A multicenter multinational study of abdominal candidiasis: epidemiology, outcomes and predictors of mortality

Matteo Bassetti
Elda Righi
Filippo Ansaldi
Maria Merelli
Claudio Scarparo
Massimo Antonelli
Jose Garnacho-Montero
Ana Diaz-Martin
Inmaculada Palacios-Garcia
Roberto Luzzati
Chiara Rosin
Leonel Lagunes
Jordi Rello
Benito Almirante
Pier Giorgio Scotton
Gianmaria Baldin
George Dimopoulos
Marcio Nucci
Patricia Munoz
Antonio Vena
Emilio Bouza
Viviana de Egea
Arnaldo Lopes Colombo
Carlo Tascini
Francesco Menichetti
Enrico Tagliaferri
Pierluigi Brugnaro
Maurizio Sanguinetti
Alessio Mesini
Gabriele Sganga
Claudio Viscoli
Mario Tumbarello

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Collaborators Marina Busetti, Montserrat Pujol, Joan Balcells, Tomas Pumarola, Maria Teresa Martin, Simone A. Nouér, Teresa Pelaez, Enzo Raise, Stefano Grandesso, Valerio Del Bono, Patricia Esteves, Cecilia Trucchi, Assunta Sartor, Gennaro De Pascale, Brunella Posteraro, Claudio Scarparo, Patricia Esteves.

M. Bassetti (✉) · E. Righi · M. Merelli · C. Scarparo
Infectious Diseases Division, Santa Maria Misericordia University Hospital, Piazzale Santa Maria della Misericordia 15, 33100 Udine, Italy
e-mail: mattba@tin.it
Tel.: +39 0432 559353

F. Ansaldi
IRCCS San Martino IST, Department of Health Sciences, University of Genoa, Genoa, Italy

M. Antonelli
Care Department, Università Cattolica del Sacro Cuore, Rome, Italy

J. Garnacho-Montero · A. Diaz-Martin · I. Palacios-Garcia
Critical Care and Emergency Clinical Unit, Virgen del Rocio University Hospital, Seville, Spain

R. Luzzati · C. Rosin
Infectious Diseases Unit, University Hospital of Trieste, Trieste, Italy

L. Lagunes · J. Rello · B. Almirante
Critical Care Department, Vall d'Hebron University Hospital, CIBERES, Universitat autonoma de Barcelona, Barcelona, Spain

P. G. Scotton · G. Baldin
Infectious Diseases Unit, Treviso Hospital, Treviso, Italy

G. Dimopoulos
Critical Care Department, Attikon University Hospital, Medical School, University of Athens, Athens, Greece

M. Nucci
Department of Internal Medicine, University Hospital, Federal University of Rio de Janeiro, Rio De Janeiro, Brazil

P. Munoz · A. Vena · E. Bouza · V. de Egea
Department of Clinical Microbiology and Infectious Diseases, Hospital General Universitario Gregorio Marañón, School of Medicine, Universidad Complutense de Madrid, Madrid, Spain

A. L. Colombo
Hospital São Paulo, Escola Paulista de Medicina, Federal University of São Paulo, São Paulo, Brazil

C. Tascini · F. Menichetti · E. Tagliaferri
U.O. Malattie Infettive, Azienda Ospedaliera Universitaria Pisana, Pisa, Italy

P. Brugnaro
Infectious Diseases Division, Venezia Hospital, Venice, Italy

M. Sanguinetti
Institute of Microbiology, Università Cattolica del Sacro Cuore, Rome, Italy

A. Mesini · C. Viscoli
Infectious Diseases Division, San Martino Hospital, Genoa, Italy

G. Sganga
Division of General Surgery and Organ Transplantation, Department of Surgery, Università Cattolica del Sacro Cuore, Rome, Italy

M. Tumbarello
Institute of Infectious Diseases, Università Cattolica del Sacro Cuore, Rome, Italy

Abstract *Purpose:* Clinical data on patients with intra-abdominal candidiasis (IAC) is still scarce. *Methods:* We collected data from 13 hospitals in Italy, Spain, Brazil, and Greece over a 3-year period (2011–2013) including patients from ICU, medical, and surgical wards. *Results:* A total of 481 patients were included in the study. Of these, 27 % were hospitalized in ICU. Mean age was 63 years and 57 % of patients were male. IAC mainly consisted of secondary peritonitis (41 %) and abdominal abscesses (30 %); 68 (14 %) cases were also candidemic and 331 (69 %) had concomitant bacterial infections. The most commonly isolated *Candida* species were *C. albicans* ($n = 308$ isolates, 64 %) and *C. glabrata* ($n = 76$, 16 %). Antifungal treatment included echinocandins (64 %), azoles (32 %), and amphotericin B (4 %). Septic shock was documented in 40.5 % of patients. Overall 30-day hospital mortality was 27 % with 38.9 % mortality in ICU. Multivariate logistic regression showed that age (OR 1.05, 95 % CI 1.03–1.07, $P < 0.001$), increments in 1-point APACHE II scores (OR 1.05, 95 % CI 1.01–1.08, $P = 0.028$), secondary peritonitis (OR 1.72, 95 % CI 1.02–2.89, $P = 0.019$), septic shock (OR 3.29, 95 % CI 1.88–5.86, $P < 0.001$), and absence of adequate abdominal source control (OR 3.35, 95 % CI 2.01–5.63, $P < 0.001$) were associated with mortality. In patients with septic shock, absence of source control correlated with mortality rates above 60 % irrespective of administration of an adequate antifungal therapy. *Conclusions:* Low percentages of concomitant candidemia and high mortality rates are documented in IAC. In patients presenting with septic shock, source control is fundamental.

Keywords Abdominal candidiasis · Candida · Antifungal therapy · Source control · Mortality · Adequate treatment

Abbreviations

CLSI	Clinical Laboratory Standards Institute
COPD	Chronic obstructive pulmonary disease
CVC	Central venous catheter
ESRD	End stage renal diseases
GI	Gastrointestinal
IAC	Intra-abdominal candidiasis
ICU	Intensive care unit

Introduction

Intra-abdominal candidiasis (IAC) is the predominant type of invasive candidiasis after candidemia. IAC is associated with mortality rates around 25–60 % [1–6]. The majority of epidemiological studies on *Candida* are focused only on bloodstream infections. Nevertheless, the role of blood cultures has a limited application in patients with abdominal candidiasis [7]. IAC, which includes peritonitis and intra-abdominal abscesses, may occur in around 40 % of patients following repeat gastrointestinal (GI) surgery, GI perforation, or necrotizing pancreatitis [8]. *Candida* was reported to be isolated in 41 % of upper gastrointestinal (GI) sites, 35 % of small bowel, 12 % of colorectal, and less than 5 % of appendicular sites in [6, 8, 9]. European studies have demonstrated a predominance of *C. albicans* isolates (ranging from 65 to 82 %), followed by *C. glabrata* in intra-abdominal *Candida* infections in surgical patients [4, 6]. Increased rates of non-albicans *Candida* isolates from abdominal samples in comparison to other studies have been reported in ICU patients by Montravers et al. (42 vs. 26 %, respectively) [10]. Although no specific predictors of mortality have been identified, the outcome of IAC is known to be

influenced by selected site-dependent (i.e., infection extension, non-appendicular origin) and host-related factors (i.e., age, comorbidities) [7]. IAC high mortality is partly related to diagnostic difficulties, such as the low sensitivity and specificity of cultures along with the prolonged time to obtain results both before and after the occurrence of IAC. Moreover, it is still unclear which patients could benefit from empiric antifungal treatment and which ones might be at risk of dwelling fluconazole-resistant strains [10]. Recently, abdominal candidiasis has been described as a hidden reservoir for the emergence of echinocandin-resistant *Candida* [11].

Recently updated international guidelines preferentially targeted candidemia and not complicated intra-abdominal infections, probably because of the lack of standardized diagnostic criteria [12, 13]. The aim of our study was to determine the clinical aspects and the risk factors associated with mortality of patients with abdominal infections due to *Candida* spp.

Materials and methods

Patient population and study design

This retrospective multicenter cohort study was conducted at 13 teaching hospitals of different size (minimum 500 beds, maximum 1550 beds) across Italy, Spain, Greece, and Brazil over a 3-year period (2011–2013). The study was approved by the institutional review board of the coordinating center (Udine) and written patient consent was not required because of the observational nature of this study.

An episode of IAC was defined as follows [7]:

- *Candida* detection by direct microscopy examination or growth in culture from purulent or necrotic intra-abdominal specimens obtained during surgery or by percutaneous aspiration
- *Candida* growth from bile, intra-biliary ducts devices, and biopsy of intra-abdominal organs
- *Candida* growth from blood cultures in 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

Organ dysfunction and septic shock definitions have been previously reported [14].

Patient baseline characteristics and infection-related variables were collected from the hospital medical records, microbiology database, and pharmacy database of the participating centers. The baseline characteristics collected included age, gender, comorbidities, previous surgery, use of immunosuppressants, Acute Physiology and Chronic Health Evaluation (APACHE) II score, number of acquired organ dysfunctions, and need of ICU admission. The APACHE II was calculated on the basis of clinical data present during the 24 h after the positive cultures were obtained. Infection and therapy-related characteristics examined were infection source, *Candida* species, prior antibiotic exposure (more than 7 days in the past 30 days), adequate abdominal source control [defined as (1) drainage of infected fluid collections, (2) debridement of infected solid tissue and the removal of devices or foreign bodies, and (3) definitive measures to correct anatomic derangements resulting in ongoing microbial contamination and to restore optimal function within 48 h after diagnosis of IAC], timing of antifungal therapy relative to time of IAC diagnosis, and type of antifungal used. Peritonitis were defined as secondary (related to a pathologic process in a visceral organ, such as perforation or trauma, including iatrogenic trauma) or tertiary (if persistent or recurrent infection after adequate initial therapy). The primary outcome variable was all-cause 30-day hospital mortality.

Initial treatment was considered adequate when the infecting organism was ultimately shown to be susceptible and the dosage of antifungal used was adequate within the first 24 h from culture positivity. Adequate abdominal source control measures were considered within the first 48 h from culture positivity.

The following antifungal dosages were considered adequate: fluconazole 800 mg loading dose [for obese patients (BMI $>$ 30), 1200–1600 mg) followed by a daily dosage of at least 400 mg (600–800 mg for BMI $>$ 30), liposomal amphotericin B (L-AmB) 3 mg/kg/day, amphotericin lipid complex (ABLC) 5 mg/kg/day, caspofungin 70 mg loading dose (100 mg) followed by 50 mg/day (70 mg/day), micafungin 100 mg/day, anidulafungin 200 mg loading dose followed by 100 mg/day.

During the study period there were no changes in microbiological laboratory techniques among the 13 hospitals. *Candida* species were isolated using the BACTEC 860 system (Becton–Dickinson, Inc., Sparks, MD) and BacT/Alert 3D (BioMèrieux). The species were identified using API ID 32C system (bioMérieux, Marcy l'Etoile, France) or Vitek 2 system (bioMérieux). In the case of inconclusive results by both the systems, isolates were definitively identified using supplemental tests, e.g., 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 to amphotericin B, 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 (BioMèrieux, France) and interpreted by the Clinical Laboratory Standards Institute (CLSI) breakpoints.

Statistical analysis

Continuous and categorical data were reported as median, 25th and 75th percentile and frequency distributions, respectively. The Wilcoxon test and χ^2 test were used to determine if differences existed between groups for continuous and categorical variables, respectively. Multiple logistic regression analysis was performed to identify risk factors that were associated with hospital mortality (JMP, SAS, NC, USA). Covariates that were significant at 0.10 in the univariate analysis and therapy-related variables (i.e., initial antifungal agent adequate antifungal therapy, etc.) were further evaluated for inclusion in multivariable regression models, using a stepwise algorithm. All tests were two-tailed, and a P value less than 0.05 was determined to represent statistical significance.

Results

A total of 481 patients with IAC were included in the study. Overall, 252 (52.4 %) patients were hospitalized in surgical wards, 131 (27 %) in ICUs, and 98 (21 %) in other wards. Table 1 summarizes the demographic characteristics, the risk factors for acquisition of *Candida* infection, and the clinical and treatment variables of patients with IAC. A total of 195 patients (40.5 %) presented with septic shock and required the use of vasopressors. Previous surgery was documented in 338 (70 %) patients, with upper GI and colorectal being the most common surgical interventions (38 vs. 27 %). In the majority of cases, IAC consisted of secondary peritonitis or abdominal abscesses (41 and 30 %, respectively); less common were pancreatitis, tertiary peritonitis, and biliary tract infections (Table 1). Most frequent surgical risk factors for the development of *Candida* infection were reoperation in 202 (42 %) cases, and recurrent GI perforation in 91 (19 %) patients. *C. albicans* (CA) represented the most common species and was isolated in 308 (64 %) patients. Among non-albicans *Candida* (NAC), *C. glabrata* (16 %) was the most isolated species followed by *C. tropicalis* (7 %), *C. parapsilosis* (4.8 %), and others; 4 % of patients had polyfungal IAC. A total of 203 (64 %) patients received an echinocandin as antifungal therapy; other therapies included azoles (32 %) and lipid formulations of amphotericin B (4 %). Of note, 10 % of the patients with IAC did not receive any antifungal treatment. A total of 98 % of *Candida* strains were susceptible to echinocandins, 89 % to fluconazole, and 96 % to voriconazole; all isolates were susceptible to amphotericin B. Fifty-seven (13 %) patients with IAC were treated with fluconazole within 30 days before IAC diagnosis; of these, 34 % had IAC caused by a fluconazole-resistant *Candida* strain. Around 60 % and 70 % of patients received an adequate empiric antifungal therapy and source control, respectively. The overall 30-day hospital mortality was 26.8 %. Table 2 summarizes the significant differences between patients who died within 30 days from the diagnosis of IAC compared with survivors by univariate analysis. Patients who died were significantly older than survivors (72 vs. 61 years, $P < 0.001$) and were mostly female ($P = 0.048$). Compared to patients who died, the survivors had significant lower APACHE II scores (13 vs. 18, $P < 0.001$) and number of organ dysfunctions and presented a shorter duration of hospitalization (11 vs. 13 days, $P < 0.001$) at the time of the diagnosis. Patients with IAC who died had also significantly higher rates of septic shock and vasopressor use (67.4 vs. 30.5 % and 69 vs. 31 % respectively, $P < 0.001$) and were more frequently hospitalized in the ICU (49.5 vs 22.8 %, $P = 0.01$) compared to survivors. IAC due to secondary peritonitis was more common among the patients who died compared to survivors (50 vs. 35 %, $P = 0.004$). Patients who died were more likely to have a CVC, parenteral nutrition, concomitant candidemia, and presented comorbidities such as chronic obstructive pulmonary disease (COPD), heart disease, and renal impairment (e.g., end stage renal disease (ESRD) and dialysis). A higher proportion of patients receiving source control survived compared to patients who did not receive adequate source control (69 vs. 41 %, $P < 0.001$). Distribution of *Candida* species, type of antifungal therapy, and antifungal resistance rates were similar between the two groups. No significant differences were detected between survivors and non-survivors in the percentage of patients receiving adequate antifungal therapy (74 vs. 73 % respectively, $P = 0.90$) and regarding timing of therapy initiation (median 24 h, IQR 5–72 vs. 24 h, IQR 12–72 respectively, $P = 0.49$).

Table 3 summarizes the significant differences between patients with IAC admitted to ICU vs. non-ICU. Patients with IAC in ICU also had significantly higher mortality (38.9 vs. 22.4 %, $P < 0.001$) and were more frequently treated adequately with antifungals (70.1 vs. 56.1 %, $P < 0.001$) compared to patients admitted in other wards.

Backwards stepwise multivariate analyses for hospital mortality selected the following variables: age, secondary peritonitis, septic shock, APACHE II score, adequate source control, and adequate antifungal therapy. As variable "age" is included in the calculation of APACHE II score, collinearity was evaluated and lack of collinearity was confirmed. Multivariate logistic regression analysis demonstrated that age ($P < 0.001$), 1-point increments in APACHE II scores ($P = 0.028$), secondary peritonitis ($P = 0.019$), septic shock ($P < 0.001$), and absence of adequate abdominal source control ($P < 0.001$) were independent predictors of mortality in patients with IAC (Table 4).

Table 1 Clinical characteristics of patients with IAC ($N = 481$)

Characteristics	$N = 481$
Age, years (mean ± SD)	62.53 ± 18.5
Male *n* (%)	276 (57)
Hospital ward (%)	
Internal medicine	35 (7.2)
Surgical ward	252 (52.4)
ICU	131 (27.2)
Hematology/oncology	12 (2.5)
Solid organ transplant unit	4 (0.8)
Other	47 (9.8)
APACHE II score at the time of diagnosis (mean ± SD)	15.35 ± 9.53
Septic shock (%)	196 (40.7)
Median duration of hospitalization at the time of diagnosis (IQR)	11 (5, 22)
Previous abdominal surgery (%)	338 (70.2)
Type of surgery (%)	
Colorectal	91 (27)
Small bowel	54 (16)
Upper gastrointestinal	129 (38)
Liver transplant	17 (5)
Other	47 (14)
Central venous catheter (%)	340 (71)
Parenteral nutrition (%)	265 (55)
Previous use of antibacterial (%)[a]	347 (72)
Candida colonization (%)	118 (24.5)
Diabetes (%)	108 (22.4)
Hematological malignancy (%)	12 (2.5)
Solid tumor (%)	185 (38.5)
End stage renal disease (%)	44 (9.2)
Pancreatitis (%)	70 (14.6)
Heart disease (%)	88 (18.3)
COPD (%)	55 (11.4)
Trauma (%)	16 (3.3)
Dialysis (%)	30 (6.2)
Immunosuppressive therapy (%)	73 (15)
Previous steroid therapy (10 mg/day for >30 days) (%)	92 (19)
BMI > 30	43 (9)
Type of abdominal candidiasis (%)	
Secondary peritonitis	189 (41)
Tertiary peritonitis	34 (7)
Abdominal abscess	138 (30)
Pancreatitis	46 (10)
Biliary tract infection	56 (12)
Reoperation (%)	202 (42)
Recurrent gastrointestinal perforation (%)	91 (19)
Anastomotic leakage	103 (23.3)
Surgery for cancer	121 (28.8)
Prior azole exposure[b]	57 (13)
Concomitant candidemia (%)	68 (14)
Candida species (%)	
C. albicans	308 (64)
C. glabrata	76 (15.8)
C. tropicalis	34 (7)
C. parapsilosis	23 (4.8)
C. krusei	10 (2)
Others	11 (2.2)
Mixed *Candida* infection	19 (3.9)
Initial antifungal agent (%)	
Echinocandin	203 (63.8)
Azole/triazole	102 (32)
Amphotericin B	13 (4)
Adequate antifungal treatment (%)	283 (58.8)
Adequate source control (%)	335 (69.6)
30-day mortality (%)	129 (26.8)

Values are expressed as numbers with percentages in parentheses
SD standard deviation, *IQR* interquartile range, *ICU* intensive care unit, *COPD* chronic obstructive pulmonary disease, *HIV* human immunodeficiency virus

[a] >7 days in the previous 30 days

[b] In the previous 30 days

Table 5 reports the differences between patients with IAC presenting with or without septic shock. Specifically, septic shock was more frequently associated with the presence of dialysis, COPD, parenteral nutrition, and previous surgery. Patients who received an initial empirical antifungal therapy were more likely to present septic shock compared with patients who did not receive a therapy (36.9 vs. 14.5 %, $P < 0.001$). Among patients with septic shock, the choice of using an echinocandin as antifungal therapy was preferred (56.4 %) compared to fluconazole (20.5 %) or amphotericin B (3.6 %). Although not significant, a higher number of patients with septic shock died during the 30 days after IAC diagnosis (44.6 vs. 37.4 %, $P = 0.12$).

Thirty-day mortality of patients with or without adequate antifungal therapy and/or source control is reported in Fig. 1. The mortality of patients with septic shock and adequate source control was higher in the presence of inadequate antifungal administration compared to adequate therapy (48 vs. % 26.1, $P < 0.05$). In the absence of both septic shock and adequate source control, an adequate therapy was associated with a lower mortality compared to inadequate therapy (13 vs. 32.7 %, $P = 0.05$). Nevertheless, the mortality was significantly increased (>60 %) in the case of septic shock and absent source control, with or without adequate therapy.

Discussion

Our report represents the first multicenter multinational study investigating exclusively cases of abdominal candidiasis. Compared to other studies, we collected data from 13 large centers in four different countries including patients admitted to ICU and medical or surgical wards.

Since clinical signs of IAC are not specific and early microbiological documentation remains a major challenge, data regarding patients' outcome and predictors of mortality in IAC are still scarce [15]. Although abdominal candidiasis is still burdened by high mortality rates, current international guidelines mainly address candidemia. However, as confirmed by our report, candidemic IAC represents only 10–15 % of all abdominal candidiasis. For

Table 2 Characteristics of survivors ($N = 352$) compared with patients with IAC who died ($N = 129$)

Characteristic	Alive ($N = 352$)	Dead ($N = 129$)	P value
Age, years	62 (48.3–73)	71 (62–80)	<0.001
Male	192 (54.6)	84 (65.1)	0.048
Type of abdominal candidiasis			
Secondary peritonitis	124 (35.2)	65 (50.4)	0.004
Abdominal abscesses	109 (31)	29 (22.5)	0.62
Biliary tract infection	44 (12.5)	12 (9.3)	0.77
Pancreatitis	40 (11.4)	15 (11.7)	0.82
Tertiary peritonitis	27 (7.7)	7 (5.4)	0.550.58
Biliary tract infection	8 (2.3)	1 (0.8)	
Hospital wards			
Internal medicine	26 (7.4)	9 (7)	0.88
Surgical ward	194 (55.3)	58 (45)	0.84
ICU	80 (22.8)	51 (39.5)	0.01
Hematology/oncology	9 (2.6)	3 (2.3)	0.98
Solid organ transplant unit	2 (0.6)	1 (0.8)	1.00
Other	40 (11.4)	7 (5.4)	0.06
CVC	238 (67.8)	102 (79.1)	0.017
Parenteral nutrition	182 (52.5)	83 (64.8)	0.017
Septic shock	107 (30.5)	87 (67.4)	<0.001
APACHE II score	13 (8–18)	18 (14–24.75)	<0.001
Duration of hospitalization	11 (3.5–21)	13 (7–24.5)	0.014
ESRD	24 (6.8)	20 (15.6)	0.007
COPD	34 (9.7)	21 (16.3)	0.052
Heart disease	53 (15.2)	35 (27.1)	0.005
Dialysis	17 (4.9)	13 (10.2)	0.053
Number of acquired organ dysfunction	0 (0–2)	2 (1–3)	<0.001
Concomitant candidemia	43 (12.7)	25 (20.2)	0.053
Concomitant isolation of bacteria	245 (69.8)	86 (67.2)	0.579
Concomitant use of antibacterials	248 (71.7)	99 (76.7)	0.297
Adequate source control	238 (69)	52 (40.9)	<0.001

Qualitative and quantitative values are expressed as number (percentage) and median (25th and 75th percentile), respectively
ICU intensive care unit, *CVC* central venous catheter, *ESRD* end stage renal disease, *COPD* chronic obstructive pulmonary disease

these reasons, we have previously published recommendations endorsed by a multidisciplinary panel of experts for the management of IAC including specific diagnostic and therapeutical aspects [7].

Compared to other studies collecting mainly data on peritonitis, our report also included abdominal abscesses, pancreatitis, and biliary tract infections due to *Candida* spp. Overall, around 70 % of patients with IAC underwent surgery; nevertheless, secondary peritonitis and abdominal abscesses accounted for the majority of IAC cases, while tertiary peritonitis represented only a minority of IAC cases.

Similarly to our report, other studies have demonstrated a predominance of *C. albicans* isolates (65–82 %) in abdominal samples, followed by *C. glabrata* (17–20 %) among European ICUs [4, 6].

Our proportion of fluconazole-resistant strains (11 %) was slightly higher than the rates observed with European (5.1 %) and North American (6.6 %) isolates from patients with candidemia [16–18]. Echinocandins demonstrated excellent activity displaying only 2 % of non-susceptibility, in contrast with recent American data that showed the abdomen as an important reservoir of echinocandin-resistant *Candida* [11]. In our study only three strains of *C. glabrata* resistant to echinocandins were isolated in patients previously treated with long courses of echinocandins.

Compared to other studies that did not identify differences in mortality depending on the type of IAC acquisition, our study showed that the occurrence of secondary peritonitis was independently associated with greater 30-day mortality [4, 10]. Montravers et al. showed mortality rates of 38 % among patients with *Candida* peritonitis in ICU but no specific factors for death were identified [10]. Overall, mortality rates for *Candida* peritonitis ranging from 25 % to 60 % have been previously reported [4, 6, 19]. In our study the mortality rate, although relevant (27 %), was lower compared to those in the literature. The mortality was higher and similar to other reports in patients admitted to ICU (38.9 %). Nevertheless, when the mortality was analyzed in the subgroups of patients without adequate therapy or without source control, the rates increased to 48 % and above 60 %, respectively.

In patients with candidemia, rates of septic shock between 20 and 38 % and mortality rates above 60 % have been documented [20–24]. Our study showed rates of septic shock around 40 %; the majority of patients with

Table 3 Characteristics of patients admitted to ICU ($N = 129$) compared with patients admitted to non-ICU ($N = 344$)

	Non-ICU ($N = 344$)	ICU ($N = 129$)	P value
Age, years	63 (51–75)	68 (57–75)	0.139
Male	197 (56.5)	79 (59.5)	0.536
Previous abdominal surgery			
Total			
Type of abdominal candidiasis			
1 = secondary peritonitis	138 (39.5)	51 (38.6)	0.822
2 = tertiary peritonitis	23 (6.6)	11 (8.3)	
3 = abdominal abs	104 (29.8)	34 (25.8)	
4 = pancreatitis	34 (9.7)	12 (9.1)	
5 = biliary tract infection	40 (11.5)	17 (12.9)	
6 = other	5 (1.4)	4 (3)	
CVC	213 (61.2)	128 (97)	<0.001
Parenteral nutrition	164 (47.5)	101 (77.7)	<0.001
Septic shock	102 (29.3)	93 (70.5)	<0.001
APACHE score II at the time of diagnosis	13 (8–18)	18 (14–24)	<0.001
Duration of hospital admission at the time of diagnosis	11 (3–20)	13 (6–30)	0.007
Previous abdominal surgery	235 (67.3)	103 (78)	0.025
ESRD	29 (8.4)	15 (11.4)	0.376
COPD	36 (10.3)	19 (14.4)	0.261
Heart disease	52 (15.1)	36 (27.3)	0.004
Dialysis	15 (4.3)	15 (11.4)	0.01
Number of acquired organ dysfunctions	0 (0–2)	2 (1–3)	<0.001
Candidemia	39 (11.6)	29 (22.7)	0.005
Candida species			
C. albicans	225 (64.5)	83 (62.9)	0.64
C. glabrata	55 (15.8)	21 (15.9)	
C. tropicalis	22 (6.3)	12 (9.1)	
C. parapsilosis	33 (9.5)	11 (8.3)	
Initial antifungal agent			
Echinocandin	148 (44.4)	61 (51.3)	0.012
Azole/triazole	66 (19.8)	34 (28.6)	
Amphotericin B	10 (3)	3 (2.5)	
None	109 (32.7)	21 (17.7)	
Adequate antifungal treatment	193 (56.1)	89 (70.1)	0.006
Adequate source control	215 (62.7)	75 (58.1)	0.397
30-day mortality	78 (22.4)	51 (38.9)	<0.001

Qualitative and quantitative values are expressed as number with percentages in parenthesis and median (25th and 75th percentile), respectively

CVC central venous catheter, *ESRD* end stage renal disease, *COPD* chronic obstructive pulmonary disease

Table 4 Variables selected by backward stepwise multiple logistic regression analysis for hospital mortality

	χ^2	OR	P value
Age (per unit change)	20.74	1.05 (1.03–1.07)	<0.001
APACHE II score at the time of diagnosis (per unit change)	6.22	1.05 (1.01–1.08)	0.013
Secondary peritonitis	4.17	1.72 (1.02–2.89)	0.04
Septic shock	16.86	3.29 (1.88–5.86)	<0.001
No adequate abdominal source control	21.32	3.35 (2.01–5.63)	<0.001
No adequate antifungal therapy	4.41	1.81 (1.04–3.16)	0.035

The variables initially included in the model were age, gender, secondary peritonitis, ICU, CVC, septic shock, APACHE II score, duration of hospitalization, ESRD, COPD, heart disease, dialysis, number of organ dysfunctions, concomitant candidemia, adequate source control, adequate antifungal therapy, Initial antifungal agent

septic shock (70 %) were hospitalized in ICU where the mortality rates reached 40 %. We have previously identified APACHE II score and lack of adequate antifungal therapy and source control as risk factors associated with a higher mortality in patients with septic shock attributable to candidemia [20]. In our report, the occurrence of septic shock was frequently associated with the absence of an initial antifungal therapy and represented an independent risk factor for mortality in patients with IAC.

Our study, like others, emphasizes the importance of source control in abdominal *Candida* infections and in

Table 5 Characteristics of patients with IAC and septic shock compared with patients without septic shock

Characteristics	No septic shock ($N = 286$)	Septic shock ($N = 195$)	P value
Initial antifungal agent			
Echinocandin	99 (35)	110 (56.4)	<0.001
Azole/triazole	61 (21.6)	40 (20.5)	
Amphotericin B	6 (2.1)	7 (3.6)	
No initial empirical antifungal therapy	120 (41.3)	38 (19.5)	<0.001
Candida species (%)			
C. albicans	190 (66.4)	124 (63.6)	0.28
C. glabrata	49 (17.1)	38 (19.5)	
C. tropicalis	22 (7.7)	15 (7.8)	
C. parapsilosis	11 (3.8)	12 (6.2)	
Previous abdominal surgery	191 (66.8)	147 (75.4)	0.053
Adequate abdominal source control	180 (64.5)	110 (57)	0.103
Dialysis	8 (2.8)	21 (10.8)	<0.001
Heart disease	41 (14.5)	47 (24.1)	0.011
ESRD	24 (8.5)	19 (9.7)	0.629
COPD	23 (8.1)	32 (16.4)	0.006
Parenteral nutrition	124 (43.8)	141 (73.1)	<0.001
Adequate antifungal based on susceptibility	147 (52.9)	135 (69.9)	<0.001
30-day mortality	107 (37.4)	87 (44.6)	0.13

Values are expressed as numbers with percentages in parentheses
ESRD end stage renal disease, *COPD* chronic obstructive pulmonary disease

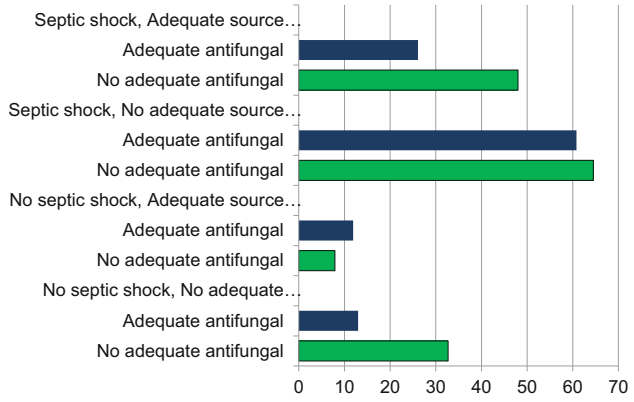

Fig. 1 Thirty-day hospital mortality in patients with or without septic shock and adequate antifungal therapy and/or source control

case of *Candida* septic shock in order to improve patient outcomes [20, 25, 26].

The absence of an adequate and timely initial antifungal treatment has also been associated with increased mortality in patients with invasive candidiasis and septic shock attributed to *Candida* infection [22–24]. In the specific setting of surgical patients with intra-abdominal infection, only few retrospective studies have reported a significant reduction of mortality in the presence of an early adequate antifungal therapy [27]. Our study showed how the absence of antifungal therapy was associated with an increased mortality, yet the timing of antifungal therapy was not significantly different between survivors and non-survivors. Furthermore, in patients with septic shock, the presence of adequate antifungal administration had a positive impact on the mortality in the presence of source control but did not make a difference when an adequate source control was lacking; however, a positive impact of antifungal administration was not demonstrated by multivariate analysis. Other recent investigations were unable to identify a correlation between the timing of antifungal therapy and mortality in patients with candidemia [20, 28, 29]. A possible explanation could be the clinical efficacy of echinocandins that potentially reduces the negative effect of delayed therapy [30]. As a consequence of the most recent guidelines for the treatment of candidiasis, the use of echinocandins has increased in severely ill patients. In our study, the use of an echinocandin was significantly higher compared to other antifungals in patients with septic shock.

There are some important limitations of our study that should be noted. We did not examine all aspects of hospital care that may have influenced the clinical outcomes and we could not capture the reasons for the choice of the different antifungals. Also, prescription and source control practices may have varied from one site to another.

In conclusion, our study represents the largest multicenter investigation of intra-abdominal candidiasis. We identified clinical severity, presentation as secondary peritonitis, presence of septic shock, and lack of source control as the most important determinants of outcome among patients with IAC. Among patients with IAC and septic shock, an adequate source control represented a critical parameter for mortality.

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