Trauma Surgery & Acute Care Open

Empiric antifungals do not decrease the risk for organ space infection in patients with perforated peptic ulcer

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Received 17 December 2020
Revised 24 February 2021
Accepted 24 April 2021

To cite: Barmparas G, Alhaj Saleh A, Huang R, *et al*. *Trauma Surg Acute Care Open* 2021;**6**:e000662.

ABSTRACT

Introduction Infection control in patients with perforated peptic ulcers (PPU) commonly includes empiric antifungals (AF). We investigated the variation in the use of empiric AF and explored the association between their use and the subsequent development of organ space infection (OSI).

Methods This was a secondary analysis of a multicenter, case–control study of patients treated for PPU at nine institutions between 2011 and 2018. Microbiology and utilization of empiric AF, defined as AF administered within 24 hours from the index surgery, were recorded. Patients who received empiric AF were compared with those who did not. The primary outcome was OSI and secondary outcome was OSI with growth of *Candida* spp. A logistic regression was used to adjust for differences between the two cohorts.

Results A total of 554 patients underwent a surgical procedure for PPU and had available timing of AF administration. The median age was 57 years and 61% were male. Laparoscopy was used in 24% and omental patch was the most common procedure performed (78%). Overall, 239 (43%) received empiric AF. There was a large variation in the use of empiric AF among participating centers, ranging from 25% to 68%. The overall incidence of OSI was 14% (77/554) and was similar for patients who did or did not receive empiric AF. The adjusted OR for development of OSI for patients who received empiric AF was 1.04 (95% CI 0.64 to 1.70), adjusted p=0.86. The overall incidence of OSI with growth of *Candida* spp was 5% and was similar for both groups (adjusted OR 1.29, 95% CI 0.59 to 2.84, adjusted p=0.53).

Conclusion For patients undergoing surgery for PPU, the use of empiric AF did not yield any significant clinical advantage in preventing OSI, even those due to *Candida* spp. Use of empiric AF in this setting is unnecessary.

Study type Original article, case series.

Level of evidence III.

INTRODUCTION

The medical management of peptic ulcer disease with eradication of *Helicobacter pylori* and utilization of agents targeting gastric acid production has resulted in a substantial reduction of associated complications, including bleeding, perforation, and gastric outlet obstruction.[1] In the USA alone, between 1993 and 2006, there was an almost 40% fall in hospitalizations related to these complications.[2 3] Although bleeding is the most common, perforation remains the one that carries the highest risk for mortality, which may exceed 20%.[4] Source control and empiric antibiotics remain the mainstay of initial treatment, all in accordance with widely accepted guidelines, including those from the Surviving Sepsis Campaign.[5]

Adhering to evidence-based practices for the selection and duration of antimicrobial therapy is increasingly necessary to mitigate the risk for antimicrobial resistance, toxicity, adverse outcomes, and even cost.[6] For perforated peptic ulcers (PPU) in particular, the high prevalence of fungal isolates in the peritoneal cultures and previously reported associated worse outcomes when they are present,[7] prompt many clinicians to use empiric antifungal (AF) therapy in these patients to decrease the risk for surgical site infections and even mortality.[8] Interestingly, this practice does not appear to decrease the risk for perioperative complications and death.[8] The alarming emergence of resistance to AF requires stewardship and scrutiny of practices that may exacerbate this problem.[9 10]

Using data from a multicenter collaborative study, we sought to characterize the current practices related to the use of empiric AF in patients with PPU and examine their impact on perioperative morbidity. We hypothesized that due to the lack of adequate evidence, a large variation exists in the utilization of empiric AF for these patients. In addition, we hypothesized that despite the high prevalence of fungal isolates in the peritoneal cultures, the use of empiric AF would not be associated with decreased perioperative organ space infections (OSI).

METHODS

This was a secondary analysis of a Southwestern Surgical Congress Multi-Center Trials Group retrospective study evaluating surgical practices for patients with PPU. After local Institutional Review Board approvals, patients with PPU (International Classification of Diseases, Ninth Revision

530.1x) admitted from January 2011 to June 2018 to one of the following nine institutions were included: (1) Texas Tech University Health Sciences Center, Lubbock, Texas; (2) Cedars-Sinai Medical Center, Los Angeles, California; (3) University of Maryland Medical System, Baltimore, Maryland; (4) Oklahoma University Health Sciences Center, Oklahoma City, Oklahoma; (5) University of Texas Health Sciences, San Antonio, Texas; (6) University of Colorado Health Memorial Hospital Center, Colorado Springs, Colorado; (7) Baylor Scott and White Health, Temple, Texas; (8) Denver Health and Hospital Authority, Denver, Colorado; (9) Baylor College of Medicine, Ben Taub, Texas. Demographics and clinical data were collected using a standardized data collection sheet as previously described.[11]

For this study, additional data points were reviewed, including use of AF therapy (fluconazole, micafungin or other) with the time interval from the index surgery to the first dose, blood cultures obtained in the perioperative period (preoperative and up to 48 hours postoperatively), intraperitoneal (IP) cultures obtained at the index surgery with microbiology results, and development of OSI, defined as an event occurring within 30 days after the operative procedure (where day 1=the procedure date) and involving any part of the abdomen deeper than the fascial/muscle layers that was opened or manipulated during the operative procedure and the patient had at least one of the following: (A) purulent drainage from a drain that is placed into the abdomen; (B) organism(s) identified from fluid or tissue in the abdomen by a culture or non-culture-based microbiological testing method which was performed for purposes of clinical diagnosis or treatment; (C) an abscess or other evidence of infection involving the abdomen that was detected on gross anatomic or histopathological examination, or imaging test evidence suggestive of infection.[12]

Statistical analysis

Empiric AF administration was defined as an AF administered within 24 hours from the index surgery. Empiric AF utilization and availability of IP cultures from the index surgery were initially plotted based on participating center. A random number from 1 to 9 was assigned to participating centers for the purpose of the analysis.

Patients who received empiric AF were compared with those who did not receive any AF or received AF in a delayed fashion (beyond 24 hours after the index surgery). The two cohorts were compared using standard statistical tools including t-test or Mann-Whitney test for normally and abnormally distributed means, respectively and, accordingly, χ^2 or Fisher's exact test for proportions. The primary outcome was OSI and the secondary outcome was OSI with microbiology including *Candida* spp. To adjust for differences between the two cohorts, variables that were different at a $p<0.05$ were entered into a logistic regression model to calculate the adjusted OR and 95% CI. All analyses were performed using SPSS V.25.0 (IBM).

RESULTS

A total of 622 patients met inclusion criteria from the nine participating centers. Overall, 59.8% were male, with a mean±SD age of 57.0±17.5 years and a Charlson Comorbidity Index (CCI) score of 4.1±3.7. Non-operative management was employed in 5.9% (37/622). For those who underwent surgery, the majority had an open procedure (67.0% or 417/585), whereas the remaining underwent a laparoscopy (27.0% or 168/585) with 16.7% (28/168) subsequently converted to open procedure.

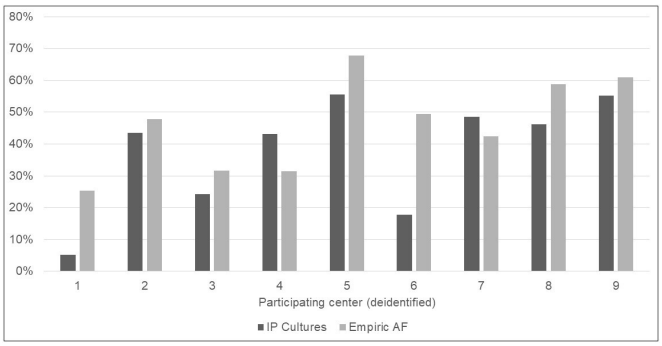

Figure 1 Proportion of patients receiving empiric antifungals (AF) and having intraperitoneal (IP) cultures obtained at the index surgery for perforated peptic ulcer.

The timing of the first AF dose was not available for 31 patients (9.1%). After excluding patients who underwent non-operative management (n=37) and patients with unavailable timing of first AF dose, 554 patients were left for analysis. Of those, 239 (43.1%) received empiric AF and 72 (13.0%) received AF in a delayed fashion. Patients who received empiric AF (n=239) had a median duration of AF therapy of 5 days (mean±SD: 7.4±8.7; IQR: 4). The duration of therapy was similar for those with IP cultures at the index surgery that were negative for *Candida* spp (n=51; median duration: 5 days; mean±SD: 6.8±5.6; IQR: 3). Figure 1 depicts the variation in the use of empiric AF among participating centers, ranging from 25.3% to 67.7%. IP cultures were obtained from 191 patients (32.6%) at the index surgery. There was a large variation between centers in obtaining these cultures (range 5.2%–55.6%).

Patients who received empiric AF (n=239) were compared with patients who did not (n=315). There was no difference regarding age, sex or CCI between the two cohorts (table 1). Patients who received empiric AF were significantly more likely to present with pneumoperitoneum on imaging (97.1% vs. 93.3%, p=0.048). The use of laparoscopy in both cohorts was similar, as was the type of surgical procedure performed. Patients receiving empiric AF tended to have a surgical drain placed at the index surgery more often; however, this difference was not statistically significant (56.5% vs. 48.4%, p=0.060). Only 164 patients (29.6%) had blood cultures obtained at admission. There was no difference in the presence of positive blood cultures with growth of *Candida* spp between the two cohorts. IP cultures from the index surgery were significantly more likely to be available for patients who received empiric AF (39.7% vs. 26.0%, p=0.001); however, there was no difference in the presence of *Candida* spp in these cultures between the two cohorts (table 1).

Table 2 outlines the microbiology of the 177 available IP cultures obtained at the index surgery for the two groups. *Candida* spp were the most common isolates, followed by polymicrobial cultures. Overall, 29.4% of these cultures had no growth.

The overall incidence of OSI was 13.9% (77/554): 14.2% for those who received empiric AF and 13.7% for those who did not. The microbiology from available OSI cultures (n=59 out of 77) is included in table 3. After adjusting for the presence of pneumoperitoneum, which was the only statistically significant difference between the two groups, the adjusted OR for development of OSI for patients who received empiric AF was 1.04 (95% CI 0.64 to 1.70), adjusted p=0.864 (Hosmer-Lemeshow goodness of fit test p=0.757 and area under the curve (AUC) for

Table 1 Comparison of patients according to whether they received empiric antifungal (AF) therapy or not

	Total (n=554)	Empiric AF (n=239)	No empiric AF (n=315)	P value
Age (year), mean±SD (median)	56.7±17.8 (57.0)	56.8±18.4 (58.0)	56.6±17.3 (57.0)	0.909
Male	60.5% (335/554)	59.8% (143/239)	61.0% (192/315)	0.789
CCI, mean±SD (median)	4.0±3.7 (3.0)	4.1±3.5 (3.0)	4.0±3.9 (3.0)	0.744
Previous PUD	23.7% (131/553)	25.1% (60/239)	22.6% (71/314)	0.495
Steroid use	9.4% (52/553)	11.7% (28/239)	7.6% (24/314)	0.104
PPI use	18.1% (100/553)	20.9% (50/239)	15.9% (50/314)	0.130
Pneumoperitoneum	94.9% (525/553)	97.1% (231/238)	93.3% (294/315)	0.048
Fever >38 C	4.4% (24/546)	5.5% (13/237)	3.6% (11/309)	0.277
Laparoscopic approach	23.5% (130/554)	23.4% (56/239)	23.5% (74/315)	0.751
Surgery type				
Omental patch	78.3% (434/554)	79.5% (190/239)	77.5% (244/315)	0.843
Gastrectomy	4.5% (25/554)	4.2% (10/239)	4.8% (15/315)	
Other	17.1% (95/554)	16.3% (39/239)	17.8% (56/315)	
Surgical drain at index surgery	51.9% (287/553)	56.5% (135/239)	48.4% (152/314)	0.060
Blood cultures at admission (+) for *Candida* spp	7.9% (13/164)	6.8% (6/88)	9.2% (7/76)	0.572
IP cultures obtained at index surgery	31.9% (177/554)	39.7% (95/239)	26.0% (82/315)	0.001
IP cultures (+) for *Candida* spp	42.9% (76/177)	46.3% (44/95)	39.0% (32/82)	0.328

P values were obtained from t-test or Mann-Whitney test for continuous variables, and from χ^2 or Fisher's exact test for dichotomous variables.
CCI, Charlson Comorbidity Index; IP, intraperitoneal; PPI, proton pump inhibitor; PUD, peptic ulcer disease.

regression: 0.954). The overall incidence of OSI with growth of *Candida* spp was 4.7% and was similar in both groups (5.4% vs. 4.1%). After adjusting for the presence of pneumoperitoneum on imaging, patients who received empiric AF had similar odds for developing OSI with growth of *Candida* spp (adjusted OR 1.29, 95% CI 0.59 to 2.84, adjusted p=0.528; AUC for regression: 0.969). Only 29 patients had IP cultures obtained at the index surgery and had available microbiology from a subsequent OSI. Due to this low sample size and associated selection bias, further correlation between IP cultures obtained at the index surgery with subsequent microbiology of OSI was not pursued.

DISCUSSION

In this large multicenter study evaluating the role of empiric AF in patients with PPU, we found that over 4 out of 10 patients receive these agents in the perioperative period. There was a large variation in the utilization of empiric AF among patients and institutions. Fungal isolates are commonly found in IP cultures obtained at the index surgery. The use of empiric AF, however, was not associated with a decreased risk for postoperative OSI, even when *Candida* spp were present. These findings support the limited use of empiric AF agents for patients with PPU, independent of the presence of fungal species in the IP cultures.

The advantage of empiric AF for patients with PPU is debated and the lack of specific guidelines amplifies the variation among surgeons and clinicians who use these agents. The World Society of Emergency Surgery and the Surgical Infection Society both recommend the use of empiric AF in high-risk patients with intra-abdominal infections requiring surgery; however, these recommendations were based on weak evidence and were not specific to patients with PPU.[13 14] Most recently, the Surgical Infection Society recommended against the routine use of empiric AF in these patients given the lack of evidence in support of this practice.[15] These often conflicting recommendations may lead to a large variability in related practices. This was indeed observed with our analysis, where the use of empiric AF varied widely between participating institutions. Overall, over 40% of these patients received empiric AF therapy, with some institutions reporting a proportion as low as 25%, and others as high as 67%. Another interesting finding was that patients who received empiric AF were significantly more likely to have IP cultures obtained at the index surgery. It is possible that selection

Table 2 Microbiology data for patients with available intraperitoneal (IP) cultures from the index surgery (n=177 out of 554), according to whether they received empiric antifungals (AF) or not

	Total (n=177)	Empiric AF (n=95)	No empiric AF (n=82)	P value
No growth	29.4% (52/177)	30.5% (29/95)	28.0% (23/82)	
Candida spp	42.9% (76/177)	46.3% (44/95)	39.0% (32/82)	0.854
In isolation	32.8% (58/177)	33.7% (32/95)	31.7% (26/82)	
Escherichia coli	1.1% (2/177)	0.0% (0/95)	2.4% (2/82)	
Enterobacter/Klebsiella	6.2% (11/177)	5.3% (5/95)	7.3% (6/82)	
Pseudomonas	0.6% (1/177)	1.1% (1/92)	0.0% (0/82)	
Streptococci	7.3% (13/177)	7.4% (7/95)	7.3% (6/82)	
Enterococci	2.3% (4/177)	2.1% (2/95)	2.4% (2/82)	
Staphylococci	2.8% (5/177)	2.1% (2/95)	3.7% (3/82)	
Polymicrobial	17.5% (31/177)	17.9% (17/95)	17.1% (14/82)	
Included *Candida* spp	10.2% (18/177)	12.6% (12/95)	7.3% (6/82)	

Table 3 Microbiology data for patients with available cultures from organ space infections (OSI) (n=59 out of 77), according to whether they received empiric antifungals (AF) or not

	Total (n=59)	Empiric AF (n=27)	No empiric AF (n=32)	P value
No growth	27.1% (16/59)	25.9% (7/27)	28.1% (9/32)	
Candida spp	44.1% (26/59)	48.1% (13/27)	40.6% (13/32)	0.532
In isolation	32.2% (19/59)	44.4% (12/27)	21.9% (7/32)	
Enterobacter/Klebsiella	10.2% (6/59)	7.4% (2/27)	12.5% (4/32)	
Pseudomonas	1.7% (1/59)	3.7% (1/27)	0.0% (0/32)	
Streptococci	5.1% (3/59)	3.7% (1/27)	6.3% (2/32)	
Stenotrophomonas	1.7% (1/59)	3.7% (1/27)	0.0% (0/32)	
Polymicrobial	18.6% (11/59)	11.1% (3/27)	25.0% (8/32)	
Included *Candida* spp	11.9% (7/59)	3.7% (1/27)	18.9% (6/32)	

P values were obtained from a χ^2 test.

bias may have occurred as surgeons may have been more prone to obtaining these cultures in patients with a presumed higher degree of contamination or peritonitis and this could have potentially led to a higher utilization of empiric AF.

A large proportion of patients had fungal isolates in the IP cultures obtained at the index surgery. Over 40% of these cultures were positive for *Candida* spp and in most, they were found in isolation. This finding is in line with previous reports that have found similar proportions of patients having these isolates in the IP cultures.[7 8 16] Differentiating between colonization and an active infection may be exceedingly difficult based only on cultures of non-sterile sites. *Candida* spp may be part of the normal flora in the stomach and duodenum as it is one of the few organisms that can survive the acidic gastric environment.[17] Therefore, culture of *Candida* spp in patients with PPU may not be surprising given the direct communication between the gastrointestinal tract and the peritoneum. However, that does not necessarily translate into *Candida* peritonitis which appears to be a separate entity.[18–20] Although a large proportion (over 55%) of cultures from OSI grew *Candida* spp, there was no difference in this proportion between patients who received empiric AF and those who did not. However, further analysis or explanation of this finding would be prone to misinterpretation, given the exceedingly small sample size with available cultures and the presumed selection and other bias.

The presence of *Candida* spp in IP cultures of patients with PPU has been associated with a higher mortality risk.[7 21 22] The reported mortality exceeds 30% in some series.[22] Interestingly, treatment with empiric or directed AF does not appear to impact this mortality risk.[8 23] In a critical review of the available literature evaluating the role of empiric AF for patients with PPU, Huston *et al* found that there was no clinical advantage of using these agents as their use has not been shown to improve outcomes.[15] We found that the use of empiric AF was not associated with decreased odds for OSI. The high mortality associated with the presence of *Candida* spp in patients with PPU may be related to selection bias in several of these studies, as the denominator was not reported. Rather, only patients with available cultures were analyzed. We found that less than a third of our total study population (30.7%) had IP cultures obtained, further supporting the potential selection bias in other studies reporting high mortality risk for patients with *Candida* spp peritonitis. In addition, a wide range of patients were included in these studies, such as patients with perforated cancer. Our study cohort comprised only of patients with PPU that occurred out of the hospital, explaining the substantially lower mortality that we observed (5.1%), whereas for those who had IP cultures available, it was slightly higher (6.7%). Patients with *Candida* spp had a mortality of 4.9%. These findings are more in line with large studies reporting a mortality rate of 11% or lower for patients with PPU requiring surgical intervention.[2 24]

This study is limited by its retrospective nature and the non-standardized approach to the management of these patients among participating centers. This was a secondary analysis of previously collected data and several variables that may have been important in identifying patients who could potentially benefit from empiric AF may have not been accounted for. These may include circulatory shock, degree of IP contamination, *H. pylori* status, and the differentiation between a gastric and duodenal ulcer. Mortality was not analyzed due to the relatively low number of patients with this outcome. Further exploration of subgroups of patients who could potentially benefit from empiric AF therapy, such as those on home PPI and/or steroids with IP cultures positive for *Candida* spp, was not feasible due to selection bias related to availability of IP cultures from the index surgery, and microbiology from OSI. Lastly, it should be noted that patients who received AF in a delayed fashion were summed in the group of patients who received no AF. Nonetheless, even when a separate analysis was conducted excluding patients who received AF in a delayed fashion, the findings of no difference in the odds for OSI between those who received empiric AF and those who did not were not altered (results available on request).

In conclusion, the use of empiric AF for patients with PPU varies significantly among surgeons and institutions indicating a lack of consensus and highlighting the gap in knowledge regarding the appropriate utilization of these agents. In this study, the use of empiric AF did not appear to yield any significant clinical advantage in preventing OSI, even those due to *Candida* spp. Routine use of empiric AF in this setting should be discouraged. Further studies are required to identify subgroups of patients who may benefit from the use of empiric AF.

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Contributors Study design: GB, AAS, DRM, SD. Data acquisition: GB, AAS, RH, BCE, AR, CEC, EM, JLR, EMC, JM. Analysis and interpretation: GB, BRB, CB, EPS, TJS, RF, EMC, MB, JW, DRM, SD. Article drafting and critical revision: GB, AAS, BCE, BRB, AR, CB, CEC, EPS, TJS, EM, JLR, RF, EMC, MB, JM, JW, DRM, SD.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval This was a secondary analysis of a multicenter study. Institutional Review Board approval was granted from Cedars-Sinai Medical Center (CSMC IRB). IRB approval number: Pro00053298. Date: May 14, 2018. All participating institutions had local IRB approvals. All institutional IRBs granted a waiver of informed consent due to the retrospective nature of the study and the minimal risk involved for participants.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Additional data from this study population are available to the participating centers in this multi-institutional trial.

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