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Original Article

Prognostic factors for patients with culture-positive *Candida* infection undergoing abdominal surgery

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Background and purpose: Increased risk for fungal infections has been observed in high-risk surgical patients, but the prognostic factors and impact of antifungal agents in this patient population are uncertain, especially in patients undergoing abdominal operation. This study was performed to ascertain the prognostic factors for patients with culture-positive *Candida* spp. who have had abdominal surgery.

Methods: From 2003 through 2006, all adult patients with positive candidal culture from abdominal specimens (peritoneal fluid obtained during laparotomy or drain effluent, abscess, or bile) at China Medical University Hospital, Taichung, Taiwan, were included in this retrospective study. Patients' demographic data, prognostic factors, and 30-day mortality rate related to fungal infection were analyzed by reviewing the medical charts.

Results: Thirty nine patients were enrolled in the study. The overall mortality rate was 35.9%. *Candida albicans* was the most common isolate (82.5%). The major prognostic factors were number of surgical interventions, Gram-negative bacteremia, high Acute Physiology And Chronic Health Evaluation (APACHE) II score, corticosteroid use, and subsequent candidal infection ($p < 0.05$).

Conclusions: In patients with positive intra-abdominal candidal culture, greater numbers of surgical intervention, Gram-negative bacilli bacteremia, and high APACHE II score were the prognostic factors for mortality. Corticosteroid use might be a risk factor for subsequent candidal infection.

Key words: Abdomen; *Candida*; Prognosis; Risk factors; Surgical procedures, operative

Introduction

Candida spp. are part of the normal microflora of human skin and mucous membranes. Clinically, these microorganisms can cause infections in humans, especially in people with compromised immune function [1,2]. In the past few decades, the incidence of nosocomial fungal infections, including *Candida* spp., has increased [3]. In the study by Krzemińska-Jaśkowiak et al, the most common pathogens isolated from patients undergoing abdominal surgery were *Enterococcus* spp., *Enterobacteriaceae*, and *Bacteroides* spp.; *Candida* spp. accounted for 14.5% [4]. For the treatment of complicated intra-abdominal infection, the Infectious Disease Society of America has proposed a guideline [5]. With the exception of patients receiving immunosuppressive therapy or those with recurrent or postoperative intra-abdominal infections, use of antifungal agents is regarded as unnecessary. In contrast, some authors have suggested prophylactic use of antifungal agents for high-risk surgical patients [6-8]. These studies found that the rate of fungal infection decreased significantly, although the mortality rate did not change [6-8]. This retrospective study was conducted to clarify the prognostic factors for patients undergoing intra-abdominal surgery, and the impact of antifungal agents on mortality.

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Methods

Patients

In a 4-year retrospective study from January 2003 to December 2006, all adult patients undergoing abdominal

surgery who had positive culture of *Candida* spp. from an intra-abdominal specimen (peritoneal fluid obtained during laparotomy or drained effluent, abscess, or bile) were included. Patients' demographic data, underlying diseases (including heart disease, diabetes mellitus, liver cirrhosis, and chronic renal insufficiency), prior history of surgery and antibiotics, use of parenteral nutrition, corticosteroids (5 mg/day for at least 1 week), and antifungal agents, number of surgical interventions, presence of central venous catheters, disease severity (evaluated by the Acute Physiology And Chronic Health Evaluation [APACHE] II score), duration of hospital stay, duration of intensive care unit stay before the use of antifungal agents, and outcomes were reviewed. All of the clinical data were determined when obtaining culture from the abdominal specimen. Antifungal agents were prescribed according to the clinical judgment of the treating doctor. If patients died within 30 days of fungal isolation and the death was not due to other infection or non-infectious disease, it was attributed to fungal infection [9].

Definitions

Sepsis-induced hypotension was defined as systolic blood pressure of <90 mm Hg, mean arterial blood pressure <70, or reduction in systolic blood pressure of >40 mm Hg from baseline in the absence of other causes for hypotension [10,11]. Chronic kidney disease (CKD) was defined according the criteria proposed by the Kidney Disease Outcomes Quality Initiative of the National Kidney Foundation (NKF) [12]. Patients with impaired renal function (serum creatinine, >2.5 mg/dL or elevating serum creatinine level >0.5 mg/dL from baseline), but who did not meet the criteria proposed by the NKF, were diagnosed as having acute renal failure [11,13].

Significant intra-abdominal candidal infection was defined as positive fungal culture from an intra-abdominal specimen and the following criteria: fever (>38°C), sepsis-induced hypotension, absence of response to adequate antibiotic treatment, and absence of adequate draining for a bacterial infection. Candidemia was defined as: at least 2 blood cultures obtained at different times from a peripheral vein or 1 blood culture obtained peripherally and 1 blood culture obtained through an indwelling central venous catheter that grew the same *Candida* spp. [14]; or *Candida* spp. recovered from 1 blood culture and absence of response to adequate antibiotic treatment for a suspected bacterial infection [15]. Clinically meaningful bacteremia [10,16] was diagnosed on the basis of a combination of clinical infection signs and at least 1 positive blood culture. All positive blood cultures were collected within 14 days of the collection of the abdominal specimens and only blood cultures from clinically meaningful infections were further analyzed.

Laboratory methods

The samples from peritoneal fluid, abscess, bile, blood, or the tip of a central venous catheter were collected during operation or in the presence of signs of infection after operation. All specimens were identified in the clinical laboratory. Samples of body fluid from the peritoneal cavity and bile were streaked across Trypticase® soy agar (TSA) with 5% sheep blood (TSA II/Levine eosin methylene blue [EMB] agar [Becton Dickinson, Franklin Lakes, NJ, USA]) and incubated at 35°C for 18 to 24 h. The tip of the central venous catheter was streaked across TSA II and incubated at 35°C for 18 to 24 h. Blood culture was processed initially by the BACTEC 9000 system (Becton Dickinson). Positive bottles were subcultured onto TSA II/Levine EMB agar and incubated at 35°C for 18 to 24 h. Isolates were identified as various *Candida* spp. by Gram stain, CHROMagar™ culture (Becton Dickinson), and ID 32 C (bioMérieux SA, Marcy l'Etoile, France) system for yeast [17,18]. The results were reported after incubation at 29 ± 2°C for 48 h. The biochemical assimilation and fermentation data were read automatically using the mini API software, version 3.0 (Glasgow, UK).

Statistical analyses

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) for Windows (Version 12.0; SPSS, Inc., Chicago, IL, USA). Continuous variables were analyzed by means, standard deviations (SD), medians, and ranges; categorical variables were analyzed with proportions. Independent Student's *t* test was used to assess the significance of differences between groups of continuous variables, and Fisher's exact and Pearson's chi-squared tests were used for the categorical variables. A p value of ≤0.05 was considered statistically significant and all tests of significance were 2-tailed.

Results

In this 4-year retrospective study, 58 patients with positive candidal culture from intra-abdominal specimens

were identified. Eighteen patients with continuous ambulatory peritoneal dialysis peritonitis and 1 with previous use of antifungal agents were excluded. Thirty nine patients were enrolled in the study. The patients' demographic data and underlying diseases are summarized in Table 1. There were 23 men (59.0%) and 16 women (41.0%). The median age was 68 years (range, 36-93 years), and 22 patients (56.4%) were older than 65 years. Diabetes mellitus was the most common underlying disease, followed by CKD, previous abdominal surgery, cardiovascular disease, and liver disease. Seven patients (18.0%) had more than 1 underlying disease. Twenty six patients (66.7%) had gastrointestinal (GI) perforation, 21 of which involved the upper GI tract and 6 involved the lower GI tract; 1 patient had perforation of both upper and lower GI tracts due to blunt abdominal trauma. Thirteen patients (33.3%) underwent operation for tumors of the GI tract and hepatobiliary system, pancreatitis, and uncontrolled bleeding from gastric varices. The mortality rate for patients with or without perforation of the GI tract did not differ significantly ($p = 0.813$). The overall mortality rate was 35.9% (n = 14), and most of the patients who died were older than 65 years.

Eight patients (20.5%) had Gram-negative bacilli bacteremia, and 6 (15.4%) had Gram-positive bacteremia. Among the 39 patients, 5 had candidemia, and all the isolates were *Candida albicans*. Corticosteroid use was recorded for 21 patients (53.9%). After univariate analysis, increased number of surgical interventions, Gram-negative bacilli bacteremia, and prior corticosteroid use were the prognostic factors most associated with mortality ($p < 0.05$). The mortality rate was higher for patients with concomitant candidemia and those receiving antibacterial or antifungal agents, but the differences were not statistically significant.

The microbiological findings are listed in Table 2. Among the collected specimens, 40 *Candida* spp. isolates were identified. *C. albicans* (n = 33; 82.5%) was the leading pathogen, followed by *Candida glabrata* (n = 3; 7.5%), *Candida tropicalis* (n = 3; 7.5%), and *Candida krusei* (n = 1; 2.5%). One patient had

Table 1. Clinical characteristics and demographic data of patients undergoing abdominal surgery (n = 9).

Variable	Survived (n = 25) No. (%)	Died (n = 14) No. (%)	*p*
Sex (male/female)	16/9	7/7	
Age (years; mean ± SD)	64.2 ± 16.4	64 ± 14.1	
<65	11 (44.0)	6 (46.9)	
≥65	14 (56.0)	8 (57.1)	0.945
Underlying illness			
Diabetes mellitus	3 (12.0)	4 (28.6)	
Cardiovascular disease	1 (4.0)	2 (14.3)	
Liver cirrhosis	1 (4.0)	2 (14.3)	
Chronic kidney disease	3 (12.0)	3 (21.4)	
More than 1 underlying disease	1 (4.0)	3 (21.4)	
Underlying surgical condition			
Gastrointestinal cancer	5 (20.0)	1 (7.1)	0.391
Gastrointestinal perforation	17 (68.0)	9 (64.3)	0.813
Upper gastrointestinal tract	14 (56.0)	7 (50.0)	0.718
Lower gastrointestinal tract	4 (16.0)	2 (14.3)	0.635
Others[a]	5 (20.0)	2 (14.3)	0.507
Surgical interventions (median)	1-2 (1)	1-4 (2)	0.018
Bacteremia	6 (24.0)	6 (42.9)	0.287
Gram-negative bacilli	2 (8.0)	6 (42.9)	0.016
Candidemia	2 (8.0)	3 (21.4)	0.329
Central venous catheter	24 (96.0)	14 (100)	0.528
Parenteral nutrition	12 (48.0)	6 (42.9)	0.757
Antibiotic therapy	16 (64.0)	11 (78.6)	0.277
Corticosteroid use	10 (40.0)	11 (78.6)	0.020
Antifungal agent use	16 (64.0)	11 (78.6)	0.477
Duration of hospital stay (days; mean ± SD)	48.7 ± 40.8	34.6 ± 17.1	0.229

[a]Tumor of the liver or biliary system, pancreatitis, bleeding gastric varices.

Abbreviation: SD = standard deviation.

Table 2. *Candida* spp. culture from patients undergoing abdominal surgery (n = 39).

Variable	*Candida albicans*[a]	*Candida glabrata*	*Candida tropicalis*	*Candida krusei*
Ascites	28	3	3	1
Intra-abdominal abscess	4	0	0	0
Bile	1	0	0	0
Concomitant candidemia	5	0	0	0

[a]Gram-negative bacilli bacteremia was present in 8 patients with *C. albicans* isolates (5 with ascites and 3 with intra-abdominal abscess).

Table 3. Comparison of patients receiving antifungal therapy who survived with patients receiving antifungal therapy who died (n = 27).

Variable	Survived (n = 16) No. (%)	Died (n = 11) No. (%)	*p*
Underlying illness			
Diabetes mellitus	2 (12.5)	4 (36.4)	0.187
Cardiovascular disease	1 (6.3)	2 (18.2)	0.549
Liver cirrhosis	1 (6.3)	2 (18.2)	0.549
Chronic kidney disease	2 (12.5)	2 (18.2)	0.545
More than 1 underlying disease	1 (6.3)	3 (27.3)	0.273
No. of surgical interventions (median)	1-2 (1)	1-4 (2)	0.040
1	13 (81.2)	4 (36.4)	
>1	3 (18.8)	7 (63.6)	
Fever >38°C	10 (62.5)	10 (90.9)	0.098
Bacteremia	3 (18.8)	3 (27.3)	0.662
Gram-negative bacilli	1 (6.3)	3 (27.3)	
APACHE II score (mean ± SD)	14.1 ± 7.0	19.6 ± 6.4	0.049
Acute renal failure	4 (25.0)	4 (36.4)	0.675
Corticosteroid use	9 (56.3)	9 (81.8)	0.231
Parenteral nutrition	10 (62.5)	6 (54.5)	0.710
Vasopressor use	4 (25.0)	8 (72.7)	0.022
Duration of hospital stay (days; mean ± SD)	63 ± 43.8	39 ± 16.0	0.096
Duration of ICU stay (days; mean ± SD)	21.8 ± 20.0	29.2 ± 13.9	0.300

Abbreviations: APACHE = Acute Physiology And Chronic Health Evaluation; SD = standard deviation; ICU = intensive care unit.

2 *Candida* spp. (*C. albicans* and *C. glabrata*) in the abdominal specimen. *C. albicans* was more commonly isolated from patients in the non-survival group (92.9% vs 80.0%), but this difference was not significant.

Table 3 summarizes the characteristics of the 27 patients who received antifungal agents. Most patients (85%) were treated within 7 days of *Candida* spp. being isolated (mean, 5.7 days); only 41% were treated early (within 3 days). There was no difference in survival rate between early and late treatment ($p = 0.679$). Of the 27 patients receiving antifungal agents, 3 (11.1%) had cardiovascular disease, 6 (22.2%) had diabetes mellitus, 4 (14.8%) had CKD, and 3 (11.1%) had liver cirrhosis. Ten patients (37.0%) underwent more than 1 surgical intervention. Four patients (14.8%) had Gram-negative bacilli bacteremia. Use of vasopressors was recorded in 12 patients (44.4%). The crude mortality rate was 40.7%. After univariate analysis, higher APACHE II scores, vasopressor use, and greater number of surgical interventions were the prognostic factors most associated with mortality ($p < 0.05$). The proportion of patients with underlying diseases and steroid use was lower in the survival group, and shorter duration of intensive care unit stay was also noted in this population.

Thirty patients (77.0%) developed clinically significant candidal infection, and 9 remained asymptomatic even without antifungal agents. Further analysis of the 2 groups of patients who were infected or colonized was done, and the demographic data and underlying diseases are summarized in Table 4. The time between the blood culture and intra-abdominal specimens ranged from 1 to 14 days (mean, 8.4 days). The time between specimen collection and the report of positive candidal isolates ranged from 3 to 10 days (median, 7 days). There were no significant differences in sex, age, rate of GI perforation, or underlying diseases between

Table 4. Comparison of *Candida* spp. colonization and infection in patients undergoing abdominal surgery (n = 39).

Variable	Colonization (n = 9) No. (%)	Infection (n = 30) No. (%)	*p*
Sex (male/female)	7/2	16/14	0.262
Age (years; mean ± SD)	68.6 ± 13.9	62.8 ± 15.8	0.336
<65	3 (33.3)	14 (46.7)	
≥65	6 (66.7)	16 (53.3)	
Underlying illness			
Diabetes mellitus	1 (11.1)	6 (20.0)	0.542
Cardiovascular disease	0 (0)	3 (10.0)	0.323
Liver cirrhosis	0 (0)	3 (10.0)	0.323
Chronic kidney disease	1 (11.1)	5 (16.7)	0.685
More than 1 underlying disease	0 (0)	3 (10.0)	0.323
Underlying surgical condition			
Gastrointestinal perforation	6 (66.7)	20 (66.7)	1
Upper gastrointestinal tract	5 (55.6)	16 (53.3)	
Lower gastrointestinal tract	1 (11.1)	5 (16.7)	
Previous antibiotic therapy	4 (44.4)	13 (43.3)	0.953
Corticosteroid use	1 (11.1)	20 (66.7)	0.005

Abbreviation: SD = standard deviation.

these 2 groups. In the infected group, 67% of patients received corticosteroids and 43% had a history of antibiotic use. Only the use of corticosteroids increased the risk for subsequent candidal infection ($p < 0.05$).

Discussion

The culture rate of yeast from intra-abdominal specimens during intra-abdominal surgery was high (>30%), and is associated with morbidity and a complicated postoperative course [19]. Approximately one-third of patients with *Candida* spp. isolates in intra-operative specimens will develop significant candidal infections [20,21]. Although Eggimann et al have shown that prophylaxis with fluconazole reduced the incidence of candidal peritonitis in very high-risk patients with recurrent GI perforation or anastomotic leakage [15], there are few studies that follow the natural course of patients with culture-positive *Candida* spp. from ascites or intra-abdominal drainage [22]. If all patients with candidal isolates from intra-abdominal surgical specimens are treated with anti-fungal agents, two-thirds of them will receive unnecessary treatment [20,21].

In this retrospective study, the mean age of the patients was 64 years, which is similar to previous studies [15,19]. In the studies by Pelz et al [7] and Eggimann et al [15], diabetes mellitus was the most common underlying disease in patients with intra-abdominal candidal infection, and this study found the same result. Similar to the study by Sandven et al [19], this study found that GI tract perforation was the most common source of intra-abdominal candidal infection, especially for those perforations that involved the upper GI tract. This may be due to the higher rate of colonization of *Candida* spp. in the upper GI tract [23].

Sandven et al found no difference in mortality rates between patients with perforation involving the upper or lower GI tract [19], and this observation was similar in the present study. Increased number of surgical interventions and prior corticosteroid use were the prognostic factors for mortality in this study, and these prognostic factors have also been reported by other researchers [7,14,15,24-26]. Corticosteroids have been shown to impair innate and acquired immunity against fungal infections [27]. Repeated abdominal surgery and corticosteroid use have been associated with invasive candidiasis [28]. Gram-negative bacilli bacteremia occurred in 21% of the patients in this study, a result that is similar to that reported by De Waele et al [26]. Most patients (75%) with Gram-negative bacilli bacteremia died; univariate analysis showed that Gram-negative bacilli bacteremia was a predictive factor for mortality ($p = 0.016$). To summarize the findings of this study and others [14,25], increased number of surgical interventions, Gram-negative bacilli bacteremia, and previous corticosteroid use had a major impact on the mortality of patients undergoing abdominal surgery with concomitant isolation of *Candida* spp. from the abdominal specimen.

Among critically ill surgical patients with candidal infection, *C. albicans* is the major isolated species [7,15].

Eighty three percent of isolates in this study were *C. albicans*, suggesting that *C. albicans* might be the dominating species of colonization in patients with abdominal perforation [22]. Other *Candida* spp. isolated from this study included *C. glabrata*, *C. tropicalis*, and *C. krusei.* Nearly 70% of patients (n = 27) were treated with antifungal agents, and the mortality rate was 41% (11/27 patients). Higher mortality rates in patients with higher APACHE II scores and longer duration of stay on the intensive care unit have also been noted in other studies [14,26]. It has been suggested that early antifungal therapy might have a beneficial effect for high-risk surgical patients with candidal infection/colonization [14,26]. Early antifungal therapy was not associated with better survival rates in this study, although this might be due to delayed diagnosis of candidal infection rather than delayed early treatment.

In this study, more than two-thirds (77%) of patients had clinically significant candidal infections; this observation is different from reports by other researchers [20,21]. One explanation of this difference might be the timing and frequency of specimen collection, as most of the specimens in this study were collected when patients had signs or symptoms of new-onset or persistent infection. The only significant risk factor for subsequent candidal infection was corticosteroid use ($p < 0.05$). This risk factor was not mentioned in the reports by Pittet et al [14] and Eggimann et al [15], which might be due to different patient populations in their studies.

This study had several limitations. First, the retrospective nature of this study means that the number of *Candida* spp. isolates and subsequent infection rate might have been underestimated, since not all patients receiving intra-abdominal operation had specimens collected. Second, this study was not a case-control study, and some clinically significant differences might not have been detected. In the future, a well-designed prospective or case-controlled study may answer questions such as the necessity and impact of antifungal agents for patients receiving intra-abdominal surgery.

In conclusion, increased number of surgical interventions, Gram-negative bacilli bacteremia, and high APACHE II score were poor prognostic factors for patients with positive candidal culture undergoing abdominal surgery. Prior corticosteroid use might predispose patients to subsequent candidal superinfection.

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