ORIGINAL SCIENTIFIC REPORT

Appropriate Source Control and Antifungal Therapy are Associated with Improved Survival in Critically Ill Surgical Patients with Intra-abdominal Candidiasis

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Abstract

Background Intra-abdominal candidiasis (IAC) is the predominant type of invasive candidiasis with high mortality in surgical intensive care patients. The purpose of this study was to investigate the impact of appropriate source control and antifungal therapy on the outcomes of critically ill surgical patients with IAC.

Methods This was a retrospective single-center cohort study. Adult surgical patients who were admitted to the intensive care unit and diagnosed with IAC from January 1, 2003, to December 31, 2016, were enrolled. The patients' data including risk factors of IAC, infection-related information, antifungal treatment and 30-day outcomes were collected. The primary endpoint was 30-day mortality. A COX proportional hazards model was used to analyze the association between appropriate treatment and 30-day survival.

Results A total of 82 patients were included in the analysis. Of these, 45 (54.9%) were complicated with septic shock at IAC diagnosis. Types of IAC included peritonitis (61.0%), intra-abdominal abscesses (23.2%) and biliary tract infections (15.9%). Of the included patients, 53 (64.6%) received appropriate source control and 44 (53.7%) appropriate antifungal therapy. Compared with patients with neither of these treatments, appropriate source control (HR 0.08, 95% CI 0.02–0.30; $P < 0.001$), appropriate antifungal therapy (HR 0.14, 95% CI 0.04–0.55; $P = 0.005$), and a combination of these treatments (HR 0.02, 95% CI 0.00–0.08; $P < 0.001$) were associated with reduced risk of death within 30 days after IAC diagnosis.

Conclusion For critically ill surgical patients with IAC, both appropriate source control and appropriate antifungal therapy were associated with reduced risk of 30-day mortality, and the protective effects of the two appropriate treatments were additive.

Abbreviations

IAC	Intra-abdominal candidiasis
ICU	Intensive care unit
IC	Invasive candidiasis
MIC	Minimum inhibitory concentration
APACHE II	Acute physiology and chronic health evaluation II
SOFA	Sepsis-related organ failure assessment
COPD	Chronic obstructive pulmonary disease
BMI	Body mass index
MDRO	Multidrug-resistant organism

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Introduction

Intra-abdominal candidiasis (IAC) is the most common type of deep-seated candidiasis in critically ill surgical patients, which accounts for 34–59% of invasive candidiasis (IC) [1, 2] and 10–20% of intra-abdominal infections [3]. IAC is a life-threatening complication with high morbidity and mortality. According to the epidemiological data over the last decades, the mortality rate of patients with IAC was about 25–40%; for those combined with septic shock, the mortality rate was up to 60% [4–6]. Unfortunately, IAC remains poorly understood when compared with candidemia [7–9]. Previous studies showed that, for patients with candidemia, early antifungal therapy and timely source control improve survival [10–13]. However, results regarding the treatment for IAC are insufficient and conflicting. Some authors reported that delayed or insensitive initial antifungal therapy was an independent risk factor of 30-day mortality in patients with IAC [6, 14], whereas some others did not find an association between the antifungal therapy and 30-day mortality [15]. On the other hand, available evidence supports the use of early source control in managing IAC [6, 14–16].

In the present study, we focused on IAC in critically ill surgical patients in whom surgical interventions to reduce microbiological burden are strongly indicated and the effect of antifungal therapy is still expected to be determined. The purpose of this retrospective cohort study was to explore the effects of appropriate treatments (including source control and antifungal therapy) on 30-day survival in critically ill surgical patients with IAC.

Materials and methods

This was a single-center retrospective cohort study. The study protocol was approved by the Clinical Research Ethics Committee of Peking University First Hospital (2017–1303). Because of the retrospective and observational nature of the study, the local Ethics Committee agreed to exempt written informed consent.

Patients

This study screened all the patients who were admitted to the surgical ICU of Peking University First Hospital between January 1, 2003, and December 31, 2016. The inclusion criteria were as follows: (1) age over 18 years; (2) confirmed intra-abdominal infection after abdominal surgery or required surgical intervention; (3) IAC diagnosed during ICU stay. Patients who met any of the following criteria were excluded: (1) neutropenia (absolute neutrophil count < 500 cells/μL); (2) recipient of bone marrow or solid organ transplantation; (3) chemotherapy in the last 6 months; (4) receiving immunosuppressants or systemic steroids (prednisone equivalent $\geq$ 20 mg/day) within 7 days prior to ICU admission; (5) acute pancreatitis; (6) primary peritonitis; (7) documented invasive candidiasis within 6 months, or received systemic antifungal therapy within 14 days; or (8) incomplete data.

Diagnosis of intra-abdominal candidiasis

According to the 2013 European consensus [6, 9, 17], an episode of IAC was diagnosed in one of the following four conditions: (1) Candida detection by direct microscopy examination or growth in culture from purulent or necrotic intra-abdominal specimens obtained during surgery or by percutaneous aspiration; (2) Candida growth from bile, intra-biliary ducts devices, and biopsy of intra-abdominal organs; (3) Candida growth from blood cultures in clinical setting of secondary and tertiary peritonitis in the absence of any other pathogen; (4) Candida growth from drainage tubes only if placed less than 24 h before the cultures.

To ensure the accuracy of IAC diagnosis, two researchers determined IAC independently. In case of a difference between the two researchers, final agreement was achieved by rechecking the records and full discussion with a senior physician. Documented IAC were identified by reviewing hospital medical records. The clinical specimens suspected of yeast infection were primarily cultured in the Sabouraud agar plates, and suspected colonies were screened for further identification. The identification of different yeasts to species level was performed by the CHROMagar[TM] Candida (BD Difco, Detroit, MI) and the Vitek 2 Compact automated system (BioMérieux, Marcy l'Etoile, France) with YST card. The equivocal results were confirmed by sequencing of the internal transcribed spacer (ITS) region. Antifungal susceptibility testing was performed with the ATB[TM] FUNGUS 3 stripe (BioMérieux, Marcy l'Etoile, France), in which the susceptibility testing for echinocandin was not included, so the susceptibility results for echinocandin were unavailable. The results interpretation was made following the NCCLS document M27-A [18].

Appropriate treatment

Appropriate source control was defined as adequate source control within 5 days since the positive cultures were obtained. Adequate abdominal source control was defined as: (1) adequate drainage of infected fluid collections, (2) debridement of infected necrotic tissue, and (3) definitive intervention to correct anatomic derangements resulting in ongoing microbial contamination and restore optimal

function [19]. The surgical interventions could be combined with irrigation, but simple irrigation couldn't be judged as adequate source control.

Appropriate initial antifungal therapy was considered if the following conditions were satisfied: (1) early: antifungal treatment started within 5 days since the positive cultures were obtained [14]; (2) active: the infecting organism was ultimately shown to be susceptible, and the dose of antifungal agent was adequate [20]. The echinocandins were assessed as susceptible for all Candida species. The following antifungal doses were considered adequate: (1) for fluconazole-susceptible Candida isolates (MIC ≤ 8 mg/L), a minimal daily dose of 400 mg was considered appropriate. For fluconazole-susceptible dose-dependent isolates (SDD; MIC 16–32 mg/L), a minimal daily dose of 800 mg was considered adequate. For patients with a calculated creatinine clearance < 50 mL/min, a daily dose of fluconazole of 50% of the normal dose was considered adequate based on standard dosing adjustments made in renal dysfunction; (2) ≥0.5 mg/kg of amphotericin B deoxycholate once daily; ≥3 mg/kg of amphotericin B lipid formulations once daily; (3) caspofungin 70 mg loading dose followed by 50 mg/day (or 35 mg once daily for patients with significant liver impairment), micafungin ≥ 100 mg/day (formulary echinocandin beginning in 2008); (4) 6 mg/kg of voriconazole twice daily followed by ≥3 mg/kg twice daily [20].

Data collection

Patients' data were screened through the electronic medical record system of the hospital, and eligible patients were identified according to the inclusion/exclusion criteria.

For included patients, detailed information was collected. The baseline data included demographic parameters, surgical diagnosis, comorbidities, classical risk factors for IAC, as well as the assessment of disease severity. The acute physiology and chronic health evaluation (APACHE) II score and the sepsis-related organ failure assessment (SOFA) score were calculated for each patient within 24 h prior to the collection of cultures indicating IAC. Organ failure was diagnosed when the SOFA score of this organ was greater than 2 [21]. Septic shock was diagnosed according to the third international consensus definitions [22]. The characteristics of IAC included surgical conditions, type of IAC, Candida species, concomitant candidemia, and bacterial co-infection. IAC-related treatments included source control (surgical intervention, percutaneous drainage, and the appropriateness of source control) and initial antifungal therapy (type of antifungal medication and the appropriateness of antifungal therapy).

The primary outcome was 30-day survival after the diagnosis of IAC, including all-cause 30-day mortality and the time to death or loss to follow-up within 30 days. The secondary outcome was mortality during hospitalization.
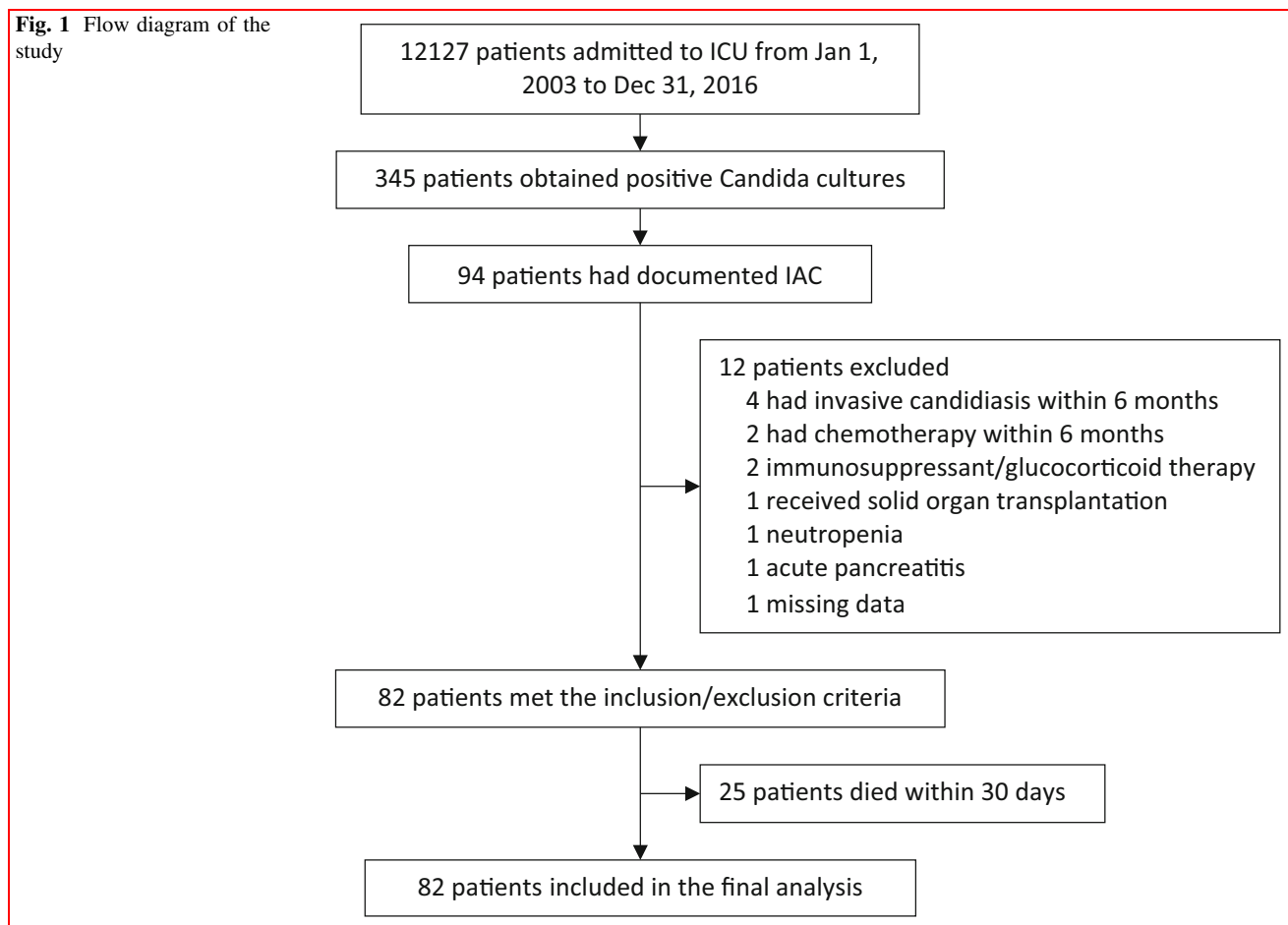
Statistical analysis

Patients were divided into four treatment groups according to the combination of appropriate source control and antifungal therapy. Data were tested for normality using the Kolmogorov–Smirnov test. Continuous variables with normal distribution were compared with one-way ANVOA and post hoc student t test; continuous variables with non-normal distribution or ranked data were compared with Kruskai–Wallis H test and post hoc Mann–Whitney U analysis. Categorical variables were compared with Fisher's exact test and post hoc Chi-squared test or Fisher exact test. Survival data were analyzed with the Kaplan–Meier estimator, with differences between groups assessed by the log-rank test. Factors in association with 30-day survival were identified using a Cox proportional hazards model; variables with a P value of <0.10 in univariate analyses were included in a multivariate model (backward). Two-sided P values of <0.05 were regarded as statistically significant. For multiple comparisons among the four groups, P values of $<0.05/6 = 0.0083$ were considered statistically significant (Bonferroni correction). Statistical analyses were performed with SPSS statistical package version 25.0 (IBM SPSS Inc, Chicago, IL, USA).

Results

Patients

From January 1, 2003, to December 31, 2016, 12,127 patients were admitted to the surgical ICU. Of these, 94 (7.8‰) were diagnosed with IAC, 82 met the inclusion/exclusion criteria and were included in final analysis (Fig. 1). Of the included patients, the median age was 70.1 years, 44 (53.7%) were male, the mean APACHE II score was 17.7 ± 6.9, 45 (54.9%) presented with septic shock at the time of the diagnosis, and 59 (72.0%) had at least one organ failure during hospital stay. The baseline characteristics and the risk factors for IAC are summarized in Table 1.

In our patients with IAC, 50 (61.0%) had secondary or tertiary peritonitis, 19 had (23.2%) abdominal abscesses, and 13 (15.9%) had hepatobiliary system infections. A total of 84 Candida strains were isolated from 82 patients. Two (2.4%) patients suffered from polyfungal IAC. Of the isolated Candida strains, 83 had antifungal susceptibility testing results; 3 (3.6%) of *C. glabrata* and 1 (1.2%) of *C. albicans* were resistant to fluconazole; the others were susceptible to azoles. Bacterial co-infections and

Fig. 1 Flow diagram of the study

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│ 12127 patients admitted to ICU from Jan 1,    │
│           2003 to Dec 31, 2016                │
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┌─────────────────────────────────────────────┐
│ 345 patients obtained positive Candida cultures│
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│        94 patients had documented IAC          │
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                     │───────▶│ 12 patients excluded                          │
                     │        │   4 had invasive candidiasis within 6 months  │
                     │        │   2 had chemotherapy within 6 months          │
                     │        │   2 immunosuppressant/glucocorticoid therapy  │
                     │        │   1 received solid organ transplantation       │
                     │        │   1 neutropenia                               │
                     │        │   1 acute pancreatitis                        │
                     │        │   1 missing data                              │
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│  82 patients met the inclusion/exclusion criteria│
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                     │───────▶│ 25 patients died within 30 days│
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│    82 patients included in the final analysis  │
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candidemia occurred in 70.7% and 20.7% of patients, respectively (Table 2).

Treatment and outcomes

Of the included patients, 53 (64.6%) received appropriate source control and 44 (53.7%) received appropriate antifungal therapy. The overall 30-day mortality was 30.5% (25/82). One patient died of cerebrovascular event and the rest died of infection-related multiple organ failure. Comparison among groups showed that the 30-day mortality rate in patients with both appropriate source control and appropriate antifungal therapy was significantly lower than in those with neither appropriate treatment ($P < 0.001$) and those with only appropriate antifungal therapy ($P = 0.003$) (Table 3 and Fig. 2).

Association between appropriate treatment and 30-day survival

Univariable analyses identified 7 factors that might be associated with 30-day survival ($P < 0.10$), including age > 65 years, SOFA score, septic shock, the year of IAC

diagnosis, colonization by Candida species, appropriate source control, and appropriate antifungal therapy. Of these, SOFA score was excluded because of collinearity with septic shock; other 6 factors were included in the multivariable Cox proportional hazards model. The results showed that both appropriate source control (HR 0.09, 95% CI 0.03–0.26; $P < 0.001$) and appropriate antifungal therapy (HR 0.18, 95% CI 0.07–0.47; $P = 0.001$) were the independent protective factors of 30-day survival in patients with IAC. We also analyzed the combined effect of appropriate treatment, and the results showed that the protective effects of appropriate source control and appropriate antifungal therapy were additive. When compared with patients with neither appropriate treatment, those with only appropriate antifungal therapy (HR 0.14, 95% CI 0.04–0.55; $P = 0.005$), only appropriate source control (HR 0.08, 95% CI 0.02–0.30; $P < 0.001$), and both (HR 0.02, 95% CI 0.00–0.08; $P < 0.001$) had significantly improved 30-day survival (Table 4).

Table 1 Baseline characteristics and risk factors

Variables	All patients (n = 82)	Appropriate source control (−), appropriate antifungal therapy (−) (n = 19)	Appropriate source control (−), appropriate antifungal therapy (+) (n = 10)	Appropriate source control (+), appropriate antifungal therapy (−) (n = 19)	Appropriate source control (+), appropriate antifungal therapy (+) (n = 34)	P value
Age (years)	74.0 (63.5, 80.0)	72.0 (69.0, 79.0)	71.0 (63.5, 79.0)	76.0 (55.0, 80.0)	74.0 (56.8, 80.3)	0.995
Age > 65 years	57 (69.5%)	17 (89.5%)	6 (60.0%)	13 (68.4%)	21 (61.8%)	0.157
Male gender	44 (53.7%)	10 (52.6%)	6 (60.0%)	12 (63.2%)	16 (47.1%)	0.726
BMI (kg/m^2)	23.0 ± 4.2	23.3 ± 3.7	21.9 ± 3.8	22.6 ± 4.4	23.4 ± 4.5	0.764
Comorbidities						
Coronary artery disease	12 (14.6%)	3 (15.8%)	1 (10.0%)	2 (10.5%)	6 (17.6%)	0.965
Diabetes mellitus	22 (26.8%)	4 (21.1%)	4 (40.0%)	4 (21.1%)	10 (29.4%)	0.695
End stage renal disease[a]	8 (9.8%)	3 (15.8%)	1 (10.0%)	1 (5.3%)	3 (8.8%)	0.828
COPD	11 (13.4%)	2 (10.5%)	1 (10.0%)	5 (26.3%)	3 (8.8%)	0.383
Malignant tumors	55 (67.1%)	16 (84.2%)	8 (80.0%)	11 (57.9%)	20 (58.8%)	0.167
Classical risk factors[b]						
Mechanical ventilation > 48 h	44 (53.7%)	3 (15.8%)	4 (40.0%)	11 (57.9%)	26 (76.5%)*	<0.001
Total parenteral nutrition > 3 days	53 (64.6%)	13 (68.4%)	8 (80.8%)	8 (42.1%)	24 (70.6%)	0.134
Central venous catheter > 48 h	64 (78.0%)	13 (68.4%)	6 (60.0%)	13 (68.4%)	32 (94.1%)†	0.013
Broad-spectrum antibiotics > 7 days	50 (61.0%)	13 (68.4%)	9 (90.0%)	9 (47.4%)	19 (55.9%)	0.117
Candida colonization[c]	26 (31.7%)	9 (47.4%)	3 (30.0%)	4 (21.1%)	10 (29.4%)	0.381
Corticosteroid therapy[d]	4 (4.9%)	0 (0.0%)	1 (10.0%)	1 (5.3%)	2 (5.9%)	0.558
Surgical conditions						
Gastrointestinal perforation[e]	29 (35.4%)	1 (5.3%)	0 (0.0%)	14 (73.7%)*†	14 (41.2%)*	<0.001
Anastomotic leakage[f]	41 (50.0%)	15 (78.9%)	9 (90.0%)	4 (21.1%)*†	13 (38.2%)*†	<0.001
Gastrointestinal obstruction[g]	13 (15.9%)	2 (10.5%)	3 (30.0%)	2 (10.5%)	6 (17.6%)	0.539
Abdominal reoperation	4 (4.9%)	1 (5.3%)	0 (0.0%)	0 (0.0%)	3(8.8%)	0.814
Recurrent perforation	3 (3.7%)	0 (0.0%)	0 (0.0%)	1 (5.3%)	2 (5.9%)	0.861
Severity assessments[h]						
APACHE II (score)	17.7 ± 6.9	16.0 ± 7.5	21.4 ± 4.7	14.4 ± 5.0†	19.5 ± 7.1‡	0.010
APACHE II score ≥ 15	52 (63.4%)	10 (52.6%)	9 (90.0%)	8 (42.1%)†	25 (73.5%)	0.027
SOFA (score)	7.3 ± 3.6	7.2 ± 4.0	9.1 ± 2.6	5.4 ± 3.2†	7.8 ± 3.6	0.036
Organ failure[i]	59 (72.0%)	14 (73.7%)	9 (90.0%)	10 (52.6%)	26 (76.5%)	0.166
Number of failure organ	1.0 (0, 2.0)	1.0 (0.0, 2.0)	1.0 (1.0, 2.0)	1.0 (0.0, 2.0)	1.0 (0.8, 2.0)	0.159

Table 1 continued

Variables	All patients (n = 82)	Appropriate source control (−), appropriate antifungal therapy (−) (n = 19)	Appropriate source control (−), appropriate antifungal therapy (+) (n = 10)	Appropriate source control (+), appropriate antifungal therapy (−) (n = 19)	Appropriate source control (+), appropriate antifungal therapy (+) (n = 34)	P value
Septic shock[j]	45 (54.9%)	7 (36.8%)	6 (60.0%)	10 (52.6%)	22 (64.7%)	0.269

Data were presented as mean ± standard deviation, number of patients (percentage), or median (interquartile range)

BMI body mass index, COPD chronic obstructive pulmonary disease, APACHE II acute physiology and chronic health evaluation II scoring system, SOFA sepsis-related organ failure assessment

[a] Glomerular filtration rate < 15 mL/(min 1.73 m^2) or requirement of persistent renal replacement therapy

[b] From the time of the collection of culture-positive samples

[c] Candida was isolated in non-infected sites in the same time or before the culture-positive samples were obtained

[d] Systemic glucocorticoid therapy with a dose of prednisone equivalent < 2 mg/kg/day

[e] Confirmed by imaging examination or surgical findings

[f] Appearance of gut luminal contents in the abdominal drainage tube, or confirmed by imaging examination or surgical findings [23]

[g] Presence of typical signs and symptoms of intestinal obstruction, such as vomiting, abdominal distention, cessation of exhaust and defecation, and confirmed by imaging examination

[h] Assessed within 24 h of the collection of culture-positive samples

[i] Diagnosed when the SOFA score of this organ ≥ 2

[j] Sepsis with persistent hypotension despite adequate volume resuscitation requiring vasopressors to maintain mean arterial pressure ≥ 65 mmHg and a serum lactate level > 2 mmol/L

* P < 0.05/6 = 0.0083 (Bonferroni-corrected post hoc multiple comparisons) when compared with the appropriate source control (−) and appropriate antifungal therapy (−) patients

† P < 0.0083 when compared with the appropriate source control (−) and appropriate antifungal therapy (+) patients

‡ P < 0.0083 when compared with the appropriate source control (+) and appropriate antifungal therapy (−) patients

Table 2 Clinical features of intra-abdominal candidiasis

Variables	All patients (n = 82)	Appropriate source control (−), appropriate antifungal therapy (−) (n = 19)	Appropriate source control (−), appropriate antifungal therapy (+) (n = 10)	Appropriate source control (+), appropriate antifungal therapy (−) (n = 19)	Appropriate source control (+), appropriate antifungal therapy (+) (n = 34)	P value
Type of IAC						
Peritonitis	50 (61.0%)	6 (31.6%)	4 (40.0%)	16 (84.2%)*	24 (70.6%)*	0.002
Secondary peritonitis[a]	42 (51.2%)	5 (26.3%)	2 (20.0%)	15 (78.9%)*†	20 (58.8%)	0.001
Diffuse peritonitis	31 (37.8%)	4 (21.1%)	1 (10.0%)	11 (57.9%)	15 (44.1%)	0.024
Tertiary peritonitis[b]	8 (9.8%)	1 (5.3%)	2 (20.0%)	1 (5.3%)	4 (11.8%)	0.483
Intra-abdominal abscess[c]	19 (23.2%)	8 (42.1%)	4 (40.0%)	1 (5.3%)	6 (17.6%)	0.020
Biliary tract infection[d]	13 (15.9%)	5 (26.3%)	2 (20.0%)	2 (10.5%)	4 (11.8%)	0.479
Location of IAC development						
Hospital-acquired[e]	52 (63.4%)	19 (100.0%)	8 (80.0%)	8 (42.1%)*	17 (50.0%)*	<0.001
Community-acquired[f]	30 (36.6%)	0 (0.0%)	2 (20.0%)	11 (57.9%)*	17 (50.0%)*	<0.001
Species of isolated Candida						
C. albicans	57 (69.5%)	11 (57.9%)	8 (80.8%)	18 (94.7%)	20 (58.8%)‡	0.016
C. glabrata	11 (13.4%)	6 (31.6%)	0 (0.0%)	0 (0.0%)	5 (14.7%)	0.018
C. tropicalis	9 (11.0%)	1 (5.3%)	0 (0.0%)	1 (5.3%)	7 (20.6%)	0.204
C. parapsilosis	4 (4.9%)	0 (0.0%)	1 (10.0%)	0 (0.0%)	3 (8.8%)	0.326
Others[g]	3 (3.7%)	1 (5.3%)	1 (10.0%)	0 (0.0%)	1 (2.9%)	0.621
Candidemia	17 (20.7%)	7 (36.8%)	3 (30.0%)	2 (10.5%)	5 (14.7%)	0.157
Bacterial co-infection	58 (70.7%)	15 (78.9%)	9 (90.0%)	11 (57.9%)	23 (67.6%)	0.275
MDRO infection	54 (65.9%)	14 (73.7%)	7 (70.7%)	11 (57.9%)	22 (64.7%)	0.796

Data were presented as number of patients (percentage)

IAC intra-abdominal candidiasis, MDRO multidrug-resistant organism

[a] Resulted from a pathological process or breach of the gastrointestinal tract, such as perforation, surgical leak or trauma [14]

[b] Persisted or recurred peritonitis for more than 48 h after apparently successful management of a secondary peritonitis [23]

[c] Localized collection of Candida and pus that is walled-off from healthy tissue [14]

[d] Intra-abdominal Candida infection resulting from a pathologic process of the biliary system

[e] Diagnosed ≥ 48 h after hospitalization

[f] Diagnosed < 48 h after hospitalization

[g] Include C. sphaerica, C. krusei and C. stella

* P < 0.05/6 = 0.0083 (Bonferroni-corrected post hoc multiple comparisons) when compared with the appropriate source control (−) and appropriate antifungal therapy (−) patients

† P < 0.0083 when compared with the appropriate source control (−) and appropriate antifungal therapy (+) patients

‡ P < 0.0083 when compared with the appropriate source control (+) and appropriate antifungal therapy (−) patients

Table 3 Treatments and outcomes

Variables	All patients (n = 82)	Appropriate source control (−), appropriate antifungal therapy (−) (n = 19)	Appropriate source control (−), appropriate antifungal therapy (+) (n = 10)	Appropriate source control (+), appropriate antifungal therapy (−) (n = 19)	Appropriate source control (+), appropriate antifungal therapy (+) (n = 34)	P value
The year of IAC diagnosis						<0.001
2003–2007	13 (15.9%)	8 (42.1%)	1 (10.0%)	3 (15.8%)	1 (2.9%)*	
2008–2012	39 (47.6%)	9 (47.4%)	5 (50.0%)	12 (63.2%)	13 (38.2%)	
2013–2016	30 (36.6%)	2 (10.5%)	4 (40.0%)	4 (21.1%)	20 (58.8%)	
Source control intervention						
Surgical operation	46 (56.1%)	1 (5.3%)	0 (0.0%)	16 (84.2%)*†	29 (85.3%)*†	<0.001
Percutaneous drainage	9 (11.0%)	1 (5.3%)	0 (0.0%)	3 (15.8%)	5 (14.7%)	0.576
Appropriate source control	53 (64.6%)	0 (0.0%)	0 (0.0%)	19 (100.0%)*	34(100.0%)*†	<0.001
Initial antifungal therapy						<0.001
Echinocandins	36 (43.9%)	1 (5.3%)	5 (50.0%)*	0 (0.0%)†	30 (88.2%)*‡	
Azoles	31 (37.8%)	14 (73.7%)	2 (20.0%)	12 (63.2%)	3 (8.8%)	
Amphotericin B	6 (7.3%)	2 (10.5%)	3 (30.0%)	0 (0.0%)	1 (2.9%)	
None	9 (11.0%)	2 (10.5%)	0 (0.0%)	7 (36.8%)	0 (0.0%)	
Appropriate antifungal therapy	44 (53.7%)	0 (0.0%)	10 (100.0%)*	0 (0.0%)†	34 (100.0%)*‡	<0.001
Duration of survival, day	22.0 (11.8, 30.0)	14.0 (3.0, 30.0)	28.5 (8.0, 30.0)	15.0 (12.0, 29.0)	30.0 (14.8, 30.0)‡	0.033
30-day mortality	25 (30.5%)	12 (63.2%)	5 (50.0%)	5 (26.3%)	3 (8.8%)*†	<0.001
In-hospital mortality	33 (40.2%)	13 (68.4%)	6 (60.0%)	6 (31.6%)	8 (23.5%)	0.006

Data were presented as number of patients (percentage) or mean (95% confidence interval)

*$P < 0.05/6 = 0.0083$ (Bonferroni-corrected post hoc multiple comparisons) when compared with the appropriate source control (−) and appropriate antifungal therapy (−) patients

†$P < 0.0083$ when compared with the appropriate source control (−) and appropriate antifungal therapy (+) patients

‡$P < 0.0083$ when compared with the appropriate source control (+) and appropriate antifungal therapy (−) patients
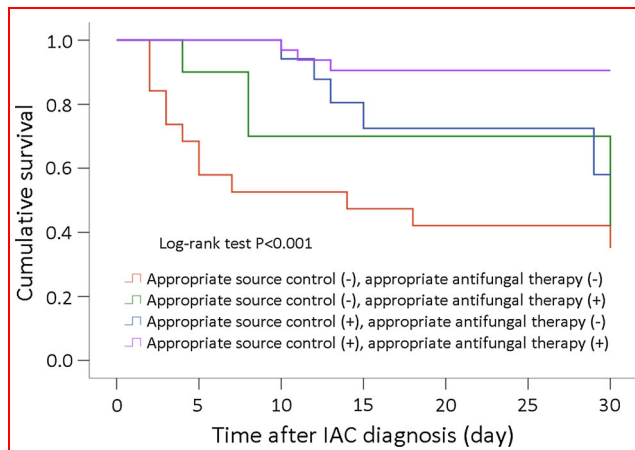
Fig. 2 The 30-day survival curve of patients with four combinations of appropriate treatments. Patients with both appropriate source control and appropriate antifungal therapy had significantly higher survival than those with neither appropriate treatment ($P < 0.001$) and those with only appropriate antifungal therapy ($P = 0.003$). $P < 0.05/6 = 0.0083$ were considered statistically significant (Bonferroni correction)

Discussion

Results of our study showed that the overall 30-day mortality was 30.5% in critically ill surgical patients with IAC; whereas appropriate source control and appropriate antifungal therapy were associated with improved 30-day survival, and the protective effects of the two appropriate treatments were additive. To our knowledge, this is the first study investigating the additive impact of appropriate treatments on the outcome of IAC patients.

In the present study, the target population was patients in a surgical ICU with documented IAC. These patients had high average APACHE II score, high proportion of septic shock and organ failure, and were at high risk of IAC-related death [9, 17]. Therefore, it is of high clinical significance to investigate the impact of appropriate treatments on the outcome in these patients.

There were three types of intra-abdominal infections leading to IAC in our patients, i.e., peritonitis (61.0%), abdominal abscesses (23.2%) and biliary tract infection (15.9%). This study did not include patients with acute necrotizing pancreatitis, because it was difficult to obtain standard pathogenic specimens and there was no uniform criterion for adequate source control in those patients complicated with abdominal infections. As in other studies, *C. albicans* was the main pathogen of IAC in this study [1, 3]; *Candida glabrata* (13.4%) and *Candida tropicalis* (11.0%) were common in non-albicans Candida species.

For patients with IAC, the clinical signs and symptoms are usually not specific, and the definitive culture results are difficult to obtain. Therefore, the diagnosis of IAC and

treatment initiation is often delayed, which might explain the reasons of poor outcome in these patient populations. In the present study, 30.5% of IAC patients died within 30 days, which was in line with the previously reported results [6, 24]. The role of antifungal agents in the treatment of IAC remains somewhat controversial. For example, in a multicenter retrospective cohort study, Bassetti et al. [6] found that inadequate antifungal therapy (adequate therapy was define as susceptible and sufficient dose antifungal agents administered within 24 h from positive culture) was associated with 30-day mortality in IAC patients. In the study of Vergidis et al. [14], antifungal therapy was defined early when administered within 5 days of collecting culture-positive sample. Their results showed that early antifungal therapy was associated with better survival only for IAC stemming from gastrointestinal tract sources [14]. On the other hand, Lagunes et al. [15] reported that inadequate source control, but not inadequate antifungal therapy, was a risk factor for 30-day mortality in both ICU and non-ICU patients with IAC. It should be noted that, in the above studies, the effect of combined appropriate treatments (source control and antifungal therapy) had not been analyzed, and the effect of appropriate antifungal therapy need to be clarified further in surgical ICU patients.

In the present study, we defined interventions as early according to the same criteria of Vergidis et al. [14], i.e., those that were administered within 5 days of culture-positive sample collection. Our results showed that patients with higher APACHE II score, higher SOFA score and mechanical ventilation were more likely to receive appropriate antifungal therapy; similar phenomenon was also reported by others [14, 15, 24]. Despite of these, appropriate antifungal therapy remained as a protective factor of 30-day survival after correcting confounding factors in our patients. Furthermore, our results showed an additive effect of combined appropriate source control and appropriate antifungal therapy, i.e., those with both appropriate treatments had an even lower 30-day mortality. Therefore, combined appropriate treatments should begin as early as possible for surgical patients with IAC in the ICU.

Except the retrospective nature, there were some other limitations in our study. Firstly, the 2016 guideline recommends echinocandin susceptibility testing for patients who had prior echinocandin exposure or were infected with *C. glabrata* or *C. parapsilosis* [20], whereas such susceptibility testing was not routinely performed for isolated Candida species in our hospital. However, resistance to echinocandin-class drugs remains relatively low, i.e., less than 3% of *Candida albicans* and most Candida species [25]. The multicenter study of Bassetti et al. [6] revealed that only 2% of Candida strains are resistant to echinocandin. Furthermore, our study excluded patients

Table 4 Factors in association with 30-day survival (Cox proportional hazard model)

	Univariate analysis		Multivariate analysis[a]	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Separate effects of appropriate treatment				
Appropriate source control	0.21 (0.90–0.48)	<0.001	0.09 (0.03–0.26)	<0.001
Appropriate antifungal therapy	0.30 (0.13–0.71)	0.006	0.18 (0.07–0.47)	0.001
Age > 65 years	3.20 (0.96–10.68)	0.059	–	–
Septic shock[b]	2.03 (0.88–4.71)	0.099	10.97 (3.54–33.93)	<0.001
Candida colonization[c]	2.11 (0.96–4.62)	0.063	–	–
The year of IAC diagnosis				
2013–2016	1.00		–	–
2008–2012	2.14 (0.75–6.06)	0.154	–	–
2003–2007	4.33 (1.41–13.24)	0.010	–	–
Combined effect of appropriate treatment				
Treatment combination				
Appropriate source control (−), appropriate antifungal therapy (−)	1.00		1.00	
Appropriate source control (−), appropriate antifungal therapy (+)	0.59 (0.21–1.67)	0.315	0.14 (0.04–0.55)	0.005
Appropriate source control (+), appropriate antifungal therapy (−)	0.35 (0.12–0.99)	0.050	0.08 (0.02–0.30)	<0.001
Appropriate source control (+), appropriate antifungal therapy (+)	0.09 (0.03–0.33)	<0.001	0.02 (0.00–0.08)	<0.001
Age > 65 years	3.20 (0.96–10.68)	0.059	–	–
Septic shock[b]	2.03 (0.88–4.71)	0.099	12.26 (3.53–42.59)	<0.001
Candida colonization[c]	2.11 (0.96–4.62)	0.063	–	–
The year of IAC diagnosis				
2013–2016	1.00		–	–
2008–2012	2.14 (0.75–6.06)	0.154	–	–
2003–2007	4.33 (1.41–13.24)	0.010	–	–

HR hazard ratio, *CI* confidence interval, *SOFA* sepsis-related organ failure assessment

[a]Factors with a *P* value of <0.10 in univariate analyses were included in multivariate model (backward). SOFA score was excluded because of collinearity with septic shock

[b]Sepsis with persistent hypotension despite adequate volume resuscitation requiring vasopressors to maintain mean arterial pressure $\geq$ 65 mmHg and a serum lactate level > 2 mmol/L

[c]Candida was isolated in non-infected sites in the same time or before the culture-positive samples were obtained

who received systemic antifungal therapy within 14 days. Therefore, the rate of echinocandin resistance might be very low in our patients. Secondly, because of the low incidence of IAC, we collected data over a 13-year period. The changes of routine practice during this long period might have confounded patients' outcomes. However, inclusion of the year of IAC diagnosis in the multivariate model did not change our results. Finally, because of the rarity of IAC cases, the sample size and the number of cases with positive events (25 deaths within 30 days) were relatively small in the present study, leaving a risk of estimation bias. However, with a backward elimination procedure, the factors remained significant in the multivariate model were no more than three; thus the "ten events per variable" rule was observed. This further confirmed the clinical significance of our results.

Conclusion

Our results showed that, in critically ill surgical patients with IAC, both appropriate source control and appropriate antifungal therapy were associated with reduced risk of mortality within 30 days, and the protective effects of two appropriate treatments were additive. Prospective trials are needed to verify these findings.

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