Journal of Microbiology, Immunology and Infection (2017) 50, 370–376

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.e-jmii.com

ORIGINAL ARTICLE

Antifungal therapy did not improve outcomes including 30-day all-cause mortality in patients suffering community-acquired perforated peptic ulcer-associated peritonitis with *Candida* species isolated from their peritoneal fluid

Wei-Sin Li [a], Chen-Hsiang Lee [a,b], Jien-Wei Liu [a,b,*]

[a] *Division of Infectious Diseases, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital, Taiwan*
[b] *School of Medicine, Chang Gung University College of Medicine, Kaohsiung, Taiwan*

Received 9 March 2015; received in revised form 7 June 2015; accepted 6 July 2015
Available online 31 July 2015

KEYWORDS
antifungal therapy;
Candida peritonitis;
mortality

Abstract *Background/purpose:* Although patients suffering community-acquired perforated peptic ulcer (PPU)-associated peritonitis with *Candida* species isolated from their peritoneal fluid have higher chances of mortality and experiencing a complicated postoperative clinical course, universal antifungal therapy for these patients remains controversial.
Methods: This is a retrospective analysis of the impacts of antifungal therapy on outcomes of patients suffering community-acquired PPU-associated peritonitis with *Candida* species isolated from their ascites at a medical center in Taiwan. All included patients received source control and antibiotic treatment, with or without additional postoperative antifungal therapy with fluconazole or an echinocandin for at least 3 days.
Results: Among the 133 included patients, 76 did not receive (Group 1) and 57 did receive (Group 2) antifungal therapy. Sixteen (12%) of the overall included patients died within 30 days. Shock [odds ratio (OR), 5.6; 95% confidence interval (CI), 1.9–16.5; $p = 0.002$] and higher Acute Physiology and Chronic Health Evaluation II score (>20; OR, 9.5; 95% CI, 1.1–80.7; $p = 0.04$) were independently associated with 30-day mortality. Among the 80 matched patients from Groups 1 and 2 (1:1 matched) with the closest propensity score, no significant difference was found in 30-day all-cause mortality, time to mortality, the need for reoperation/

* Corresponding author. Division of Infection Diseases, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital, 123 Ta Pei Road, Niao Sung District, Kaohsiung 833, Taiwan.
E-mail addresses: 88b0@cgmh.org.tw, jwliu@cgmh.org.tw (J.-W. Liu).

http://dx.doi.org/10.1016/j.jmii.2015.07.004

abscess formation/anastomotic leakage, prolonged intensive care unit stay, and prolonged mechanical ventilator dependence between patients with and without antifungal therapy.
Conclusion: Our study provides solid evidence supporting the notions that antifungal therapies do not benefit patients suffering PPU peritonitis with *Candida* species isolated from their ascites in general, and antifungal therapy could be reserved for patients who are critically ill and/or severely immunocompromised.

Introduction

It has been well documented that candidemia causes substantial mortality, and thus, initiating necessary antifungal therapy in the initial stages of the infection is necessary to lower the mortality rate in these patients.[1] Although isolation of *Candida* species from patients with intra-abdominal infections was reported to be associated with an increase in mortality and a complicated postoperative course,[2–6] antifungal agents prescribed in these scenarios are still controversial. Antifungal therapy is recommended for treatment of peritonitis with *Candida* isolation in peritoneal fluid for patients who acquired the infection from hospital settings,[4] staying at an intensive care unit (ICU) and with recurrent peptic ulcer,[5,7] as well as for those who are critically ill and/or severely immunocompromised.[2,7,8] However, when it comes to peritonitis resulting from perforated peptic ulcer (PPU) involving the upper gastrointestinal tract with the isolation of *Candida* species from ascites, there is no consensus yet on whether or not an antifungal agent should be added to antibiotic therapy. The Surgical Infection Society and the Infectious-Diseases Society of America recommends antifungal treatment for community-acquired intra-abdominal infections in only clinically severe cases.[7] However, these recommendations were not made based on any solid research evidence.[7,8] To clarify the role of antifungal therapy for patients suffering community-acquired PPU-associated peritonitis with *Candida* species isolated from their ascites, we performed a retrospective study analyzing this patient population at a large medical center in Taiwan.

Methods

Study design, patients, and *Candida* isolates

This is a retrospective study conducted at Kaohsiung Chang Gung Memorial Hospital (KCGMH), a 2700-bed facility serving as a primary care and tertiary referral center in Southern Taiwan. Included patients were adults (aged ≧ 18 years) hospitalized between January 2008 and December 2012 with a PPU diagnosed within 48 hours upon their arrival and a subsequent growth of *Candida* species from their ascites sampled during surgical operation. Demographic, clinical, and laboratory information of the included patients was retrieved from their medical records at chart review. This study was approved by the Institutional Review Board of Chang Gung Memorial Hospital with a waiver of patient consent (Document No. 103-4156B).

The collected ascites were inoculated on a blood agar medium for incubation. If colonies that grew were microscopically found to be yeast-like organisms, they were identified as a *Candida* species by inoculation on a Sabouraud dextrose agar, inhibitory mold agar, Mycosel agar, and brain–heart infusion agar media with 10% sheep blood (Becton-Dickinson Microbiology System, Becton Dickinson, MD, USA), in accordance with standard methods prescribed for *Candida* culture.[9] The identification to species level for a *Candida* was carried out using either CHROMagar *Candida* (CHROMagar, Paris, France) or API-ID 32C (bioMérieux VITEK, Hazelwood, MO, USA) only under the request of the physicians.

Definitions

After the diagnosis of PPU was made, all included patients received an immediate empirical antibiotic therapy, and a surgical operation was performed within the next 12 hours. The patient's physician decided whether or not to initiate additional antifungal therapy. If antifungal agents were used on either an empirical or a definitive basis, they were started only after the operation. All antifungal therapies administered were considered appropriate, as either fluconazole or an echinocandin (micafungin, anidulafungin, or caspofungin) was used for at least 3 days.[10,11] All *Candida* species recently isolated at KCGMH were found to be susceptible to both fluconazole and echinocandins (data not shown).

Variables included for analysis were age, body mass index, sex, underlying diseases/conditions, preoperative clinical manifestations and laboratory data, appropriateness of antibiotic therapy, and adequacy of infection source control. Specifically, underlying diseases/conditions included heavy alcohol drinking (men consumed $>$ 30 g alcohol/d, whereas women consumed $>$ 15 g alcohol/d, for ≧1 year),[12] liver cirrhosis (diagnosed by abdominal sonography),[13] type 2 diabetes mellitus,[14] chronic kidney disease [estimated glomerular filtration rate (eGFR) $<$ 60 mL/min/1.73 m^2],[15] solid tumors, hematologic diseases, high-dose steroid use (≧20 mg prednisolone daily for $>$3 weeks),[16] and receipt of organ transplantation. Antibiotic therapy was considered suboptimal when (1) the empirically prescribed antibiotic(s) was (were) not in accordance with the principles of antibiotic use for intra-abdominal infection

recommended by the Infectious Diseases Society of Taiwan, as judged by an infectious diseases specialist,[17] and/or (2) for definitive treatment, the pathogenic microbes were resistant to the prescribed antibiotic(s). An inadequate source control for a patient with PPU included the postoperative findings of (1) persistent sepsis in the absence of other infection focus (e.g., pneumonia and/or catheter-related infection), (2) persistent contraindications for oral feeding or enteral feeding through a nasogastric tube indwelled for 1 week or more, and/or (3) fluid accumulation, pus formation, or anastomotic leakage disclosed by abdominal computed tomography (CT) and/or during reoperation. The duration of abdominal pain (in days) referred to the time lapse from the onset of symptoms to the patient presenting to our emergency services. Acute kidney injury was defined as an eGFR below 50% of the normal range.[18] The disease severity was stratified using Acute Physiology and Chronic Health Evaluation (APACHE) II scores.[19] The primary study endpoint was the 30-day all-cause mortality rate, and the secondary endpoints included (1) the presence of intra-abdominal abscess or anastomotic leakage found by CT and/or during reoperation; (2) ventilator use for 14 days or more after the operation; and (3) ICU stay for 14 days or more after the surgery.

Statistical analysis

The included patients were divided into the following groups for analyses: Group 1 and Group 2. Patients in Group 1 did not receive antifungal therapy, whereas those in Group 2 received antifungal therapy. In univariate analyses between Groups 1 and 2, the *t* test or Mann—Whitney *U* test was used for comparisons of continuous variables, whereas the χ^2 test or Fisher exact test was used for comparisons of dichotomous variables, when appropriate. Variables with a *p* value less than 0.1 in univariate analyses were entered into a multiple logistic regression model to identify independent predictor(s) of 30-day mortality. The propensity score for for patients in both groups described the probability for including them on the basis of his or her demographic, clinical, and laboratory characteristics. The estimated propensity scores could then be used either as a stratification variable or as a controlling variable in a multivariable model, or it could also be used to derive a propensity score-matched cohort where all the variables used to derive the propensity score are balanced.[20] Subsequently, patients in Group 1 were matched with those in Group 2 (1:1 match) with the closest propensity score, and a maximal difference of 5% in the likelihood of the mortality was allowed in the matching process. If there was more than one possible match with an identical propensity score, APACHE II scores (secondary matching variable) were considered in the matching process. Matched patients were reanalyzed as described earlier. The 30-day all-cause mortality rates in these two matched groups were compared with each other, and time to mortality was evaluated using the Kaplan—Meier curve and log-rank test. A *p* value less than 0.05 was considered statistically significant. Data were analyzed using the SPSS software for Windows, version 12.0 (SPSS Inc., Chicago, IL, USA).

Results

Among the 347 patients with ascites culture being positive for *Candida* at KCGMH during the study period, 133 fulfilled the inclusion criteria and were included for analysis. Of note, none of the included patients experienced candidemia and/or bacteremia; simultaneous bacterial growth from ascites culture was found in 58 patients included in this study, and the major isolated bacteria were *Streptococcus* spp. (44.8%), *Escherichia coli* (27.6%), and *Klebsiella pneumoniae* (24.1%). The 30-day mortality of the 58 patients with concurrent bacteremic peritonitis was not significant different from that of the other 75 patients who had no concurrent bacteremic peritonitis (15.5% vs. 9.3%, $p = 0.277$).

Among these 133 included patients, 57 (42.8%) received antifungal therapy. Between Group 1 ($N = 76$) and Group 2 ($N = 57$), no significant difference was found in demographics, laboratory data, and percentage of suboptimal antibiotic therapy; however, higher degree of clinical severity was found among patients in Group 2 than among those in Group 1, which were reflected by the higher proportions of fever (31.6% vs. 13.2%, $p = 0.01$), tachycardia (71.9% vs. 42.1%, $p = 0.001$), shock (38.6% vs. 11.8%, $p < 0.001$), acute kidney injury (49.1% vs. 28.9%, $p = 0.02$), and high APACHE II scores (>20 points; 75.4% vs. 40.8%, $p < 0.001$; Table 1).

A total of 16 patients (12%) died within 30 days after the surgery. Risk factors for 30-day crude mortality found in univariate analyses included the following (Table 2): malignancy (31.3% vs. 11.1%, $p = 0.04$), preoperative fever (43.8% vs. 17.9%, $p = 0.04$), tachycardia (81.3% vs. 51.3%, $p = 0.02$), shock (56.3% vs. 18.8%, $p = 0.002$), acute kidney injury (62.5% vs. 34.2%, $p = 0.03$), higher APACHE II score (>20 points, 93.8% vs. 50.4%, $p < 0.001$), and not starting empirical antifungal therapy (7.7% vs. 31.1%, $p = 0.01$) as well as inadequate source control (62.5% vs. 29.9%, $p = 0.01$). In the multivariate analysis, shock [odds ratio (OR), 5.6; 95% confidence interval (CI), 1.9—16.5; $p = 0.002$] and high APACHE II score (>20; OR, 9.5; 95% CI, 1.1—80.7; $p = 0.04$) were independent risk factors for 30-day crude mortality.

Because clinical severity was independently associated with the 30-day mortality, 80 patients, 40 from Group 1 and another 40 Group 2, were matched using propensity score for the Kaplan—Meier survival analysis (Figure 1). All the patients were matched with less than 1% difference in their propensity scores. The demographic, clinical, and laboratory information of the matched patients is presented in Table 3. Between patients who received antifungal therapy and those who did not, no significant differences were found in 30-day all-cause mortality, time to mortality, the need for reoperation/abscess formation/anastomotic leakage, prolonged ICU stay, and prolonged mechanical ventilator dependence.

Discussion

Patients suffering PPU are destined for development of peritonitis that requires surgical intervention for source control and antimicrobial therapy for treating the

Table 1 Demographic, clinical, and laboratory characteristics of patients suffering perforated peptic ulcer with *Candida* isolated from their ascites without (Group 1) and with postoperative antifungal therapy (Group 2).

Characteristics	Group 1 $N = 76$	Group 2 $N = 57$	p
Age (y, range)	63 (27–89)	70 (38–88)	0.07
BMI (kg/m^2, range)	22.1 (15.1–31.8)	23.3 (13.8–36.0)	0.05
Sex (male)	51 (67.1)	36 (63.2)	0.64
Underlying diseases			
Heavy alcohol drinking	8 (10.5)	5 (8.8)	0.74
Liver cirrhosis	4 (5.3)	7 (12.3)	0.21
Diabetes mellitus, type 2	19 (25.0)	18 (31.6)	0.40
Chronic kidney disease	18 (23.7)	14 (24.6)	0.91
Solid tumors	10 (13.2)[a]	8 (14.0)[b]	0.88
Hematologic disease	1 (1.3)	0 (0)	>0.99
High-dose steroid use	0 (0)	1 (1.8)	0.43
Organ-transplant recipient	0 (0)	1 (1.8)	0.43
Preoperative clinical and laboratory features			
Fever ≧ 38°C	10 (13.2)	18 (31.6)	0.01
Tachycardia (HR ≧ 100 bpm)	32 (42.1)	41 (71.9)	0.001
Shock[c]	9 (11.8)	22 (38.6)	<0.001
Abdominal pain (d, range)[d]	1 (0–7)	1 (0–7)	0.46
WBC counts: >10,000/mm^3, <3000/mm^3, or band form >10%	50 (65.8)	43 (75.4)	0.23
C-reactive protein (mg/L, range)	143.1 (0.3–376.8)	148.7 (0.3–388.0)	0.31
Acute kidney injury	22 (28.9)	28 (49.1)	0.02
High APACHE II scores (>20)	31 (40.8)	43 (75.4)	<0.001
Positive growth of bacteria from ascites culture	28 (36.8)	30 (52.6)	0.07
Suboptimal antibiotic therapy	2 (2.6)	4 (7.0)	0.40

[a] Including hepatocellular carcinoma in three, pancreatic cancer in one, as well as nonsmall cell lung carcinoma, rectal cancer, and buccal cancer each in two patients.
[b] Including hepatocellular carcinoma, breast cancer, buccal cancer, cervical cancer each in one, and nonsmall cell lung carcinoma in four patients.
[c] MBP < 60 mmHg, SBP < 90 mmHg or inotropic agents being used.
[d] From symptoms onset to presenting to Emergency Services.
Data presented as *n* (%), unless stated otherwise.
APACHE II = Acute Physiology and Chronic Health Evaluation II; BMI = body mass index; HR = heart rate; MBP = mean blood pressure; SBP = systolic blood pressure; WBC = white blood count.

infection.[7,17,21–23] PPU-associated peritonitis is always a polymicrobial infection caused by microbes including bacteria and *Candida* that normally colonize the upper gastrointestinal tract.[7,24,25] The isolation of *Candida* species from ascites of patients with PPU-associated peritonitis was reportedly associated with higher mortality rate in this patient group.[3,4] Previously published series that evaluated the role of antifungal therapy in peritonitis with *Candida* species isolated from intraperitoneal fluid included cases with heterogeneous causes[24] and clinical severities/underlying immunocompromises,[2,26] and acquisition of peritonitis from both community and hospital settings,[26,27] and thus, these provided little information concerning the need for antifungal therapy specifically for peritonitis resulting from PPU. To our knowledge, this is the largest series addressing community-acquired PPU-associated peritonitis with *Candida* species isolated from intraperitoneal fluid.

Major pathogens including *Streptococcus* spp., *E. coli*, and *K. pneumoniae* isolated from the ascites of our patients were consistent with pathogens that were previously reported in patients with this infectious entity.[2–7,26] Our data showed that the outcomes of patients with PPU-associated peritonitis under the source control and antibiotic treatment were not significantly influenced by additional antifungal therapy, but were associated with shock and high APACHE II scores, which were reflective of the patients' clinical severity and vulnerability.

To minimize possible confounding(s), our evaluation of the role played by antifungal therapy in patients with PPU-associated peritonitis included using a multivariate analysis model. In addition, propensity score matching reduced possible potential bias. Limitations of this study include (1) nonrandomized patient allocation and inevitable missing data, which are always inherent in a retrospective study, and (2) the lack of identification of all the species of *Candida* isolated from the intraperitoneal fluid, which was done only at our hospital under the request of the clinician. Nonetheless, most of the *Candida* isolates that grew from the intraperitoneal fluid of patients suffering PPU peritonitis are *Candida albicans*.[2–7,26,27] All *C. albicans* isolates at KCGMH have been found to be susceptible to fluconazole and echinocandins (data not shown).

In conclusion, this study provides solid evidence supporting the notions that (1) antifungal therapies do not benefit patients suffering PPU peritonitis with *Candida*

Table 2 Demographic, clinical, and laboratory characteristics of patients who survived and those who died within 30 days after the operation among patients suffering perforated peptic ulcer with *Candida* isolated from peritoneal fluid.

Characteristics	Deceased patients $N = 16$	Survived patients $N = 117$	p
Age (y, range)	71.5 (55–87)	66 (27–89)	0.11
BMI (kg/m^2, range)	22.1 (19.7–30.4)	23 (13.8–36.0)	0.39
Sex (male)	12 (75.0)	75 (64.1)	0.39
Underlying diseases			
Heavy alcohol drinking	0 (0)	13 (11.1)	0.37
Liver cirrhosis	1 (6.3)	10 (8.5)	>0.99
Diabetes mellitus, type 2	4 (25)	33 (28.2)	>0.99
Chronic kidney disease	6 (37.5)	26 (22.2)	0.21
Solid tumors	5 (31.3)[a]	13 (11.1)[b]	0.04
Hematologic disease	0 (0)	1 (0.9)	>0.99
High-dose steroid use	0 (0)	1 (0.9)	>0.99
Organ-transplant recipient	0 (0)	1 (0.9)	>0.99
Preoperative clinical and laboratory features			
Fever ≧ 38°C	7 (43.8)	21 (17.9)	0.04
Tachycardia (HR ≧ 100 bpm)	13 (81.3)	60 (51.3)	0.02
Shock[c]	9 (56.3)	22 (18.8)	<0.01
Abdominal pain (d, range)[d]	1 (0–7)	1 (0–7)	0.99
WBC counts: >10,000/mm^3, <3000/mm^3, or band form >10%	12 (75.0)	81 (69.2)	0.78
C-reactive protein (mg/L, range)	176.3 (2.8–320.6)	142.6 (0.3–388.0)	0.96
Acute kidney injury	10 (62.5)	40 (34.2)	0.03
High APACHE II scores (> 20)	15 (93.8)	59 (50.4)	<0.01
Positive bacterial growth from ascites	9 (56.3)	49 (41.9)	0.28
Therapeutic modality			
Antifungal treatment	10 (62.5)	47 (40.2)	0.09
Definitive therapy	5 (31.3)	38 (32.5)	0.52
Empirical therapy	5 (31.3)	9 (7.7)	0.01
Suboptimal antibiotics	1 (6.3)	5 (4.3)	0.55
Inadequate source control	10 (62.5)	35 (29.9)	0.01

[a] Including rectal cancer in one, and nonsmall cell carcinoma of the lung in four patients.
[b] Including breast cancer, cervical cancer, pancreatic cancer, and rectal cancer each in one, hepatocellular carcinoma in four, buccal cancer in three, and nonsmall cell carcinoma of the lung in two patients.
[c] MBP < 60 mmHg, SBP < 90 mmHg or inotropic agents were used.
[d] From symptoms onset to presenting to emergency services.
Data presented as *n* (%), unless stated otherwise.
APACHE II = Acute Physiology and Chronic Health Evaluation II; BMI = body mass index; HR = heart rate; MBP = mean blood pressure; SBP = systolic blood pressure; WBC = white blood count.

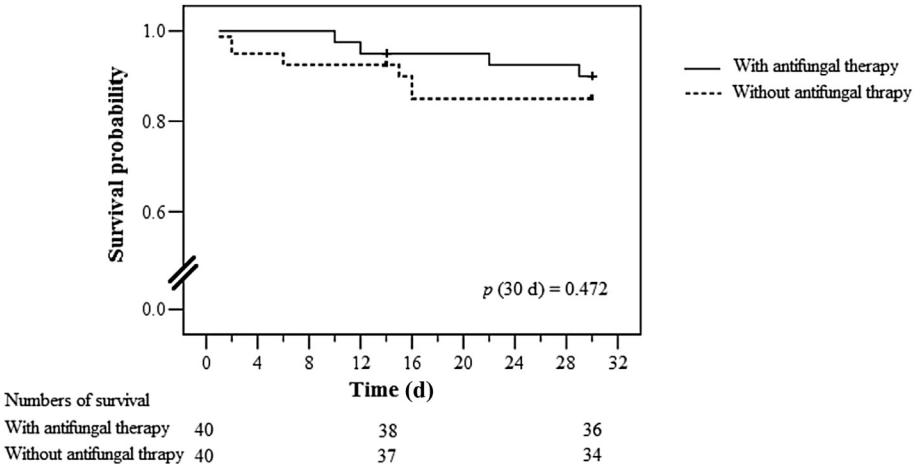

Figure 1. Kaplan–Meier survival analysis curves for patients (from Groups 1 and 2) matched by propensity score with perforated peptic ulcer and ascites culture positive for *Candida* spp. Patients who received antifungal therapy had higher survival probability on 30 days after the operation, but there were no statistical significances ($p = 0.472$).

Table 3 Demographic, clinical, and laboratory characteristics of the matched patients.

Characteristics	Without antifungal therapy $N = 40$	With antifungal therapy $N = 40$	p
Age (y, range)	69 (41–89)	69 (38–88)	0.62
BMI (kg/m^2, range)	22.1 (15.2–30.0)	23.0 (13.8–30.1)	0.19
Sex (male)	26 (65.0)	24 (60.0)	0.64
Underlying diseases			
Heavy alcohol drinking	4 (10.0)	3 (7.5)	>0.99
Liver cirrhosis	1 (2.5)	5 (12.5)	0.20
Diabetes mellitus, type 2	13 (32.5)	13 (32.5)	>0.99
Chronic kidney disease	12 (30)	9 (22.5)	0.45
Solid tumors	5 (12.5)[a]	3 (7.5)[b]	0.71
Hematologic disease	0 (0)	0 (0)	—
High-dose steroid use	0 (0)	1 (2.5)	>0.99
Organ-transplant recipient	0 (0)	1 (2.5)	>0.99
Preoperative clinical and laboratory features			
Fever ≧ 38°C	7 (17.5)	10 (25.0)	0.41
Tachycardia (HR ≧ 100 bpm)	23 (57.5)	26 (65.0)	0.49
Shock[c]	8 (20.0)	11 (27.5)	0.43
Abdominal pain (d, range)[d]	1 (0–7)	2 (0–7)	0.60
WBC counts: >10,000/mm^3, <3000/mm^3, or band form >10%	27 (67.5)	29 (72.5)	0.63
C-reactive protein (mg/L, range)	168.0 (4.3–380.8)	129.0 (0.3–388.0)	0.43
Acute kidney injury	15 (37.5)	17 (42.5)	0.65
High APACHE II scores (>20)	26 (65.0)	26 (65.0)	>0.99
Positive growth of bacteria from ascites culture	14 (35.0)	16 (40.0)	0.64
Suboptimal antibiotics	1 (2.5)	2 (5.0)	>0.99
Outcomes			
30-d mortality	6 (15.0)	4 (10.0)	0.45
Reoperation or abscess/leakage within 14 d	1 (2.5)	5 (12.5)	0.20
Prolonged ventilator use (>14 d)	3 (7.5)	8 (20.0)	0.11
Prolonged ICU stay (>14 d)	4 (10.0)	11 (27.5)	0.05

[a] Including rectal cancer in one, buccal cancer as well as nonsmall cell carcinoma of the lung each in two patients.
[b] Including hepatocellular carcinoma, breast cancer, and nonsmall cell carcinoma of the lung each in one patient.
[c] MBP < 60 mmHg, SBP < 90 mmHg or inotropic agents were used.
[d] From symptoms onset to presenting to emergency services.
Data presented as *n* (%), unless stated otherwise.
APACHE II = Acute Physiology and Chronic Health Evaluation II; BMI = body mass index; HR = heart rate; ICU = intensive care unit; MBP = mean blood pressure; SBP = systolic blood pressure; WBC = white blood count.

species isolated from their ascites in general, and (2) the indication for antifungal therapy could be reserved for patients who are critically ill and/or severely immunocompromised. In addition, our study again underscores the importance of the conventional therapeutic modality, which includes effective source control and optimal antibiotic therapy for patients with PPU peritonitis acquired from community setting.

Conflicts of interest

All contributing authors declare no conflicts of interest.

Acknowledgments

This study was partial supported by a grant from Chang Gung Memorial Hospital, Taiwan (CMRPG 8B0671).

References

1. Pappas PG, Kauffman CA, Andes D, Benjamin Jr DK, Calandra TF, Edwards Jr JE, et al. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2009;**48**:503–35.
2. Dupont H, Paugam-Burtz C, Muller-Serieys C, Fierobe L, Chosidow D, Marmuse JP, et al. Predictive factors of mortality due to polymicrobial peritonitis with *Candida* isolation in peritoneal fluid in critically ill patients. *Arch Surg* 2002;**137**:1341–6.
3. Lee SC, Fung CP, Chen HY, Li CT, Jwo SC, Hung YB, et al. *Candida* peritonitis due to peptic ulcer perforation: incidence rate, risk factors, prognosis and susceptibility to fluconazole and amphotericin B. *Diagn Microbiol Infect Dis* 2002;**44**:23–7.
4. Shan YS, Hsu HP, Hsieh YH, Su ED, Lee JC, Lin PW. Significance of intraoperative peritoneal culture of fungus in perforated peptic ulcer. *Br J Surg* 2003;**90**:1215–9.
5. Montravers P, Dupont H, Gauzit R, Veber B, Auboyer C, Blin P, et al. *Candida* as a risk factor for mortality in peritonitis. *Crit Care Med* 2006;**34**:646–52.

6. Montravers P, Mira JP, Gangneux JP, Leroy O, Lortholary O. A multicentre study of antifungal strategies and outcome of *Candida* spp. peritonitis in intensive care units. *Clin Microbiol Infect* 2011;**17**:1061—7.
7. Solomkin JS, Mazuski JE, Bradley JS, Rodvold KA, Goldstein EJ, Baron EJ, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. *Clin Infect Dis* 2010;**50**:133—64.
8. Pappas PG, Rex JH, Sobel JD, Filler SG, Dismukes WE, Walsh TJ, et al. Guidelines for treatment of candidiasis. *Clin Infect Dis* 2004;**38**:161—89.
9. Murray PR, Baron EJ, Jorgensen JH, Landry ML, Pfaller MA. *Manual of clinical microbiology*. 9th ed. Herndon, VA: ASM Press; 2007.
10. Basoli A, Chirletti P, Cirino E, D'Ovidio NG, Doglietto GB, Giglio D, et al. A prospective, double-blind, multicenter, randomized trial comparing ertapenem 3 vs. $\geq$ 5 days in community-acquired intraabdominal infection. *J Gastrointest Surg* 2008;**12**:592—600.
11. Solomkin J, Zhao YP, Ma EL, Chen MJ, Hampel B, DRAGON Study Team. Moxifloxacin is non-inferior to combination therapy with ceftriaxone plus metronidazole in patients with community-origin complicated intra-abdominal infections. *Int J Antimicrob Agents* 2009;**34**:439—45.
12. Health Promotion Administration, Ministry of Health and Welfare of Taiwan. Available from: http://www.hpa.gov.tw/BHPNet/Web/News/News.aspx?no=201304030002 Last accessed: 05.04.13 [in Chinese].
13. Hung CH, Lu SN, Wang JH, Lee CM, Chen TM, Tung HD, et al. Correlation between ultrasonographic and pathologic diagnoses of hepatitis B and C virus-related cirrhosis. *J Gastroenterol* 2003;**38**:153—7.
14. Handelsman Y, Mechanick JI, Blonde L, Grunberger G, Bloomgarden ZT, Bray GA, et al. American Association of Clinical Endocrinologists medical guidelines for clinical practice for developing a diabetes mellitus comprehensive care plan. *Endocr Pract* 2011;**17**:1—53.
15. Levey AS, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW, et al. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Ann Intern Med* 2003;**139**:137—47.
16. Lionakis MS, Kontoyiannis DP. Glucocorticoids and invasive fungal infections. *Lancet* 2003;**362**:1828—38.
17. Infectious Diseases Society of Taiwan. Guidelines for antimicrobial therapy of intra-abdominal infections in adults. *J Microbiol Immunol Infect* 2008;**41**:279—81.
18. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P. Acute renal failure—definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care* 2004;**8**:R204—12.
19. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med* 1985;**13**:818—29.
20. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika* 1983;**70**:41—55.
21. Crofts TJ, Park KG, Steele RJ, Chung SS, Li AK. A randomized trial of nonoperative treatment for perforated peptic ulcer. *N Engl J Med* 1989;**320**:970—3.
22. Boey J, Lee NW, Koo J, Lam PH, Wong J, Ong GB. Immediate definitive surgery for perforated duodenal ulcers: a prospective controlled trial. *Ann Surg* 1982;**196**:338—44.
23. Millat B, Fingerhut A, Borie F. Surgical treatment of complicated duodenal ulcers: controlled trials. *World J Surg* 2000;**24**:299—306.
24. Sartelli M, Viale P, Catena F, Ansaloni L, Moore E, Malangoni M, et al. 2013 WSES guidelines for management of intra-abdominal infections. *World J Emerg Surg* 2013;**8**:3.
25. Donowitz LG, Page MC, Mileur BL, Guenthner SH. Alteration of normal gastric flora in critical care patients receiving antacid and cimetidine therapy. *Infect Control* 1986;**7**:23—6.
26. Carneiro HA, Mavrakis A, Mylonakis E. *Candida* peritonitis: an update on the latest research and treatments. *World J Surg* 2011;**35**:2650—9.
27. Hasibeder W, Halabi M. *Candida* peritonitis. *Minerva Anestesiol* 2014;**80**:470—81.