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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

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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/

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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