRs): toll-like receptors (TLRs), C-type lectin receptors, and the nucleotide-binding oligomerization domain-like receptors. These PRRs initiate the pro- and anti-inflammatory cascade upon recognition of invasion.

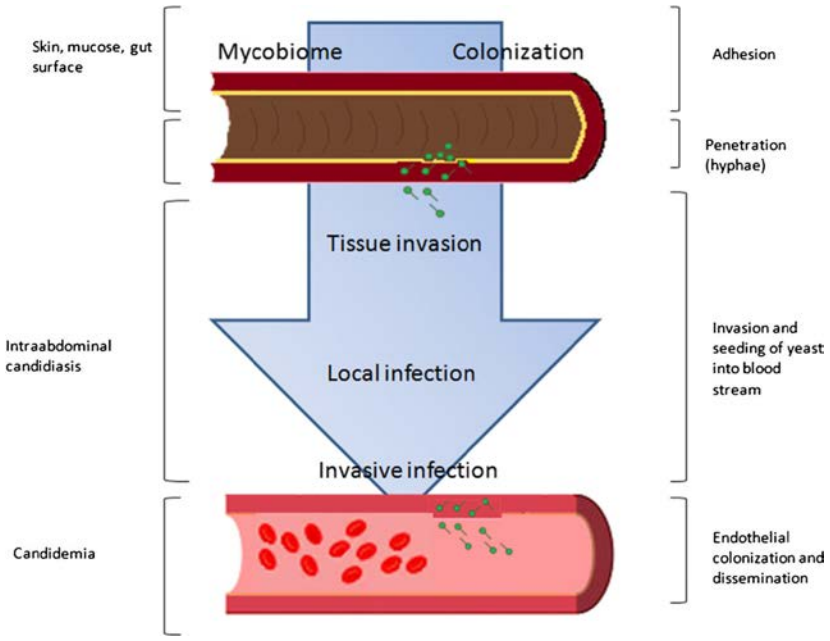

Fig. 1 Pathogenesis in invasive candidiasis

Several hypotheses have been proposed to explain the different immune responses to the dimorphic *Candida* form. One of the most recent involves caspase 1 related to the activation of T_H17 cells (a T cell subset) in the mucosal lining, depending on the load and morphology of *Candida*, which may be able to differentiate between colonization and infection [15]. However, definitive information is still scarce.

Risk factors for invasive candidiasis

Any variable that alters the commensal relation between *Candida* spp. and the host could be interpreted as a risk factor for invasive candidiasis. Its clinical manifestations may differ, depending on the clinical conditions in which the invasion takes place (Table 2) [16, 17].

Patients in the intensive care unit (ICU) are at the highest risk for invasive candidiasis, mostly due to the severity of their disease, immune-suppressive states, prolonged length of stay, septic shock, and *Candida* colonization. Colonization occurs in the ICU population during the first week in up to 80 % of cases [5, 18], but few develop an ensuing severe infection [19]. The pathophysiology route of infection will determine the clinical scenario [20]; indeed, during a large recent study [7] focusing on intra-abdominal candidiasis, only 14 % of patients also developed candidemia.

A well-known risk factor for invasive candidiasis is the use of broad-spectrum antibiotics [21]. Cephalosporins have been associated with specific species such as *C. glabrata* [22]. In recent studies, patients using ciprofloxacin-containing regimens presented a higher risk [hazard ratio (HR) 3.4, 95 % confidence interval (CI): 1.4–8.0] of developing invasive *Candida* spp. infection; this effect was not observed with other antibiotics such as meropenem, piperacillin/tazobactam, or cefuroxime [23]. In contrast to bacterial infection, the process between *Candida* colonization and infection requires time, around 7 days according to some authors [20], and, so, treatment should be individualized. Oncohematological patients and solid organ transplant (SOT) recipients have an altered neutrophil function, due to the disease or due to chemotherapy or immunosuppressive agents; in some cases, their complex healthcare routine also makes them a high-risk population.

Diagnosis

The diagnosis of invasive candidiasis [24] is still difficult because of the "common" presence of yeast cells in certain tissues. The gold standard for diagnosis remains culture from sterile sites. However, the sensitivity of blood cultures is nowhere near optimal, ranging between 21 and 71 % in autopsy studies [25]. Efforts have been made to identify predictive rules in order to initiate antifungal therapy. Some of the most widely used are characterized by their high negative predictive value and are validated in candidemia only [21, 26, 27]; this means that they are useful for screening patients to rule out invasive candidiasis, but not for initiating treatment. In recent years, the development of fungal biomarkers has emerged as a promising tool in patients in whom suspicion is high but culture remains negative, and also to identify patients who are at the highest risk for developing an intra-abdominal candidiasis episode and are, therefore, likely to benefit most from appropriate early treatment.

Mannan antigen and anti-mannan antibodies

Mannan is a polysaccharide present in the fungal structure of *Candida*. When invasive candidiasis is present, mannan can be detected in plasma along with its antibodies. Recent European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines recommend the use of these antibodies to diagnose invasive candidiasis with a level of evidence of II [28].

Beta D-glucan

Beta D-glucan (BDG) is a component of the inner layer of the fungal wall, not specific for *Candida* spp. In high-risk critically ill surgical patients, it has been identified as a good predictor for intra-abdominal candidiasis; two consecutive BDG serum levels above 80 pg/ml were positive-predictive around ~5 days earlier than regular cultures, and also achieved high sensitivity and specificity [29]. In patients with prolonged ICU stay who developed severe sepsis, a cutoff value of

Table 2 Clinical scenario and specific risk factors for invasive candidiasis

Type of patient	Risk factor
Oncohematological	Mucositis, altered neutropenic function
Solid organ transplant recipient	Immunosuppressive agents
Surgical patients (multiple abdominal surgeries, severe acute pancreatitis)	Contamination of peritoneum if repeated interventions
Non-surgical critically ill patient	Septic shock, broad-spectrum antibiotics, biofilms in central venous catheters, endotracheal tube, nasogastric tube, or urinary catheters
Surgical critically ill patients	Contamination of peritoneum plus ICU specific risk factors

80 pg/ml was again identified as a marker of early detection of invasive candidiasis [30].

Other specific biomarkers for *Candida* infection include polymerase chain reaction (PCR) detection and the *Candida albicans* germ tube specific antibody (CAGTA), but these methods are still to be validated in large populations and are currently not recommended in the guidelines [28].

Immunogenomics

Recently, a secondary analysis by the FUNGINOS group [31] evaluated the influence of genetic polymorphisms on the susceptibility to *Candida* colonization and intra-abdominal candidiasis. They found one single-nucleotide polymorphism (SNP) associated with *Candida* colonization located in TLR4 and two associated with intra-abdominal candidiasis: one located in the tumor necrosis factor alpha (TNfα) gene (rs1800629, AA/GA) and the other in the β-defensin 1 gene (DEFB1) (rs18 00971, GG/CG). If these results are confirmed in larger cohorts, this may lead to a change in approach, since the identification of these SNPs may predict patients at high risk who have a genetic predisposition to develop invasive candidiasis.

Sites other than blood or peritoneum may be involved. As mentioned above, *Candida* can infect locally or systemically. Central nervous system manifestations can occur due to disseminated candidiasis, or as a complication of a neurosurgical procedure. It may present as meningitis or as small, solitary, or epidural abscesses. Ocular involvement should be ruled out in every patient with candidemia, paying particular attention to those who cannot report visual alterations [32]. Patients with neutropenia should be evaluated when the neutrophil count recovers.

Candida endocarditis is one of the most serious manifestations of invasive candidiasis. The optimal therapy is a combination of valve replacement and a long course of antifungal therapy (according to current guidelines, liposomal amphotericin B is preferred). Urinary tract involvement is common in critically ill patients; however, asymptomatic candiduria should only be treated in patients with high-risk factors, such as severely immune-compromised patients with fever and candiduria in whom an invasive candidiasis must be ruled out.

Treatment

The opportunities for initiating antifungal treatment during the ICU stay are numerous and illustrated in Fig. 2. According to current Infectious Diseases Society of America (IDSA) and ESCMID guidelines, invasive candidiasis patients must receive prompt treatment, and the selection of the antifungal agent should be based on the patient's clinical situation. Initiation with an echinocandin is strongly recommended

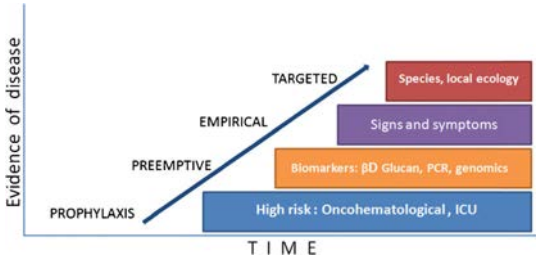

Fig. 2 Opportunities for the treatment of invasive candidiasis

when septic shock, hemodynamic instability, or high risk of an azole-resistant causal agent is suspected or present [33, 34].

Echinocandins were associated with better outcome in a recent review analysis [35]. With regard to intra-abdominal candidiasis, there is little evidence to favor the choice of a particular antifungal agent. A small recent analysis showed that micafungin in plasma and peritoneal fluid in critically ill patients with proven or suspected intra-abdominal infection achieved low to moderate penetration into the peritoneal fluid after the first dose in around 30 % of cases [36]. Nevertheless, the usefulness of biomarkers to guide initiation or cessation of empirical antifungal treatment is still to be determined [37].

Prophylaxis

Given the high mortality, prophylaxis for invasive candidiasis has been widely analyzed. Fluconazole has proved to be effective for preventing colonization and intra-abdominal candidiasis in high-risk surgical patients when compared to placebo [38, 39]. However, mortality rates were not compared and the incidence of candidemia in those patients when analyzed was too low to allow assessment (2.2 %) [40].

Other attempts have been made to introduce prophylaxis with newer antifungals. In one trial, micafungin was compared to placebo in high-risk ICU patients, but benefit was not demonstrated in mortality or in proven candidiasis [41]. It should be borne in mind that administering prophylaxis with a broad-spectrum antifungal may increase resistance and the cost could be excessive [42].

A recent meta-analysis [43] concluded that echinocandins are as effective as triazoles administered for prophylaxis. However, the RCTs presented a large variability in terms of patients and scenarios. In a recent survey [44], up to 7.5 % of ICU patients received systemic antifungal therapy without evidence of infection.

Probably the best recommendation is to use predictive scores as first screening, excluding patients with a low probability of presenting invasive candidiasis, followed by the determination of biomarkers (when available), and, in the near future, probably immune-genomics and analysis of the clinical background in order to initiate prompt and correct treatment.

Conclusion

Candida spp. is part of the healthy mycobiome but can become invasive, depending on microenvironmental determinants and host immunity status. Invasive candidiasis is a high-prevalence infection with a high mortality rate in critically ill patients. Prompt treatment and adequate source control in the more severe patients remains the ultimate goal. Strict antimicrobial policies should be imposed in order to prevent infection and restore the mycobiome.

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Review Article

Current understanding in source control management in septic shock patients: a review

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Abstract: Sepsis and septic shock is one of the leading causes of death worldwide. Antibiotics, fluid resuscitation support of vital organ function and source control are the cornerstones for the treatment of these patients. Source control measures include all those actions taken in the process of care to control the foci of infection and to restore optimal function of the site of infection. Source control represents the multidisciplinary team required in order to optimize critical care for septic shock patients. In the last decade an increase interest on fluids, vasopressors, antibiotics, and organ support techniques in all aspects whether time, dose and type of any of those have been described. However information of source control measures involving minimal invasion and new techniques, time of action and outcome without it, is scarce. In this review the authors resumes new information, recommendations and future directions on this matter when facing the more common types of infections.

Keywords: Source control; sepsis; septic shock; intra-abdominal sepsis; skin; soft tissue infection; empyema

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Introduction

Source control is an old term that makes reference to one of the oldest way for controlling an ongoing infection, records from ancient Egypt already mentioned the drainage of thoracic abscess as a source control measure (1). It involves all physical actions taken in the process of care to control a focus of infection and subsequently reduce the favorable conditions that promote microorganism growth or that keep impaired host defenses (2). The importance of source control has been retaken with the surviving sepsis campaign (3), however last recommendations (4) only make four statements on this matter, with low evidence grade endorsing a gap of 12 hours for its achievement when feasible. Most recent studies make emphasis in antibiotics (time, dose) organ support therapies, reanimation (crystalloids versus colloids, vasopressors) and more recently adjuvant strategies for septic patients, however evidence in the oldest manner to control an infection is scarce. Source control is a cornerstone in the treatment of infectious diseases and it becomes an urgent matter in septic shock patients. Here the authors present a review on the rationale of source control, recent recommendations in this matter and future directions for trials or research.

Rationale for source control

The process of infection is a complex state that involves both microorganism and host mechanisms to prevail. A local initial inflammatory responds attracts neutrophils, macrophages, and other phagocytes promotes the release of cytokines such as IL-8, IL-1 and the activation of the coagulation cascade. In some cases this is accompanied by liquefaction necrosis and the release of pus with replicating

microorganism in this site. Defensive host responses include the formation of fibrin deposits to shield healthy tissues from the dissemination, establishing an abscess (5). This abscess will protect both host and bug, where no drug will penetrate well enough to control the infection. Some other forms of persistent foci of infection have become evident with advances in modern care, aging, comorbidities, invasive procedures, chronic care facilities and in day hospitals have made that some specific population could present differently from abscess alone or with multidrug resistant microorganisms.

This local, initial process is common for almost all complicated soft tissue infections and some of intra-abdominal septic shock patients, and is what gives the basis for source control in those, whereas (I) drainage of infected fluid collections; (II) debridement of infected solid tissue and the removal of devices or foreign bodies; and (III) definitive measures to correct anatomic derangements resulting in ongoing microbial contamination and to restore optimal function conform actions included under this definition and will contribute on outcome (6,7).

Soft tissue and skin infections

This kind of infections represent the third most frequent cause of severe sepsis and septic shock following pneumonia and intra-abdominal infections (IAIs) in some series (8,9), but one of those that source control measures can be more evident. The spectre of diseases that are included in this group can presents differently and so categorized, according to causative microorganism, or extension or clinical symptoms. A clinical categorization depending on presence of septic shock and the urgency of requirement for surgical procedures in order to achieve source control has been described (10) with worst outcomes in those with inadequate therapy and sepsis. Source control in these infections comprises since topical actions, incision and drainage, debridement, up to amputation. Patients at intensive care unit (ICU) with severe soft tissue and skin infection are mostly represented by those with necrotizing fasciitis (NF), and many times with organ failure associated. Recent recommendations on the approach regarding NF (11) states that in uncertain cases time should not be wasted in extensive clinical diagnosis, or scoring severity of the patient or hesitating on extension of the first incision. A deep incision up to the fascia should be performed and if NF is diagnosed, radical debridement should be implemented. Recent guidelines (12,13) on the management of soft tissue and skin infections make recommendations on prompt and extensive surgery, and a second debridement when necessary to discard ongoing local extension, among the use of broad spectrum antibiotics. Seems prudent that, whenever possible, source control should be attempted as soon as foci is detected. A delayed first surgical intervention (more than 12 hours) is associated with higher mortality (14), however in a recent report (15) an early intervention (less than 6 hours from diagnosis) was associated with shorter ICU and hospital length of stay but no statistical differences in mortality were founded between early and late surgery. Antibiotics should be given as any septic shock patient in the first 6 hours, and administration of clindamycin is highly recommended in order to inhibit exotoxin production of Gram-positive bacteria. Duration of antibiotic treatment can be between 7–14 days according to guidelines (12,13).

IAIs

IAIs are the second cause of admission to the ICU in large series (16,17). The number of cases of peritonitis that required admission to an ICU due to organ failure had remained stable during time both community-acquired and nosocomial-related, however this latter group seems to be increasing in recent reports (18). IAI commonly represents the other group of septic shock patients that have an identified foci of infection where source control actions become feasible besides skin and soft tissues infection (7,19-21). As any other supportive action in septic shock patient time is an urgent matter. Time between admission and source control in IAI has been assessed as a critical determinant of survival in patients with GI perforation with associated septic shock (22), and in some intra-abdominal candidiasis cases (23), however in these reports “early” goes from 2 hours up to 5 days.

The quality of source control is difficult to evaluate (24,25) IAIs without it, mortality probably could reach up to 100% (26). The appropriate interventions to determine the adequacy of source control are dictated by the clinical circumstances. High risk patients as such in septic shock with high doses of inotropes or requiring other supportive measures could benefit for new approaches. Nowadays minimal invasive procedures including percutaneous and endoscopic treatments have been described for non-severe cases. It may have a role in well localized abscesses or in surgical inaccessible abdomen. Recent recommendations on source control and peritonitis use the term “damage control” surgery for this kind of critically ill patients with

Table 1 Source control actions recommended in skin and soft tissue and intra-abdominal infections

Skin and soft tissue infections
Device removal
Incision and drainage
Limited debridement for maximum preservation of vital tissue
Extended debridement for removal of all infected and necrotic tissue
Amputation
Intra-abdominal infection
Prevention in the surgical incision
Drainage of abscesses
Debridement of infected necrotic tissues
Removal of potential infected devices
Extensive intra-abdominal cleansing for decrease peritoneum inoculum
Second time abdominal wall closure
Non-pneumonic thoracic infections
Bedside image assessment (thoracic ultrasound)
Thoracocentesis
Placement of chest tubes
VATS or open thoracotomy for chronic/loculated cases

VATS, video assisted thoracoscopy surgery.

inaccessible abdomen (26). Surgery gives opportunity to take first local microbiological samples however some interventions may cause further complications and risk factors associated with the procedures. Current guidelines on the management of IAIs (21,27) discourage systematic reoperations as routine practice. In the other hand assuming risks for patients in septic shock to be carried to the operating room (OR) and the best moment for to take this measures is difficult to assess and evaluate, transfer, surgery, anaesthesia are some of the key players to address. *Table 1* resumes source control actions in skin and soft tissue and IAIs.

Non-pneumonic thoracic infection

Pleural infection is a non-rare complication for pneumonia, almost 20% of these empyema episodes will require surgical intervention as source control measure (28). Every patients presenting with a pleural effusion in association with sepsis or pneumonic illness require a prompt diagnostic pleural fluid sampling. In recent years, to employ thoracic ultrasound at the bedside to determine the presence of effusions especially in septic shock patients at the ICU has increased. It is a safe, fast and effective tool to determine volume and accessibility in order to drain abscesses or pleural infected effusions. Recent recommendations on this matter (29,30) suggested as first approach the use of thoracic ecography, following diagnostic sampling thoracocentesis, and if necessary the placement of a chest tube. The role of video assisted thoracoscopy and open thoracotomy can be reserved for those chronic or loculated cases.

Mediastinitis is a more difficult to approach infection due to anatomical difficulties, there are discrepancies whether time and surgical approach will lead to better outcomes. A recent large review of descending necrotizing mediastinitis (31) suggested that a prompt and aggressive surgical treatment was related with survival and in extended cases the transthoracic approach was recommended.

Urinary tract infections

This group of infections account for the third or fourth group of infections admitted to the ICU depending on different reports. It seems of common sense that in those where an abscess is identified or where an obstruction in the usual urinary flow (obstructive pyelonephritis) is the responsible for the infection; the prompt action taken to solve this (drainage or lithotomy and placement of catheters) are recommended as source control measures as mentioned above. A concerning issue are the catheter associated urinary tract infections a common problem in both ICU and non-ICU patients (32) more so because of it probability of preventing it. However a recent multicenter analysis (33) based on an educational program addressing many of the factors involved in this type of infection showed that these programs are efficient only on non-ICU patients when compared to ICU patients in decreasing both use and related infection.

Some other sites of infection such as pneumonia, or bacteremia have a more difficult to achieve source control goals, so probably in this patients, the importance of the correct and prompt initiation of antibiotics along with support measures have a larger effect in their outcome, however further trials are required in this matter.

Conclusions

Source control remains as a cornerstone in the treatment of septic shock patients. IAIs along with soft tissues infections are the sites where a rapid source control seems more feasible. Recommendations and educational efforts should advise a more prompt achievement of source control.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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