FUNGAL PERITONITIS DUE TO GASTRODUODENAL PERFORATION: DIAGNOSTIC AND TREATMENT CHALLENGES

D. Tzoneva¹, S. Masljankov², M. Sokolov², Y. Marteva-Proevska³, T. Velinov³

¹Clinic of Anesthesiology and Intensive Care, University Hospital "Alexandrovska", Medical University – Sofia, Bulgaria

²Department of Surgery, University Hospital "Alexandrovska", Medical University – Sofia, Bulgaria

³Laboratory of Clinical Microbiology, University Hospital "Alexandrovska", Medical University – Sofia, Bulgaria

Abstract. The gastrointestinal tract perforation is one of the leading causes of acute abdomen. Mycotic infections have become a significant clinical problem over the last few decades. Despite the advance in diagnostics and treatment of patients with fungal peritonitis, the mortality remains high. **Objective.** The objective of the study was to determine the type and incidence of causative pathogens of acute peritonitis in patients with gastroduodenal perforation, and to estimate the impact of microbial flora on the disease outcome. **Materials and methods.** We performed a retrospective study among 83 adult patients with acute peritonitis due to gastroduodenal perforation treated at our centre. **Results.** A total of 40 mycotic agents were isolated in 39 of the abdominal samples. The primary mycotic isolates were *Candida albicans* (52.5%) and *C. glabrata* (64.3%); *C. krusei* (14.3%) and *C. tropicalis* (7.1%) predominated among non-*albicans* *Candida* species (35.0%). The most common bacterial agents were *Escherichia coli* (24.0%) and *Enterococcus* spp. (24.0%). 77.1% of all enrolled patients survived, and 19 of them deceased due to sepsis and multiple organ dysfunction syndrome. **Conclusion.** *Candida albicans* is the most common mycotic pathogen in patients with acute peritonitis due to gastroduodenal perforation. It is obligatory to examine the peritoneal fluid samples for bacterial and fungal pathogens with determination of their antimicrobial susceptibility profile. Timely initiation of adequate treatment and multidisciplinary approach is crucial for the outcome of patients with fungal peritonitis.

Key words: acute peritonitis, gastroduodenal perforation, mycotic infection, critically ill, treatment

Corresponding author: Dochka Tzoneva, MD, PhD, Clinic of Anesthesiology and Intensive Care, University Hospital "Alexandrovska", Medical University, 1431 Sofia, Bulgaria, tel.: +359 878730038, e-mail: dochkatobova@hotmail.com

INTRODUCTION

Mycotic infections have become a significant clinical problem for the last few decades. Intraabdominal candidiasis (IAC) is the second most common type of invasive candidiasis after

blood infection. The fungal peritonitis may result in systemic infection, multiple organ dysfunction syndrome (MODS), and lethal outcome [1-4]. Despite the progress in the diagnostics and treatment of patients with fungal peritonitis, the mortality remains high (ranging between 11% and 60%) [1-5].

The most commonly isolated pathogen in fungal peritonitis is *Candida albicans*; however, in recent years there has been a tendency that the incidence of *Candida nonalbicans* species and strains progressively increases, with greater potential of resistance to antimycotics. [3, 6-9].

The treatment of patients with fungal peritonitis involves surgical intervention with abdominal cavity drainage and control of the source of infection, rapid and precise microbiological diagnosis, and early antimycotic therapy, based on the susceptibility profile [6, 10]. Timely initiated adequate treatment is crucial for the outcome of patients with fungal peritonitis [2, 7, 11].

The aim of this study was to determine the type and incidence of causative pathogens of acute peritonitis in patients with gastroduodenal perforation, and to estimate the impact of microbial flora on the disease outcome.

MATERIALS AND METHODS

Study design

The retrospective clinical study was implemented at the Clinic of Surgery and at the Second Clinic of Anesthesia and Intensive care of University Hospital "Alexandrovska" – Sofia, Bulgaria from January 2009 to December 2017. This study was approved by the Institutional Ethics Committee. All enrolled participants signed an informed consent. Patients' information was collected from the medical records, and, before analysis, it was anonymized and deidentified.

Study parameters

Adult patients (over 18 years of age) with acute peritonitis due to stomach/duodenum perforation were enrolled in this study. All patients were urgently operated under general anesthesia for infected materials drainage and a surgical correction of the underlying pathology; thereafter they were transferred to the Intensive Care Unit (ICU) for monitoring and future treatment.

The following information was collected for all study participants: age; sex; comorbidity; organ failure on admission evaluated by APACHE II score (Acute Physiology and Chronic Health Evaluation); recent immunosuppressive therapy; previous antibiotic therapy; main laboratory tests; gastrointestinal tract (GIT) perforation site; fungal and bacterial identification; antimicrobial susceptibility of isolated pathogens; time of onset and type of antimicrobial therapy; length of stay at ICU/hospital; duration of mechanical ventilation (MV); and disease outcome. The peritonitis was diagnosed based on clinical, laboratory and macroscopic data, and the positive culture from peritoneal fluid was collected intraoperatively.

Microbiological assays

Peritoneal fluid was collected intraoperatively from all patients, under aseptic conditions, in sterile containers, directly from the abdominal cavity for microbiological assays. The samples were transported immediately to the Hospital Microbiology Laboratory, where they were tested according to the established laboratory procedures. The following test kits consisting panels of BBL Crystal (BD), miniApi (bioMérieux SA, France), or Vitek MS (bioMérieux SA, France) were used to identify the isolated bacterial pathogens according to the manufacturer's instructions. The susceptibility to antimicrobial agents was determined by the Bauer-Kirby disc-diffusion method. Sabouraud agar and broth were used for the isolation and cultivation of *Candida* spp. Species identification of isolated *Candida* spp. was done using ID 32 C (miniApi, bioMérieux SA, France) or Vitek MS (bioMérieux SA, France) according to the manufacturer's instructions. The susceptibility to antimycotic agents was determined by ATB Fungus 3 panels (miniApi, bioMérieux SA, France; it includes 5-flucytosine, Amphotericin B, Fluconazole, Itraconazole, Voriconazole) or VITEK® 2 ASTYS08 (bioMérieux SA, France; it includes Fluconazole, Voriconazole, Caspofungin, Micafungin, Amphotericin B, 5-flucytosine) according to the manufacturer's instructions. *Candida albicans* ATCC90028 and *Candida tropicalis* ATCC750 were used as control strains.

When *Candida* spp. were isolated in the intraoperatively collected peritoneal fluid, the findings were interpreted as an infection, but not as a colonization.

The primary endpoint of the study was a lethal outcome, and the secondary endpoints were parameters for a complicated postoperative period, such as MV $\geq$ 5 days, ICU stay $\geq$ 10 days.

Statistical analysis

The data were analysed by SPSS v. 19.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were used to summarize the cohort. The results were presented in numbers and percentages. The received data were collected and the results were statistically analysed using the following methods: Mann Whitney, Fisher's exact test, and Spearman, as appropriate. The results were statistically reliable at a threshold level of significance of $p < 0.05$.

RESULTS

Main demographic and clinical characteristics

The main patients' demographic and clinical characteristics are presented in Table 1 and Table 2.

Table 1. Main clinical characteristics on patient admission according to the outcome*

Characteristics	Non-survivors 19 (22.9)	Survivors 64 (77.1)	p-value
Male gender	11 (57.9)	36 (56.3)	p = 0.5567
Age, median (range), years	72.6 (42 to 88)	58.6 (25 to 85)	p = 0.0002
ASA physical status, II/III/IV	0/4/15 (0/21.1/78.9)	24/30/10 (37.5/46.9/15.6)	p < 0.0001
Comorbidity**			
CAD	6 (31.6)	7 (10.9)	p = 0.0402
Hypertension	7 (36.8)	20 (31.3)	p = 0.4227
COPD	3 (15.8)	9 (14.1)	p = 0.5528
Diabetes mellitus type 2	6 (31.6)	6 (9.4)	p = 0.0255
CKD	6 (31.6)	8 (12.5)	p = 0.0597
Recent antimicrobial therapy	11 (57.9)	17 (26.6)	p = 0.0131
Recent corticosteroid therapy	11 (57.9)	10 (15.6)	p = 0.0005
APACHE II score on admission, mean (range)	33.1 (20.0 to 39.0)	14.7 (4.0 to 31.0)	p < 0.0001

*if not stated otherwise, data are presented as number (percentage)

**25 of all patients have two or more concomitant diseases simultaneously

Abbreviation: APACHE II = Acute Physiology and Chronic Health Evaluation; ASA = American Society of Anesthesiologists; CAD = Coronary artery disease; CKD = Chronic kidney disease; COPD = Chronic obstructive pulmonary disease

Table 2. Main cause for acute peritonitis and surgical intervention data according to the outcome*

Characteristics	Non-survivors 19 (22.9)	Survivors 64 (77.1)
Source of acute peritonitis		
Stomach perforation	11 (57.9)	32 (50.0)
Duodenum perforation	8 (42.1)	32 (50.0)
Time from symptoms' onset to surgical intervention, min		
≤ 6 hours	4 (21.1)	23 (35.9)
from 6 to 24 hours	6 (31.6)	36 (56.3)
≥ 24 hours	9 (47.3)	5 (7.8)
Mean duration of surgical intervention (range), min	136.0 (95 to 185)	126.5 (100 to 178)

*if not stated otherwise, data are presented as number (percentage)

In this study were enrolled 83 adult patients (47 male and 36 female), aged from 25 to 88 years (mean age of 61.8 years) with acute peritonitis due to stomach/duodenum perforation. Almost a half of the studied patients (n = 39; 47.0%) had concomitant diseases, for which they received systemic therapy, and, at the same time, 64.1% (n = 25) of them had two and more concomitant diseases (mainly cardio-

pulmonary diseases). Most patients (n = 34; 41.0%) were in ASA (American Society of Anesthesiologists) physical status III. Out of all study participants, 33.7% (n = 28) had recently received antibiotic treatment and 25.3% (n = 21) of the studied patients had recently underwent corticosteroid therapy. The average APACHE II score was 18.9 (range: from 4.0 to 39.0). APACHE II score ≥ 18 had 42 of the patients studied.

All patients had clinical and laboratory signs of acute abdomen: fever, abdominal pain, leukocytosis with leftward shift or leukopenia (the latter occurred in 31.6% (n = 6) of nonsurvivors), elevated C-reactive protein (CRP) level, cloudy exudate in the abdominal cavity. Acute peritonitis due to stomach perforation was diagnosed in 43 (51.8%) of the patients, and such due to duodenal perforation – in 40 (48.2%) of the patients.

The age of deceased patients, as well as the mean class of ASA physical status, were significantly greater than those of patients, who survived (p = 0.0002 and p < 0.0001, respectively). The presence of CAD (coronary artery disease) and type 2 diabetes mellitus determined with statistical significance a subsequent lethal outcome in the studied population (RR = 2.5; OR = 3.8; p = 0.0402 and RR = 2.7; OR = 4.5; p = 0.0255), while such correlation was not observed for patients with hypertension, COPD (chronic obstructive pulmonary disease), and CKD (chronic kidney disease) (p > 0.05). Previous antibiotic and corticosteroid therapy determined with statistical significance the presence of *Candida* spp. in the peritoneal fluid of patients with positive samples (RR = 1.5; OR = 3.1; p = 0.0477 and RR = 1.7; OR = 6.6; p = 0.0098, respectively), as well as a subsequent lethal outcome in the patients studied (RR = 2.7; OR = 3.8; p = 0.0131 and RR = 4.1; OR = 7.4; p = 0.0005, respectively).

Microbiological assays

The microbiological characteristics of the peritoneal fluid are presented in Table 3.

Out of the 83 peritoneal fluid samples cultured, 62 (74.7%) were found to be positive for various bacteria and/or fungi, 20 (24.1%) had no growth, and one (1.2%) was contaminated. A total of 115 pathogens were isolated in all of 62 positive samples. In 56.5% (n = 35) of patients with positive abdominal samples, more than one pathogen was found. Twenty-six of the 62 (41.9%) samples showed growth of multiple microorganisms; pure growth of *Candida* was obtained in 13 (21.0%) of the samples. In 39 of the abdominal samples, a total of 40 mycotic agents were isolated (two fungal agents – *C. albicans* and *C. tropicalis* – were isolated simultaneously in one of the samples). The main mycotic isolate was *Candida albicans* (n = 21; 52.5%), and among nonalbicans *Candida* species (n = 14; 35.0%) predominated *C. glabrata* (n = 9; 64.3%), *C. krusei* (n = 2; 14.3%), and *C. tropicalis* (n = 1; 7.1%). The remaining five (12.5%) *Candida* isolates were not specified. (Figure 1 and Table 3). The isolated strains were sus-

ceptible to Amphotericin B and Voriconazole, and 27.5% of the isolated mycotic pathogens were Fluconazole-resistant (*C. albicans* – 0/21, *C. glabrata* – 9/9, *C. krusei* – 2/2). The most common bacterial agents were *Escherichia coli* (n = 18; 24.0%) and *Enterococcus* spp. (n = 18; 24.0%).

The average APACHE II score in the group of non-survivors (n = 11) with *Candida* positive samples was significantly higher than the one in the group of survivors (32.6; range: 20.0 to 39.0 vs. 15.1; range: 4.0 to 31.0, respectively; p < 0.0001). There is a positive, statistically significant correlation between the age of patients with isolated *Candida* in peritoneal fluid and the APACHE II score (r = 0.649, p < 0.0001).

All of the eight deceased patients with repeated operation had *Candida* positive peritoneal samples, as opposed to only three in the group of survived patients (p < 0.05) (Table 4).

Table 3. Microorganisms isolated from peritoneal fluid according to the outcome*

Peritoneal fluid samples (n = 83)	Non-survivors 19 (22.9)	Survivors 64 (77.1)
Positive samples**	17 (89.5)	45 (70.3)
mixed microflora	10 (58.8)	16 (35.6)
bacterial agents only	5 (29.4)	18 (40.0)
mycotic agents only	2 (11.8)	11 (24.4)
Gram-negative bacteria		
<i>Escherichia coli</i>	7 (41.2)	11 (24.4)
<i>Klebsiella pneumoniae</i>	3 (17.6)	2 (4.4)
<i>Acinetobacter</i> spp.	4 (23.5)	0 (0.0)
<i>Enterobacter cloacae</i>	2 (11.8)	2 (4.4)
<i>Pseudomonas aeruginosa</i>	1 (5.9)	0 (0.0)
<i>Neisseria</i> spp.	0 (0.0)	1 (2.2)
Gram-positive bacteria		
<i>Enterococcus</i> spp.	8 (47.1)	10 (22.2)
<i>Streptococcus</i> spp.	1 (5.9)	15 (33.3)
<i>Staphylococcus</i> spp.	0 (0.0)	8 (17.8)
Fungi		
<i>Candida albicans</i>	5 (29.4)	16 (35.6)
<i>Candida glabrata</i>	2 (11.8)	7 (15.6)
<i>Candida krusei</i>	0 (0.0)	2 (4.4)
<i>Candida tropicalis</i>	0 (0.0)	1 (2.2)
<i>Candida non-albicans</i>	2 (11.8)	0 (0.0)
<i>Candida</i> spp.	3 (17.6)	2 (4.4)
Negative samples	2 (10.5)	18 (28.1)
Contaminated samples	0 (0.0)	1 (1.6)

* Data are presented as number (percentage)

** In 56.5% (n = 35) of positive samples were found more than one pathogen

Table 4. Main clinical characteristics after surgery according to the outcome*

Characteristics	Non-survivors 19 (22.9)	Survivors 64 (77.1)	p-value
Candida positive samples	12 (63.2)	27 (42.2)	NS
mixed flora	10 (52.6)	16 (25.0)	p < 0.001
only Candida isolates	2 (10.5)	11 (17.2)	NS
Repeated laparotomy	8 (42.1)	5 (7.8)	p = 0.0012
Infectious complications			
Sepsis	18 (94.7)	1 (1.6)	p < 0.0001
Pneumonia	3 (15.8)	3 (4.7)	p = 0.1297
Wound infection	0 (0.0)	8 (12.5)	NS
Urinary tract infection	1 (5.3)	0 (0.0)	NS
Mean duration of MV (range), days	8.7 (1 to 25)	0.9 (0 to 15)	p < 0.0001
Mean hospital stay (range), days	10.9 (1 to 46)	15.1 (4 to 50)	p = 0.0038
Mean ICU stay (range), days	9.5 (1 to 34)	7.0 (1 to 32)	p = 0.2060

*if not stated otherwise, data are presented as number (percentage)

Abbreviation: MV = mechanical ventilation; ICU = Intensive Care Unit; NS = not significant

Fig. 1. Distribution of mycotic pathogens isolated from intraoperatively collected peritoneal fluid samples

Antibacterial and antimycotic therapy

The antimicrobial therapy (antibiotics alone or in combination with antimycotics) was initiated intraoperatively, and continued until the signs of infection completely subsided and negative microbiological results were obtained. Empirical antibacterial therapy includes Ceftriaxone or Sulbactam/Cefoperazone and Metronidazole, and is adapted at the first opportunity according to the identified isolates and their susceptibility (≤ 48 hours). Within two to three hours after the positive culture obtaining, antimycotic therapy was initiated in concordance with the susceptibility data of isolated mycotic agent. Most patients received antimycotic therapy with Fluconazole 400 mg on the first day, followed by 200 mg/day for

7-14 days. When Fluconazole-resistant pathogens (*C. krusei* or *C. glabrata*) were isolated, Voriconazole was administered.

DISEASE OUTCOME

77.1% (n = 64) of the studied patients fully recovered, and 19 (22.9%) patients deceased due to sepsis and MODS. In eight (12.5%) of patients, who survived, wound infection was found; after drainage, irrigation, dressing and secondary suture, all of them recovered and were discharged (Table 4). The presence of sepsis determines with statistical significance a subsequent lethal outcome in the patients studied (OR = 286.0, RR = 24.8, Se = 91.7%, Sp = 96.3%, PPV = 91.7%, and NPV = 96.3%; p < 0.0001). Eleven (61.1%) of the deceased patients with sepsis had Candida-positive peritoneal samples, whereas among survived patients they were found in only one.

The mean hospital stay in discharged patients was significantly longer than that in nonsurvivors (15.1 vs. 10.9 days; p = 0.0038), whereas no difference was found for the ICU stay (7.0 vs. 9.5 days; p > 0.05). It should be noted that the total length of hospital stay for nonsurvivors was mainly at the expense of the ICU stay. There was no statistically significant difference between the length of hospital stay and ICU stay in patients with Candida-positive and Candida-negative peritoneal fluid samples in the population studied (p = 0.4414 and p = 0.2556, respectively).

The APACHE II score ≥ 18 determines with statistical significance the progression to lethal outcome in patients with Candida-positive peritoneal samples (OR = 41.67, Se = 100%, Sp = 63%, PPV = 55%, and NPV = 100%; $p = 0.0002$), as well as the delayed surgical intervention for more than 24 hours from the symptoms' onset (OR = 8.0, RR = 3.3, Se = 50%, Sp = 88.9%, PPV = 66.7%, and NPV = 80.0%; $p = 0.0141$).

Patients with lethal outcome had statistically significant longer duration of MV compared to the discharged patients (8.7 vs. 0.9 days; $p < 0.0001$). There was observed a statistically significant positive correlation between the age and duration of MV in the studied patients ($r = 0.38$; $p = 0.0002$), whereas no significant correlation was found between the age and duration of total hospital stay and ICU stay ($r = 0.04$; $p = 0.3777$ и $r = -0.17$; $p = 0.1386$, respectively).

There was no association found between the presence of Candida in the abdominal samples, comorbidities and disease outcome in the studied population ($p > 0.05$). Mortality was higher in patients with mixed bacterial-mycotic infection ($n = 10$) than in patients with isolated mycotic agent(s) alone ($n = 2$) ($p < 0.001$).

DISCUSSION

The perforation of gastrointestinal tract (GIT) is one of the leading causes of acute abdomen. It is often secondary to a main disease such as gastric or duodenal ulcer, and others. This acute condition requires immediate diagnosis and treatment.

The native microflora of GIT consists primarily of Gram-negative and anaerobic bacteria. It is well-known that in case of acute peritonitis due to perforation of GIT, the flora is usually polymicrobial, but recently a mycotic infection in the abdominal cavity has been reported more frequently [12, 13].

Yeasts, mainly *Candida* spp., are present in all parts of GIT in about 70% of healthy elderly individuals [14]. Under certain conditions associated with compromise of the host native defensive mechanisms, significant Candida-colonization of GIT may occur, followed by systemic spreading and development of mycotic infection [14, 15]. As an element of the endogenous flora of the GIT, *Candida* spp. may play a role in the aetiology of almost any type of abdominal infection, passing into the peritoneal cavity after hollow organ perforation or intestinal wall damage. Intraoperatively a mycotic agent is isolated from the collected samples from abdominal cavity in 19.9% to 45.0% of all cases of peritonitis [1, 4, 16]. The most common

pathogen of fungal peritonitis is *Candida albicans* [17], but there has been a tendency to increase the incidence of nonalbicans species (mainly *C. glabrata*, *C. krusei*, *C. tropicalis*, and *C. parapsilosis*) and strains with greater potential for resistance to antimycotics in recent decades [3, 6, 8].

The main risk factors for the intra-abdominal fungal infection development are: hollow organ perforation (especially upper GIT); drain in situ, intravenous and urethral catheters; total parenteral nutrition; severe sepsis; pre-existing antibiotic therapy (≥ 48 hours, especially administration of broad-spectrum antibiotics); immunosuppression (e.g., corticosteroid therapy, chemotherapy); elderly patients; comorbidities (such as diabetes mellitus, malnutrition); excessive Candida-colonization, including multifocal (*Candida* isolated simultaneously from different parts of body, e.g., oral cavity, intestine, vagina, even if the strains are different) [2, 4, 5, 8, 9, 16-18], as well as preoperative organ failure, severity of disease, and delay of surgical intervention [5, 19].

The results of our study showed that in 47.0% ($n = 39$) of patients with gastroduodenal perforation, a fungal pathogen (predominantly *Candida albicans*) was isolated. Previous treatment with both antibiotics and corticosteroids determines with statistical significance the presence of positive *Candida* isolates in the peritoneal fluid samples ($p < 0.05$). There is no statistically significant correlation between the presence of *Candida* spp. in the peritoneal fluid and patients' age, as well as the duration of ICU/hospital stay ($p > 0.05$).

The fungal peritonitis can be difficult to diagnose, as clinical manifestations (such as fever, abdominal pain, leukocytosis, cloudy exudate in the abdominal cavity, etc.) of mycotic and bacterial peritonitis are identical. The condition is ultimately diagnosed by: (i) lack of effect of antibacterial therapy for three days; (ii) positive peritoneal fluid samples for yeasts by Gram staining; and (iii) positive samples for fungi [2, 20].

European Society for Clinical Microbiology and Infectious Diseases [21] and Infectious Diseases Society of America [7] published detailed practical guidelines for prevention, diagnosis, and treatment of invasive candidiasis, thereby helping clinicians and microbiologists in clinical practice decisions. Guidelines for managing patients with intraabdominal infections were also developed by an Expert Panel of the Surgical Infection Society and Infectious Diseases Society of America [22].

Microbiological culture methods for detection of *Candida* in biological samples remain the gold standard for diagnosis. These methods, however, provide results after two to three days, and sometimes

later (depending on the causative pathogen), which may affect the early onset of treatment. Peritoneal fluid samples after GIT perforation practically always contain a mixture of different aerobic and anaerobic bacteria, and in such cases *Candida* isolation can easily be overlooked, if no selective fungal culture media (such as, Sabouraud Agar) are used. In case of fungal isolation, species identification is obligatory because the susceptibility to antimycotics may vary significantly. *Candida non-albicans* species are characterized by intrinsic resistance (*C. krusei*) or reduced susceptibility to azoles (*C. glabrata*) or echinocandins (*C. parapsilosis*) [7-9].

In the present study, all *Candida* isolates were tested for susceptibility to antimycotics. Eleven (27.5%) of the isolated *Candida* spp. were Fluconazole-resistant. We consider that the testing for susceptibility to antimycotics should be done routinely in patients with IAC, which justifies the choice of antimycotic use.

Recently new diagnostic tests for early diagnosis of fungal infections (within a few hours), based on the detection of metabolites, cell wall antigens or mycotic DNA, as well as antibody detection (such as, (1,3) beta-D-glucan, mannan antigen and anti-mannan antibody assays; polymerase chain reaction – PCR) in the circulation, are available [23]. In our study, these methods have not been used.

Most generalized infections in the abdominal cavity require surgical treatment, broadspectrum antibiotic and/or antimycotic therapy, and intensive care to stabilize patient's condition (including infusion therapy, parenteral nutrition, hypoproteinemia correction) to avoid progression of systemic infection, and development of MODS and lethal outcome [20]. Timely surgical intervention in patients with acute peritonitis due to gastroduodenal perforation with abdominal cavity drainage and suture of the perforation site is crucial for patient's survival [24].

According to the data from our study, the presence of CAD and type 2 diabetes mellitus, preoperative severity of condition (APACHE II score ≥ 18), as well as the delayed surgery (more than 24 hours after the onset of symptoms), and a need for repeated operation in patients with positive abdominal samples for *Candida* spp., determine with statistical significance a subsequent lethal outcome in these patients ($p < 0.05$). The main cause for lethal outcome in our patients was the development of sepsis and MODS (most of deceased patients were elderly).

Antimycotic therapy should be selected, based on the susceptibility profile of the specific mycotic pathogen, the drug penetration in the pathological focus, and its adverse reactions, particularly in pa-

tients with MODS and concomitant diseases [2, 7, 20, 25]. The efficacy of early empirical antimycotic therapy has been proved [7, 26], and it should be administered in patients with risk factors and suspected clinical signs for fungal infection, because the fungal peritonitis is associated with high mortality, and the isolation of mycotic pathogens is time-consuming [4, 11]. After receiving of the results of microbiological assay, alterations in the therapeutic regimen are possible.

In our study, we administered Fluconazole in most patients, and Voriconazole in patients with Fluconazole-resistant isolates of *C. krusei* or *C. glabrata*. The applied antimycotic therapeutic regimen was in concordance with recent recommendations, because the use of inadequate (i.e., low) doses is ineffective and it results in selection of resistant strains of *Candida* spp. The duration of antimycotic therapy was at least two weeks after the last isolation of mycotic pathogens, if complete regression of all clinical manifestations of infection and negative cultures were achieved.

When polyetiology of abdominal infection presents, the treatment with antibacterial agents continues [1, 5]. Data from our study indicate that approximately in one-third (31.3%) of patients, a mixed intra-abdominal infection was detected, in which cases, *Candida* spp. along with intestinal pathogens – especially *Enterococcus* spp. and *Enterobacteriales* – were isolated. In addition, in all *Candida*-infected patients, we have changed or early removed (where appropriate) intravenous and urethral catheters, as they may be a potential source of infection because of the established tendency of the fungi to colonize artificial surfaces and to form biofilm [2, 20].

CONCLUSION

In cases of acute peritonitis due to gastroduodenal perforation, it is obligatory that the peritoneal fluid samples be microbiologically tested for bacterial and fungal pathogens with determination of their susceptibility profile. Key points in the management of these patients are: (i) timely adequate surgical intervention; (ii) prompt and exact microbiological diagnosis; and (iii) early effective antimycotic therapy based on the susceptibility profile of the isolated fungal agent. The multidisciplinary approach (a surgeon, anesthesiologist, and microbiologist) in the management of these patients guarantee their successful treatment.

Conflict of interest: The authors disclose no conflicts of interest

Disclosure Summary: The authors have nothing to disclose.

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