

Implications of Bacteriological Study in Perforated Peptic Ulcer Peritonitis

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ABSTRACT

Background: In the setting of perforated peptic ulcer (PPU) peritonitis, empiric antimicrobial therapy is initiated perioperatively and adapted according to the culture sensitivity. The aim of the study is to describe the microbiota found in the peritonitis due to a PPU, and to evaluate the predictors for bacterial or fungal infection.

Material and methods: We performed a single-centre, retrospective observational study of all consecutive patients who presented with PPU peritonitis and underwent emergent surgery in Saint Pierre University Hospital, Brussels, Belgium, between January 2013 and December 2020. The medical history, parameters at admission, bacterial culture, antibiotic resistance and postoperative outcomes were analysed.

Results: A total of 43 patients were included in the study. The microbiological culture rate was positive in 31% (13/43) patients. The bacterial culture revealed that the most frequently isolated bacteria were *Klebsiella spp.* and *Enterobacter* in 7% (3/43) of the patients, while the most prevalent fungus isolation was *Candida spp.* in 16.7% (7/43) patients. The most prevalent resistances were against ampicillin (17.1% [7/43]). The Charlson Comorbidity Index was an independent predictor for bacterial infection.

Conclusion: *Candida spp.*, *Klebsiella spp.* and *Enterobacter* were the most common organisms isolated in the setting of PPU peritonitis.

Key words: perforated ulcer, bacterial flora, antibiotics

BACKGROUND

Peptic-ulcer disease (PUD) affects 4 million people around the world. One of its leading factors is *Helicobacter pylori* infection (1). About 50% of the global population presents *H. pylori* in the gastric mucosa but PUD is present in only 10–20% of people, a prevalence that increases in up to 90% in perforated peptic ulcers (PPU). Other factors include non-steroidal anti-inflammatory drug use, smoking or alcohol (2). Perforations are present in 5% and 20% of complicated ulcers (3). The occurrence of PPU is rare, but remains a life threatening disease. The lifetime prevalence of perforation in patients with PUD is about 5%. In the last decade, more than half of the patients with PPU were older than 70 years and predominantly female (3). The mortality rates vary from 10–40% (4).

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Thirty day mortality rates were reported to be around 20 %, and up to 30% in 90 days (5). The PPU morbidity and mortality can be related to complications like leaks, wound infection, fistula, shock and multiorgan failure (6).

Empiric antimicrobial therapy is initiated perioperatively and adapted, if necessarily, accordingly with peritoneal fluid culture sensitivity. This may reduce the incidence of postoperative complications, morbidity, and mortality (7). In the literature, *Escherichia coli* was the commonest organism isolated from peritonitis due to PPU, and the best bacterial sensibility reported was to piperacillin/tazobactam and cefotaxime (8).

The aim of the study is to describe the microbiota found in the peritonitis due to a PPU. The secondary outcome was to evaluate the predictors for bacterial or fungal infection.

MATERIAL AND METHODS

Study design

We performed a single-centre, retrospective observational study of all consecutive patients who presented with peptic-ulcer perforation peritonitis and underwent emergent surgery in Saint Pierre University Hospital, Brussels, Belgium, between January 2013 and December 2020.

The inclusion criteria for the 43 patients analysed were: patients over 18 years old, who underwent surgery related to PPU in an emergency setting with the presence of peritonitis, localisation of the perforation on the stomach or duodenum, and enough quantity of intraabdominal free fluid to allow a bacteriological analysis.

The exclusion criteria were: the presence of peritonitis from a different origin, conservative treatment of PPU, the absence of free fluid, the absence of a bacteriological sample or the absence of bacteriological analysis.

The study was approved by the Ethics Committee of our institution.

Intervention

All patients with the diagnosis of PPU peritonitis underwent either an open or laparoscopic emergent surgery for the suture of the perforation. Omentoplasty and drainage placement were performed at surgeons' discretion. The intraabdominal free fluid was collected in sterile conditions and sent for bacteriological analysis. Postoperative broad-spectrum antibiotics

were prescript postoperatively. The antibiotic treatment was adapted accordingly to the results and sensitivity of the bacterial culture, usually available after 48 hours of treatment. Patients were discharged in the absence of relevant postoperative complications.

Variables

Baseline characteristics collected were: age, sex, nationality, patients' personal history of hypertension, dyslipidaemia, gastritis or PUD, the Charlson Comorbidity Index (which predicts the ten-year mortality for a patient according to their comorbid conditions), and personal history of abdominal surgery or other surgeries. At admission, the physical examination signs analysed were: heart rate (HR), mean arterial pressure (MAP), and temperature; and the C-reactive protein and the white cell blood count from the blood tests. The intraoperative variables collected were the localization of the ulcer, the surgical intervention and the drainage placed.

The bacteriological sample was analysed was to identify the presence of bacteria or fungus, and its resistance to antibiotics. We also evaluated the antibiotic treatment prescribed, in the first, second and third line.

Postoperative variables were the hospital stay, blood tests at 48 and 96 hours after surgery, overall morbidity, its severity according to the Clavien Dindo classification, and the need of re intervention and the specific complications. We also evaluated the gastroscopy findings after discharge.

Statistical analysis

Categorical variables were described with numbers and percentages. Quantitative variables were described with mean and standard deviation if they followed a normal distribution and with median and interquartile range (IQR) if they followed a non-normal distribution. The Shapiro–Wilk test was used as normality test.

To explore the predictors for bacterial or fungal infection, all variables were tested in univariate logistic regression. Statistically significant variables in univariate analysis were then included in a multi-variable logistic regression model, erasing non-significant outcomes until all variables were adjusted to each other in the final model. A p-value < 0.05 in a two tailed statistical analysis was considered statistically significant. Statistical analysis was performed with the statistical software SPSS 23.0 for Windows (IBM SPSS Inc., Chicago, IL).

RESULTS

A total of 43 patients were operated for PPU perforation associated with peritonitis by laparotomy or laparoscopy in the marked period and fulfilled the inclusion criteria.

The median age of the study sample was 46 years (IQR: 32 – 60). There was a male predominance, with 83.7 % (36/43) male and 16.3% (7/43) female patients. The patient's personal medical history revealed that 9.3 % (4/43) patients had a documented history of gastritis or previous peptic ulcer, and 18.6 % (8/43) demonstrated history of previous abdominal surgeries. The median score on Charlson Comorbidity Index was 1 (IQR: 0 – 2). (table 1)

Preoperative assessment

The physical examination at admission revealed that in the median heart rate was 80 bpm (IQR: 69 – 100) with tachycardia (>100 bpm) in 25.6% (11/43) of the patients. The mean arterial pressure was 95.2 mmHg (SD: 17.6) with hypotension (< 65 mmHg) in 5.4% (2/43) of the patients. The blood test at the admission was performed, and the inflammatory syndrome was evaluated. The medium value of the C-reactive protein was 14.8 g/dL (IQR: 3 – 68.6). The median white cell blood count at admission was 12 600/mm³ (IQR: 10 500 – 15 730/mm³).

Surgical treatment

The localisation of the perforation was recorded intraoperatively and was predominantly gastric localisation in 54.8 % (23/43) patients, while 45.2 % (19/43) patients presented a duodenal perforation. The surgeries performed consisted on a suture of the perforation for all the patients in the study with omentoplasty in only 16.3 % (7/43) patients. An abdominal drainage was placed in subhepatic area and next to the suture in 60.5 % (26/43) patients, in the pelvis and peri-splenic area for 14 % (6/43) patients, and in other localisations in 36.2 % (14/43) patients.

Bacterial culture

The microbiological culture rate was positive in 31% (13/43) patients. The isolation revealed the presence of bacteria in 20.9 % (9/43) patients and fungal infection in 16.7 % (7/43). The bacterial culture revealed that the most frequently isolated bacteria was *Klebsiella spp.* and *Enterobacter* in 7 % (3/43) of the patients, followed

Table 1 - Baseline characteristics and surgical procedure

	n : 43
	n (%)
	Median (IQR)
Age (years)	46 (32 – 60)
Sex	
Female	7 (16.3)
Male	36 (83.7)
Nationality	
European, Belgian	12 (27.9)
European, other Western European	8 (18.6)
European, Eastern European	9 (20.9)
North African	5 (11.6)
Other African	5 (11.6)
Asian	4 (9.3)
Patients' Personal History	
Hypertension	4 (9.3)
Dyslipidemia	3 (7)
Gastritis/Previous peptic ulcer	4 (9.3)
Personal history of abdominal surgery	8 (18.6)
Personal history of other surgeries	5 (11.6)
Charlson Comorbidity Index	1 (0 - 2)
Physical examination at admission	
FC (bpm)	80 (69 - 100)
Tachycardia (> 100 bpm)	11 (25.6)
MAP*+ (mmHg)	95.2 (17.6)
Hypotension (MAP < 65 mmHg)	2 (5.4)
Temperature+ (°C)	1 (0.4)
Blood tests at admission	
C-reactive protein	14.8 (3 - 68.6)
White cell blood count	12 600 (10 500 - 15 730)
Localization of the ulcer	
Gastric	23 (54.8)
Duodenal	19 (45.2)
Intervention	
Suture	43 (100)
Omentoplasty	7 (16.3)
Drainage	
Subhepatic	26 (60.5)
Perisplenic	6 (14)
Pelvic	6 (14)
Other localization	14 (36.2)

by *Haemophilus spp.* and *Streptococcus spp.* in 4.7% (2/43) of the patients. The most prevalent fungus isolation was *Candida spp.*, which was positive in 16.7 % (7/43) patients (table 2).

The *Enterobacter* infection was linked to an older age and more comorbid patients, whereas the *Candida spp.* cultures were associated with younger patients without significant comorbidities (table 3).

Antibiotic/Antifungal treatment

There was a 17.5 % (7/43) rate of resistance to antibiotics. The most prevalent resistances were against ampicillin (17.1 % [7/43]), amoxicillin/clavulanic acid (9.5 % [4/43]), cefuroxime and trimethoprim/sulfamethoxazole (4.8% each [2/43]). Other resistances

Table 2 - Bacterial isolation, antibiotic resistance and antibiotic treatment

	n : 43
	n (%)
Cultures	
Negative	29 (69)
Positive	13 (31)
Isolation	
Bacteria	9 (20.9)
Fungus	7 (16.7)
Specific isolation	
<i>E. coli</i>	1 (2.3)
<i>Klebsiella spp.</i>	3 (7)
<i>Citrobacter spp.</i>	0
<i>Enterobacter</i>	3 (7)
<i>Morganella morganii</i>	1 (2.3)
<i>Haemophilus spp.</i>	2 (4.7)
<i>Streptococcus spp.</i>	2 (4.7)
Other	1 (2.3)
Candida	7 (16.7)
Other fungal infections	4 (9.3)
Antibiotic resistance	
Against any antibiotic	7 (17.5)
Ampicillin	7 (17.1)
Amoxicillin/clavulanic acid	4 (9.5)
Cefuroxime	2 (4.8)
Cefotaxime	1 (2.4)
Ciprofloxacin	1 (2.4)
Levofloxacin	1 (2.4)
Tigecycline	1 (2.4)
Trimethoprim/sulfamethoxazole	2 (4.8)
1st line antibiotic treatment	
None	2 (4.7)
Amoxicillin/clavulanic acid	39 (92.9)
Piperacillin/tazobactam	1 (2.4)
Resistance 1st line antibiotic treatment	
	3 (7)
2nd line antibiotic treatment	
None	41 (95.2)
Piperacillin/tazobactam	1 (2.4)
Levofloxacin - Ornidazole	1 (2.4)
3rd line antibiotic treatment	
None	42 (97.6)
Levofloxacin - Ornidazole	1 (2.4)

were to cefotaxime, ciprofloxacin, levofloxacin and tigecycline.

Most patients received amoxicillin/clavulanic acid as a first line of treatment (92.9% [39/43]). There was a 7 % (3/43) rate of resistance against the first line of antibiotic treatment. The second line of antibiotics administered were piperacillin/tazobactam and ciprofloxacin ornidazole (2.4% each [1/43]).

Postoperative outcomes

The median hospital stay was 5 days (IQR: 5 - 7 days). Overall morbidity was 11.6 % (5/43), while 30-day complications according to Clavien Dindo classification revealed a 4.7 % (2/43) grade II complications, 4.7 % (2/43) grade III complications, and one (2.3%) grade V complication, due to irreversible septic shock. Two patients (4.7 %) needed reoperation due to surgical site infection.

A systematic blood test was performed at the second and fourth postoperative days to follow the dynamics of the inflammatory syndrome. The C-reactive protein at 48 h postoperative presented a median value of 179 mg/dl (IQR: 94.3 - 273.3) and the white cell blood count recorded a median value of 10 200/mm³ (IQR: 7 690 - 11 920). At 96h the tendency to normalisation was more relevant for the white cell blood with a median value of 7 940/mm³ (IQR: 5 245 - 14 470). The C-reactive protein presented also a decreased value of 99.5 mg/dl (IQR: 39.5 - 175.2).

A postoperative control gastroscopy was prescribed in 6-8 weeks but only 23 (53.5%) patients underwent

Table 3 - Description of patients' characteristics according to the pathogens found in positive cultures

Pathogen	Sex	Age	Mean age	Nationality	Comorbidities	Charlson CI	Mean Charlson CI
<i>Klebsiella spp.</i>	Female	71	58.3	European, Belgian	Stroke	4	3
	Female	42		European, other Western European	None	2	
	Male	62		North African	None	3	
<i>Enterobacter</i>	Female	90	71.3	European, Belgian	Diabetes, Hypertension, hypercholesterolemia	5	4.6
	Male	62		European, Belgian	Hypertension, Peripheral artery disease	6	
	Male	62		North African	None	3	
<i>Haemophilus spp.</i>	Male	67	64.5	European, Eastern European	Hypertension	2	2
	Male	60		Asian	None	2	
<i>Streptococcus spp.</i>	Female	71	54	European, Belgian	Stroke	4	2
	Male	37		European, Eastern European	None	0	
<i>Candida spp.</i>	Male	67	48.6	European, Eastern European	Hypertension	2	1.1
	Female	42		European, other Western European	Localized oncologic disease	2	
	Male	46		European, other Western European	None	0	
	Male	58		European, other Western European	Hypercholesterolemia	1	
	Male	26		Asian	None	0	
	Male	39		North African	None	0	
	Male	62		North African	None	3	

Table 4 - Postoperative outcomes

	n : 43
	n (%)
	Median (IQR)
Morbidity	5 (11.6)
30-day complications according to Clavien-Dindo classification	
Grade I	0
Grade II	2 (4.7)
Grade III	2 (4.7)
Grade IV	0
Grade V	1 (2.3)
Reintervention	2 (4.7)
Specific complications	
Surgical site infection	2 (4.7)
Septic shock	1 (2.3)
Other medical complications	3 (7)
Blood tests at 48 hours	
C-reactive protein	179 (94.3 - 273.3)
White cell blood count	10 200 (7 690 - 11 920)
Blood tests at 96 hours	
C-reactive protein	99.5 (39.5 - 175.2)
White cell blood count	7 940 (5 245 - 14 470)
Hospital stay (days)	5 (5 - 7)
Follow-up gastroscopy	23 (53.5)
Gastroscopy findings	
Chronic gastritis	20 (46.5)
Helicobacter pylori infection	4 (9.3)
Cancer	1 (4.3)

the exam. The findings were chronic gastritis (46.5% [20/43]), *H. pylori* infection after the biopsy analysis (9.3% [4/43]) one case of cancer (4.3%) (table 4).

Predictors of bacterial and fungal infection

All variables were evaluated in univariate analysis as predictors for bacterial or fungal infection, and variables with statistical significance were evaluated in a multivariate analysis. In univariate analysis, the predictors for bacterial infection were: age, personal history of hypertension, the Charlson Comorbidity Index, and the mean arterial pressure at admission. In multivariate analysis only Charlson Comorbidity Index

was an independent predictor for bacterial infection. These results are shown in table 5. No factors could be identified as predictors of fungal infection.

DISCUSSION

The incidence of PUD is about 0.1%-0.3% per year with a prevalence that was about 5.7% in 1998, which has been progressively declining (9). PPU in some studies account for more than 70% of deaths associated with PUD. The incidence of duodenal perforation (DP) is 7–10 cases/100,000 adults per year (10). Factors associated with an adverse outcome in patients with complicated PPU include comorbid disease, poor general and medical status, sign of shock and sepsis (hypotensive shock, metabolic acidosis, acute renal failure, hypoalbuminemia), and delayed treatment (11). Independent risk factors accounted for postoperative morbidity and mortality are elevated levels of serum creatinine and advanced age. Adequate resuscitation, sepsis control, addressing comorbidities and early access to hospital can minimize the risk of morbidity and mortality in patients with PPU (12).

Surgical intervention is the most widespread attitude practiced in cases of PPU. The postoperative outcome after surgical repair is influenced by delayed presentation, presence of pus in the peritoneal cavity, sepsis and shock (13). The choice of the surgical approach (laparoscopy versus laparotomy) has an impact on the immune response in PPU. Schietroma et al., in a study on 119 patients with PPU, showed that 1 hour after the intervention, bacteraemia and the levels of endotoxin was significantly higher for the patients who undergo surgery by laparotomy. More, the laparotomy caused a significant increase in immune neutrophil concentration, neutrophil-elastase, IL-1 and IL-6, CRP and decrease of HLA-DR (14). A conservative, non-operative attitude has equally been described. Asanasak et al., in a 9-year retrospective study on 38 patients with PPU who received non-operative

Table 5 - Univariate and multivariate analysis of predictors for bacterial infection

Univariate analysis	Odds ratio	95 % Confidence Interval	p-value
Age	1.084	1.025 - 1.145	0.005
Patients' Personal History			
Hypertension	16.500	1.460 - 186.409	0.023
Charlson Comorbidity Index	1.997	1.221 - 3.267	0.006
Physical examination at admission			
MAP (mmHg)	0.945	0.894 - 0.999	0.045
Multivariate analysis	Odds ratio	95 % Confidence Interval	p-value
Charlson Comorbidity Index	1.997	1.221 - 3.267	0.006

treatment, concluded that for proper selected patients this attitude can be successful, with shorter hospital stay and decrease the number of patients that require an operation (15). Whatever the attitude, the broad-spectrum antibiotics administration is essential for the treatment.

Bacteriology in PPU

The mortality rate in patients in case of intra-abdominal sepsis can be as high as 18.55 % when gram-positive cocci are present. Along the years, due to the improved care of peritonitis, the mortality decreased from 90 % in 1900 to 15–25 % nowadays. The actual challenge is the increased microbial resistance and the administration of an appropriate empiric antibiotic treatment (16). In case of anaerobic intra-abdominal contamination, there is a significant increase in septicaemia without a significant increase in mortality. Gowda et al., in a study on 275 consecutive patients with PPU, found that the factors that increase the risk of anaerobic infection were: age over 50 years, patients' comorbidity, peritonitis of more than 48 hours, perforation diameter > 5 mm, peritoneal fluid > 1000 ml and purulent contamination (17).

Alwahed et al., in a study on PPU on 888 patients, found that 48.6% of the studied patients had positive cultures for *Bacteroides spp.*, and that patients with increase age (> 50 years) had a higher prevalence of contamination (83.7 %) (18). The review of Brook et al. sustained that anaerobic contamination in PPU was explainable by the fact that in the gastrointestinal tract flora, the ratio of anaerobe bacteria to aerobe bacteria was of 1,000 - 10,000 to 1 (19). Quantitative analyses of intestinal microbiota of the digestive tube revealed a non-homogeneous distribution. The number of bacterial cells in 1 g chime is lesser in the stomach and duodenum (101 – 103) and increase progressively until reaching their maximum in large intestine (10¹¹-10¹²) (20). In terms of isolated species in PPU, Bhavin et al. in a study on 200 patients with PPU found that *E. coli* was the commonest organism isolated, and that the patients handled with antibiotics according to culture and sensitivity presented a reduces hospital stay and morbidity (21). Lohith et al. in a study on 50 patients with different sites of perforation on the gastrointestinal tract found that *E. coli* was the most common organism isolated in all sites of perforation and that there was an increasing resistance against third generation cephalosporins (22). Tayal et al. in a study on 43 intra-operative specimens from cases of perforated peptic ulceration, found that the bacterial culture in PPU

revealed also gram-negative bacilli morphologically resembling *H. pylori* 41.86% specimens with an *H. pylori* culture positivity of 18.60% (23).

Antibiotic treatment

Initial empiric antibiotic therapy has to be adapted to the bacterial culture results and susceptibility, and it has been suggested that the most potent antibiotics should be used in cases of peritonitis, instead of the most commonly used antibiotics (24). Empiric broad-spectrum antibiotic regimen against a mixture of Gram-negative, Gram positive and anaerobic bacteria should be administered, if possible, after the peritoneal fluid has been collected. According to WSES guidelines for perforated and bleeding peptic ulcers, in patients with PUP, a short-course (3–5 days) of antibiotic therapy is recommended (2C) (25).

There is a controversy on the empiric administration of the anti-fungal agents (AF) in PPU. In most cases, fungal infections are present for surgical patients, especially intra-abdominal abscesses. The routine use of empiric AF is not sustained by the literature (26). Barmparas et al., in a study of 554 patients with PPU, found that empiric use of AF presented no clinical advantage in preventing infections, even those due to *Candida spp.*, thus its administration was unnecessary (27). Nevertheless, Lee et al., in a study on 62 patients with PPU, found that 37.1% of patients presented positive culture to *Candida spp.* This study recommended that AF agents should be administered in all cases of fungal contamination to lower the mortality rate and shorten hospital stay (28). Shan et al., in a taiwanese study on 145 patients with PPU, observed that 43 % patients presented a positive fungal infection and *Candida spp.* was the most ordinary pathogen isolated from peritoneal fluid and wound cultures. This study recommended low-dose amphotericin B for critically ill surgical patients with intraperitoneal infection (29).

Strengths and limitations

One of the strengths of this study represents a well exhaustive description of the bacteria isolated in the peritonitis secondary to PPU. However, one of its limitations was a modest number of patients suitable for analysis, mainly due to the reduced prevalence of this clinical scenario compared to other entities such as colonic or appendicular peritonitis. Otherwise, there was a limitation during follow-up because of a reduced number of postoperative upper endoscopies, which

prevented to analyse the true incidence of *H. pylori* as the aetiology of the PUD.

CONCLUSION

Candida spp., *Klebsiella spp.* and *Enterobacter* were the most common organisms isolated in the microbiological samples of perforated peptic-ulcer peritonitis, with an overall resistance to antibiotics rate of a 17.5 %. The Charlson Comorbidity Index was an independent predictor for bacterial infection, while no factors could be identified as predictors of fungal infection.

Ethical Approval and Consent to participate

The study was approved by the Ethical Committee of Saint Pierre University Hospital.

The authors confirm that all research was performed in accordance with relevant guidelines/regulations, and the consent was obtained from all participants and/or their legal guardians.

Availability of data and materials

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

No competing interests exist for any of the authors.

Authors' contributions

Sorin Cimpean: Conceptualization, Methodology, Software. Alberto Gonzalez Barranquero: Data curation, Writing - Original draft preparation. Benjamin Cadere: Writing - Reviewing and Editing. Guy Bernard Cadere: Supervision, Validation.

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