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Pre-Operative Anti-Fungal Therapy Does Not Improve Outcomes in Perforated Peptic Ulcers

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Abstract

Background: With the advent of anti-*Helicobacter pylori* therapy, hospital admissions for peptic ulcer disease (PUD) have declined significantly since the 1990s. Despite this, operative treatment of PUD still is common. Although previous papers suggest that *Candida* in peritoneal fluid cultures may be associated with worse outcomes in patients with perforated peptic ulcers (PPUs), post-operative anti-fungal therapy has not been effective. We hypothesized that pre-operative anti-fungal drugs improve outcomes in patients with PPUs undergoing operative management.

Patients and Methods: A prospectively maintained Acute and Critical Care Surgery (ACCS) database spanning 2008–2015 and including more than 7,000 patients was queried for patients with PPUs. Demographics and clinical outcomes were abstracted. Pre-operative anti-fungal use, intra-operative peritoneal fluid cultures, and infectious outcomes were abstracted manually. We compared outcomes and the presence of fungal infections in patients receiving peri-operative anti-fungal drugs in the entire cohort and in patients with intra-operative peritoneal fluid cultures. Frequencies were compared by the Fisher exact or $\chi 2$ test as appropriate. The Student's *t*-test was used for continuous variables.

Results: There were 107 patients with PPUs who received operative management; 27 (25.2%) received pre-operative anti-fungal therapy; 33 (30.8%) received peritoneal fluid culture, and 17 cultures (51.5%) were positive for fungus. The presence of fungus in the cultures did not affect the outcomes. There were no differences in length of stay (LOS), intensive care unit (ICU) LOS, ventilator days, 30-day re-admission rates, or rates of intra-abdominal abscess formation or fungemia in patients who received pre-operative anti-fungal drugs regardless of the presence of fungi in the peritoneal fluid.

Conclusion: *Candida* has been recovered in 29%–57% of peritoneal fluid cultures in patients with PPUs. However, no studies have evaluated pre-operative anti-fungal therapy in PPUs. Our data suggest that pre-operative anti-fungal drugs are unnecessary in patients undergoing operative management for PPU.

Keywords: candida; fungus; gastrointestinal perforation; peritonitis

In 1994, the National Institutes of Health released a consensus statement attributing many cases of peptic ulcer disease (PUD) to *Helicobacter pylori* and recommending treatment for all patients with *H. pylori* [1]. Coupled with the widespread availability of proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H2 blockers), there have been significant decreases in hospitalizations for complications of PUD in the past 20 years. Wang et al. noted an almost 30% decrease in admission from complications of PUD from 1993 to 2006 [2]. During this period, perforations also decreased, although there were still 14,504 hospitalizations for perforated peptic ulcers (PPUs) in 2006, which were responsible for 37% of all ulcer-related deaths in the United States [2]. Despite the decrease in hospitalizations, operative treatment of PUD remains one of the most common procedures performed in emergency general surgery and is associated with a complication rate of approximately 40% [3]. Perforations remain the most common emergency surgical indication in PUD [2,4,5].

Historically, *Candida* has been reported in 29%–57% of peritoneal fluid cultures in patients with PPUs [6–9]. The impact of positive peritoneal fluid cultures is unclear. In one series, mixed fungal and bacterial cultures were associated with advanced age and shock. They considered the fungal

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Table 1. Demographics of Patients by Pre-Operative Anti-Fungal Therapy and Intra-Operative Peritoneal Fluid Cultures

		Pre-operative anti-fungal drugs			*Intra-operative fungal culture*		
	Total (n = *107*)	*Negative* (n = *80*)	*Positive* (n = *27*)	p *Value*	*Negative* (n = *16*)	*Positive* (n = *17*)	p
Age	55.92 (17.6)	56.2 (18.6)	55.2 (14.5)	0.81	59.3 (21.0)	57.7 (15.3)	0.80
Sex (%)				0.78			0.06
Female	57 (53.3)	42 (52.5)	15 (55.6)		6 (37.5)	12 (70.6)	
Male	50 (46.7)	38 (47.5)	12 (44.4)		10 (62.5)	5 (29.4)	
Race (%)				0.05			0.10
Caucasian	62 (57.9)	51 (63.8)	11 (40.7)		7 (43.8)	13 (76.5)	
African American	40 (37.4)	26 (32.5)	14 (51.9)		8 (50.0)	4 (23.5)	
Asian	2 (1.9)	2 (2.5)	0		1 (6.3)	0	
Hispanic	0	0	0		0	0	
Native American	0	0	0		0	0	
Other	3 (2.8)	1 (1.3)	2 (7.4)		0	0	
Unknown	0	0	0		0	0	
Body Mass Index	26.7 (7.2)	26.2 (6.5)	28.2 (9.2)	0.22	26.9 (4.3)	29.6 (8.5)	0.24
Social (%)							
Alcohol	30 (34.5)	20 (30.77)	10 (45.45)	0.21	4 (30.8)	6 (37.5)	1.00
Illicit drug use	16 (19.5)	9 (14.75)	7 (33.33)	0.11	3 (27.3)	4 (26.7)	1.00
Tobacco	52 (55.3)	39 (54.93)	13 (56.52)	0.89	7 (46.7)	7 (41.2)	0.75
Co-morbidities (%)							
Myocardial infarction	8 (7.5)	8 (10.0)	0	0.20	3 (18.8)	2 (11.8)	0.66
Congestive heart failure	10 (9.3)	8 (10.0)	2 (7.4)	1.00	3 (18.8)	3 (17.6)	1.00
Peripheral vascular disease	13 (12.1)	10 (12.5)	3 (11.1)	1.00	3 (18.8)	1 (5.9)	0.34
Cerebrovascular disease	7 (6.5)	5 (6.3)	2 (7.4)	1.00	3 (18.8)	0	0.10
Chronic pulmonary disease	29 (27.1)	23 (28.7)	6 (22.2)	0.51	3 (18.8)	4 (23.5)	1.00
Connective tissue disease	1 (0.9)	1 (1.3)	0	1.00	0	0	N/A
Peptic ulcer disease	99 (92.5)	75 (93.8)	24 (88.9)	0.41	15 (93.8)	17 (100)	0.48
Mild liver disease	9 (8.4)	6 (7.5)	3 (11.1)	0.69	1 (6.3)	3 (17.6)	0.60
Moderate or severe liver disease	1 (0.9)	1 (1.3)	0	1.00	0	0	N/A
Diabetes mellitus	15 (14.0)	9 (11.3)	6 (22.2)	0.20	1 (6.3)	4 (23.5)	0.34
Diabetes mellitus with end-organ damage	1 (0.9)	1 (1.3)	0	1.0	1 (6.3)	0	0.48
Hemiplegia	2 (1.9)	1 (1.3)	1 (3.7)	0.44	1 (6.3)	0	0.48
Renal disease	12 (11.2)	7 (8.8)	5 (18.5)	0.17	4 (25.0)	1 (5.9)	0.17
Any solid organ tumor	6 (5.6)	4 (5.0)	2 (7.4)	0.64	2 (12.5)	1 (5.9)	0.60
Metastatic solid-organ tumor	6 (5.6)	5 (6.3)	1 (3.7)	1.0	1 (6.3)	2 (11.8)	1.00
Age-adjusted Charlson Comorbidity Index	3.9 (2.95)	3.96 (3.1)	3.63 (2.6)	0.61	4.94 (3.3)	4.24 (3.73)	0.57
American Society of Anesthesiologists Score	2.86 (0.86)	2.8 (0.89)	3.0 (0.72)	0.22	2.88 (0.89)	2.88 (0.70)	0.98
Duration of symptoms (h)				0.47			0.39
>24	60 (56.1)	21 (26.3)	10 (37.3)		2 (12.5)	5 (29.4)	
<24	31 (29.0)	45 (56.3)	15 (55.6)		12 (75.0)	10 (58.8)	
Unknown	16 (15.0)	14 (17.5)	2 (7.4)		2 (12.5)	2 (11.8)	
Prior H2-blocker use (%)	3 (2.9)	**0**	**3**	**(11.1)**	**0.02**	1 (6.3)	0	1.0
Prior PPI use (%)	14 (14.7)	13 (17.3)	2 (7.4)	0.34	3 (18.8)	2 (14.3)	1.0
Location of perforation (%)				0.27			0.07
Stomach	34 (31.8)	27 (33.8)	7 (25.9)		4 (25.0)	10 (58.8)	
Pyloric channel	16 (15.0)	10 (12.5)	6 (22.2)		0	1 (5.9)	
Duodenum	53 (49.5)	41 (51.2)	12 (44.4)		11 (68.8)	6 (35.3)	
Both stomach and duodenum	3 (2.8)	2 (2.5)	1 (3.7)		0	0	
Unknown	1 (0.9)	0	1 (3.7)		1 (6.3)	0	

P values are from comparisons of patients who did and did not receive pre-operative anti-fungal therapy and of patients with positive and negative intra-peritoneal fungal cultures. Statistically significant differences are shown in **boldface** type.

Table 2. Fungal Species Recovered from Intra-Operative Peritoneal Fluid Cultures

Species	*No. (%)*
Candida albicans	9 (53)
Yeast (unspeciated)	6 (35)
C. glabrara	1 (6)
C. krusei	1 (6)
C. tropicalis	1 (6)

Percentages sum to greater than 100% because multiple species were present in some cultures.

species to be non-pathogenic in this setting and due to the patient's baseline illness [7]. In contrast, Shan et al. argued that intra-operative peritoneal fluid cultures with fungal growth were associated with longer hospital stays, more deaths, and higher rates of surgical site infections. Positive fungal cultures also were associated with higher Mannheim Peritonitis Index (MPI) scores, indicating more severe illness at presentation [9,10].

Although there have been several studies examining the impact of peri-operative anti-fungal use in patients with gastrointestinal perforations, all of them focused on post-operative use or included only a few patients with perforated ulcers [11–15]. To our knowledge, there have been no studies examining the relation between pre-operative use of anti-fungal drugs and outcomes of patients undergoing surgery for PPUs in the era of readily available PPIs and H2 blockers. We hypothesized that pre-operative anti-fungal use improves outcomes in patients with PPUs.

Patients and Methods

An Institutional Review Board-approved, prospectively maintained, Acute and Critical Care Surgery (ACCS) database spanning 2008–2015 and including more than 7,000 patients was queried for patients with an International Classification of Diseases (ICD)-9 diagnosis of PPU disease of the stomach or duodenum with or without obstruction (ICD-9 codes 531.1x, 531.2x, 531.5x, 531.6x, 532.1x,532.2x, 532.5x, and 532.6x).

All patients with an ICD-9 diagnosis of a PPU were evaluated by an investigator to confirm the accuracy of the coding information. Sites of perforation, pre-operative medications, duration of symptoms, microbiologic data, social history, demographics, and clinical outcomes were abstracted. The Charlson/Deyo Comorbidity Index was applied as previously described [16,17]. The microbiologic data abstracted consisted of intra-operative peritoneal fluid cultures and results from post-operative blood, urine, sputum, and interventional radiology (IR)-guided drain cultures as appropriate.

Intra-operative fungal cultures are collected on flocked nylon swabs and transported in Liquid Amies medium [18]. The swab and media are then vortexed and plated on Blood Heart Infusion, Inhibitory Mold, and Sabourand dextrose with chloramphenicol agars. Samples are incubated for 28 days at 30°C and checked daily. Once grown, molds are identified with light microscopy, and yeasts are identified via matrix-assisted laser desorption/ionization time of flight mass spectrometry (MALDI-TOF MS) (Melanie Yarbrough, PhD, oral communication, February 25, 2017).

Demographics and outcomes of patients who received pre-operative anti-fungal therapy were compared with those who did not using univariable analysis. We then defined an established intra-abdominal infection as the presence of symptoms for more than 24 hours. Univariable analysis of this subgroup was performed in similar fashion. Finally, the subgroup of patients with intra-operative peritoneal fluid cultures yielding fungal growth and patients without such growth were evaluated in similar fashion. Frequencies were compared by the Fisher exact or χ^2 test as appropriate and continuous variables by the Student *t*-test.

Results

There were 118 patients with PPU treated at our institution during the study period; 107 patients had operative therapy, and 27 (25.2%) received empiric pre-operative anti-fungal therapy. The average age was 55.9 (standard deviation [SD] 17.6) years; 57 (53.3%) of the patients were female, and the average Body Mass Index (BMI) was 26.7 (SD 7.2). Patients who received pre-operative anti-fungal drugs were more likely to be taking H2-blockers than those who did not (11.1% vs 0; $p = 0.02$). There were no other significant differences in the demographics of patients who received anti-fungal therapy and those who did not. Complete demographics are shown in Table 1.

There were 33 patients (30.8%) who had intra-operative peritoneal fluid cultures; 17 (51.5%) grew fungus. Although there were no statistically significant differences, patients with fungi recovered were more likely to have a gastric

Table 3. Outcomes of Patients with Perforated Peptic Ulcer According to Receipt of Empiric Pre-Operative Anti-Fungal Therapy

	Total (n = *107*)	*No anti-fungal* (n = *80*)	*Anti-fungal* (n = *27*)
In-hospital death (%)	5 (4.7)	4 (5.0)	1 (3.7)
Mean LOS (SD)	14.2 (13.2)	13.9 (12.5)	15.2 (15.4)
Mean ICU LOS (SD)	6.7 (11.8)	6.7 (11.1)	6.7 (13.9)
Mean ventilator days (SD)	2.4 (6.3)	2.8 (7.0)	1.4 (3.5)
30-day re-admission (%)	19 (17.8)	15 (18.8)	4 (14.8)
Intra-abdominal abscess (%)	7 (6.5)	5 (6.3)	2 (7.4)
Post-op intra-abdominal fungal abscess (%)	3 (2.8)	2 (2.5)	1 (3.7)
Fungemia (%)	1 (0.9)	1 (1.3)	0

None of the differences is statistically significant.
ICU = intensive care unit; LOS = length of stay; SD = standard deviation.

Table 4. Outcomes of Patients with Perforated Peptic Ulcer by Presence of Fungal Species in Intra-Operative Peritoneal Fluid[a]

	Total (n = *33*)	*No fungus* (n = *16*)	*Fungus* (n = *17*)
In-hospital death (%)	1 (3.0)	1 (6.3)	0
Mean LOS (SD)	15.3 (13.4)	13.1 (10.0)	17.4 (16.0)
Mean ICU LOS (SD)	5.9 (8.7)	4.9 (7.0)	6.9 (10.2)
Mean ventilator days (SD)	2.6 (4.5)	2.4 (4.5)	2.7 (4.6)
30-day re-admission (%)	8 (24.2)	2 (12.5)	6 (35.3)
Intra-abdominal abscess (%)	2 (6.1)	1 (6.3)	1 (5.9)
Post-op. intra-abdominal fungal abscess	2 (6.1)	1 (6.3)	1 (5.9)

[a]There were no cases of fungemia, and none of the differences is statistically significant.
ICU = intensive care unit; LOS = length of stay; SD = standard deviation.

perforation than patients without fungal growth (58.8% vs. 25.0%; p = 0.07). All fungal species recovered were yeast; complete speciation is shown in Table 2.

Of the 27 patients who received pre-operative anti-fungal therapy, 23 (85%) received fluconazole; three (11%) received micafungin, and one (4%) received anidulafungin. In order to determine the effect of anti-fungal therapy, we compared in-hospital death, length of stay (LOS), intensive care unit (ICU) LOS, ventilator days, 30-day re-admission rate, formation of intra-abdominal abscesses, fungemia, and number of operations in patients who received empiric anti-fungal therapy and patients who did not. The outcomes are shown in Table 3.

We then compared outcomes of patients who had fungal growth in their intra-operative peritoneal fluid cultures and those who did not. There were no significant differences in demographics, nor were there differences in any measured outcomes. Outcomes according to the presence of fungal species are shown in Table 4.

Next, we attempted to determine whether anti-fungal agents were helpful in patients with established intra-abdominal infections, defined by the presence of symptoms for >24 hours. Of the 107 patients with operatively managed PPU, 60 (56%) presented >24 hours after the onset of symptoms. There were no significant differences in the rate of fungal isolation between patients who had <24 hours of symptoms and those with >24 hours of symptoms (86% vs. 67%; p = 0.39). Among patients with >24 hours of symptoms, there were no differences in outcomes between patients who received pre-operative anti-fungal therapy and those who did not (Table 5).

Finally, we compared the outcomes in patients with fungal isolates who received pre-operative anti-fungal therapy with those who did not. Of the 17 patients with fungal isolates present in the abdomen at surgery, 4 (24%) received pre-operative anti-fungal therapy. There were no significant differences in demographics between the groups or in the post-operative outcomes. Outcomes of patients with confirmed fungal isolates are available in Supplemental Table 1. There was no difference in the incidence of post-operative anti-fungal use between those who received anti-fungal drugs pre-operatively and those who did not (75% vs. 77%; p = 1.0).

Discussion

The rates of *Candida* recovered in the peritoneal fluid of patients with PPU have ranged from 27% to 57%. In 1986, Peoples found that *Candida* was associated with advanced age and shock and concluded that *Candida* was not pathogenic and therefore did not warrant systemic anti-fungal therapy [7]. More recently, Shan et al. analyzed 145 patients with PPU and purulent ascites; 63 (43%) had fungal species isolated. Patients with fungal infections had longer LOS, a higher in-hospital mortality rate, and more surgical site infections, although they also were likely to present later and to be sicker on admission [9]. In a retrospective analysis of 133 patients with *Candida* caused by PPU at the same institution, there were no differences in outcomes between patients started on post-operative anti-fungal drugs and those who were not [13]. Thus, those authors believed that anti-fungal therapy was indicated only for patients who were immunocompromised or critically ill [13].

Table 5. Outcomes of Patients Having >24 h of Symptoms by Receipt of Pre-Operative Anti- Fungal Therapy

	Total	*No anti-fungal*	*Anti-fungal*
N (%)	60 (100)	45 (75.0)	15 (25.0)
In-hospital death (%)	3 (5.0)	2 (4.4)	1 (6.7)
Mean LOS (SD)	12.4 (11.5)	12.2 (11.4)	13.0 (12.3)
Mean ICU LOS (SD)	4.4 (8.1)	5.3 (8.3)	3.3 (7.2)
Mean ventilator days (SD)	1.4 (3.1)	1.8 (3.3)	0.47 (1.8)
30-day re-admission (%)	10 (16.7)	8 (17.8)	2 (13.3)
Intra-abdominal abscess (%)	5 (8.3)	4 (8.9)	1 (6.7)
Post-op. intra-abdominal fungal abscess (%)	2 (3.3)	2 (4.4)	0
Fungemia (%)	1 (1.7)	1 (2.2)	0

None of the differences is statistically significant.

Two prospective studies have evaluated intra-operative or pre-operative anti-fungal therapy in patients with gastric perforation [11,12]. The Norwegian Yeast Study Group performed peritoneal fluid cultures on 109 patients with gastrointestinal perforations or anastomotic leaks and randomized them to intra-operative fluconazole or placebo [12]. Those investigators found no statistically significant difference in the mortality rate; however only 22 patients had gastroduodenal perforations, and no subgroup analysis was performed [12]. Eggimann et al. randomized 49 patients with recurrent gastrointestinal perforations or anastomotic leaks to post-operative daily fluconazole or placebo and found that prophylaxis prevented intra-abdominal *Candida* infections but did not improve the mortality rate [11]. Only five patients were classified as having upper gastrointestinal tract perforations [11]. Both the Surgical Infection Society and the Infectious Diseases Society of America recommend empiric anti-fungal therapy for patients with intra-abdominal infections after gastrointestinal leaks, defined as patients who have an upper gastrointestinal leak prior for ≥24 hours prior to source control [19,20].

Consistent with previous findings, we recovered fungal species from 52% of the peritoneal fluid cultures. There were no differences in outcomes or demographics in the group with positive fungal cultures and those with negative cultures. At our institution, the choice of whether to treat with empiric pre-operative anti-fungal therapy is made by the attending physician. There were no differences in demographics or outcomes between the patients who received pre-operative anti-fungal drugs and those who did not, either in the entire cohort or in patients who underwent operative management >24 hours except that patients on H2-blocker therapy were more likely to receive pre-operative anti-fungal drugs. In contrast to prior studies, we found no significant difference in patients with fungal isolates recovered at the time of surgery. These data suggest that pre-operative anti-fungal therapy is unnecessary in patients with PPU.

Our study has important limitations. Most notably, this was a single-center study, which may limit its reproducibility. At our institution, the choice of whether to use pre-operative anti-fungal drugs is attending-physician dependent, as is the choice to obtain intra-operative peritoneal fluid cultures. It is unclear what drove the decision to give some patients pre-operative anti-fungal drugs and not others; however, we believe that the difference in pre-operative anti-fungal usage in patients receiving H2-blocker therapy is the result of attending physician preference. Because this was a non-randomized study, it is possible that the patients given anti-fungal drugs were more ill than those who were not. We attempted to account for this by comparing the two groups' Charlson/Deyo Comorbidity indices and American Society of Anesthesiologists scores, as previous work has suggested that these scores are valid for predicting outcomes in PPU [21]. Although there are several PPU-specific scores available, we were unable to calculate them because of limitations in the data available [21]. Finally, we have only a small number of patients with confirmed fungal infections, increasing the probability of Type II error.

In summary, in this retrospective, single-center study of 107 patients with operatively confirmed PPUs, there was no difference in outcomes between patients who received empiric pre-operative anti-fungal therapy and those who did not. More than half of the patients with intra-operative peritoneal cultures were infected with yeast species. There were no significant differences in outcomes between patients with and without fungal contamination or in those who received anti-fungal therapy with confirmed fungal contamination and those who did not. On the basis of these data, patients with PPUs do not require empiric anti-fungal therapy, although further study is needed to confirm this view.

Author Disclosure Statement

No competing financial interests exist.

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