

# MICROBIOLOGICAL SPECTRE OF TERTIARY PERITONITIS AS A COMPONENT OF ITS DIAGNOSTICS AND TREATMENT

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## Abstract

The **aim** of the research was to investigate the microbial spectre of tertiary peritonitis (TP) and its antibiotic resistance as the way to improve the diagnostics and treatment of TP.

**Materials and methods.** Prospective research enrolled 109 patients with secondary peritonitis. Tertiary peritonitis developed in 18,3 % of cases. Samples of peritoneal exudate had been drawn upon index operation, relaparotomy and on the day of diagnosis of TP. Blood sampling was performed in patients with persistent fever, impaired consciousness, prolonged ( $\geq 4$  days) discharge from drainage tubes and on the 1st day of diagnosis of TP. Antibacterial susceptibility was evaluated using Hinton-Müller media.

**Results and discussion.** Patients were divided into 2 groups: with secondary peritonitis (89) and with TP (20). In TP group, cultivation of 76,2 % of primary specimens resulted in replantable and identifiable growth, presenting a shift towards Gram-negative flora and higher incidence of *Candida albicans*. Following the development of TP, hemocultures were positive in 15,1 %, presented mainly by *Proteus* spp. and non-*albicans* *Candida* spp. Second-group carbapenems, tigecycline and piperacillin-tazobactam had shown the highest activity in pathogens of TP. Caspofungin proved to be the most potent antifungal agent, especially towards non-*albicans* *Candida* spp. Antibiotic resistance in TP group was marked in 63,8 %.

**Conclusions.** Tertiary peritonitis is one of the most severe forms of abdominal sepsis with highest mortality. Causing pathogenic flora in case of TP is mainly Gram-negative and coccal with high rates of antibiotic resistance both in vitro and in vivo. Fungi, presented predominantly by *Candida non-albicans* substrains, show an increasing content in peritoneal exudate and major effect upon mortality in TP. In case of TP, a significant percent of peritoneal specimens do not provide any culture growth despite of observing stringent sampling, transportation and cultivation rules. Antimicrobial therapy of TP can never be standardized and should always be thoroughly based upon regular and proper peritoneal and blood sampling.

**Keywords:** abdominal sepsis, tertiary peritonitis, microbial spectre, fungi, antibacterial resistance.

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## 1. Introduction

Abdominal sepsis remains to be the leading problem of modern emergency surgery despite the global progress of surgical and pharmaceutical technologies [1, 2]. Tertiary peritonitis (TP) is one of the most severe forms of abdominal sepsis with dismal results of treatment, namely difficult verification of causal factors, mostly ineffective antibacterial treatment and, as a result, high rates of mortality [3, 4]. Alongside substantially impaired homeostasis, a major impact on severity of septic patient's condition is made by nosocomial microflora [5]. For decades, the latter presents high and fast increasing resistance to a vast array of antimicrobial agents, including potent and recently invented ones [6, 7]. Clinicians frequently face the failure to cultivate and even to identify the microflora, nevertheless proper techniques and media are used [8, 9]. Current studies show a di-

versity of microbial spectre both of secondary peritonitis (SP) and TP, depending on region, type of department, nosology, antibiotic treatment regimen etc. [10]. Recently, an increasing role in course and prognosis of treatment of peritonitis is given to fungal infection [11]. All abovementioned prove the topicality of the problem of TP, its causing flora, antibiotic susceptibility and the need for their further in-depth investigation.

## 2. Aim of the research

The **aim** of the research was to investigate the microbial spectre of tertiary peritonitis (TP) and its antibiotic resistance as the way to improve the diagnostics and treatment of TP.

## 3. Materials and methods

We had prospectively examined 109 patients with SP, operated in the Clinic of surgery and endoscopy of Lviv Danylo Halytsky national medical university in 2010–2015.

The etiology of SP was presented by: acute destructive appendicitis (29,4 %), perforated gastric (11 %) or duodenal (7,3 %) ulcer, perforated colon cancer (11 %), perforation of colonic diverticulitis (6,5 %), perforation of abdominal abscess (5,6 %), acute destructive cholecystitis with perforation (4,7 %), thrombosis of superior mesenteric artery with necrosis of the small intestine (3,6 %), perforated gastric cancer (3,6 %), Crohn's disease of the small intestine with perforation (3,6 %), hernia incarceration with necrosis of the small intestine (2,8 %), severe polytrauma with injury of the small bowel (2,8 %), decay of retroperitoneal tumor with formation of abscess and its perforation to abdomen (1,8 %), ingrowth of uterine tumor into small intestine and subsequent necrosis (0,9 %), pancreatic necrosis (0,9 %), volvulus of sigmoid colon with perforation (0,9 %), ulcerative colitis with necrosis of the colon (0,9 %), perforated cancer of the small bowel (0,9 %), decay of pancreatic cancer (0,9 %), gastric perforation by foreign body (0,9 %).

Concomitant somatic diseases, potentially aggravating the severity of condition, were detected in 88 (80,7 %) patients. Women slightly prevailed – 57 (52,3 %). The age of patients was within the range of 18–88 (median – 61). Postoperatively, majority (62,4 %) of patients stayed for 1–4 days (median – 2) in intensive care unit (ICU). Peritonitis was local non-separated in 104 (95,4 %), diffuse – in 88 (80,7 %) patients. Postoperative complications arose in 18 cases (16,5 %), being septic in 50 %.

Tertiary peritonitis was diagnosed on 3rd–12th day (median – 5) in 20 (18,3 %) patients. Criteria for diagnosis of TP were: persistence of peritoneal symptoms despite adequate surgical elimination of the infectious source, presence of nosocomial microflora in peritoneal exudate, multi-organ failure and time of stay in intensive care unit for  $\geq 3$  days [12]. Postoperative mortality in the whole cohort was 30,2 %. Tertiary peritonitis had a lethal outcome in 90 % of cases, with sepsis being the main cause.

Samples of peritoneal exudate had been drawn upon index operation for SP at least from 4 distant areas in case of diffuse peritonitis and from 2 in case of local each using a separate swab and container with protective environment. All specimens had been transported to microbiological laboratory within 15 min and were cultivated using different nutritional media in appropriate thermal environment. In case of programmed relaparotomy (PRL) / on-demand relaparotomy (ODRL) and on the day of diagnosis of TP, we had additionally performed sampling of peritoneal exudate directly from the peritoneal cavity and/or drainage tubes at least from 2 remote locations.

Blood sampling was performed from both cubital veins in all patients with persistent ( $\geq 48$  h) fever, impaired consciousness (according to Glasgow scale values), prolonged ( $\geq 4$  days) discharge from drainage tubes and on the 1st day of TP diagnosis. In case blood samples gave growth to skin saprophytes, the sampling was repeated once again from both cubital veins.

Actively growing colonies were identified by microscopy and/or enzyme technique. Gram-positivity and primary phenotyping of flora were evaluated by cultural features and biochemical identification systems after 24 h. Identified cultures had been replanted onto Hinton-Müller media to evaluate susceptibility to 19 antibiotics using Kirby-Bauer method. Susceptibility of pathogenic fungi to fluco- and voriconazole was evaluated on glucose-enriched agar using semi-quantitative method. *Candida* and its subspecies were identified using mannan and galactomannan serological method.

In majority of cases (98,4 %), initial antibacterial therapy consisted of 2 drugs with 1<sup>st</sup> either fluoroquinolone (3<sup>rd</sup> generation – 53 %, 4<sup>th</sup> – 47 %), cephalosporin (3<sup>rd</sup> generation – 46,3 %, 4<sup>th</sup> – 53,7 %) or ertapenem (10,4 %); 2<sup>nd</sup> – anti-anaerobic agent (44,2 % – metronidazole, 55,8 % – ornidazole). Antifungal drugs were prescribed pre-emptively before initial operation to 12,2 % patients (fluconazole – 68,1 %, voriconazole – 31,9 %). None of the patients had clinical signs of fungal infection upon admission to the hospital.

#### 4. Results

Patients were divided into 2 groups: with SP (n=89) and with TP (n=20). In SP group, cultivation of 85,7 % of primary specimens resulted in replantable and identifiable growth, in TP group – 76,2 %. As seen in **Table 1**, aerobic flora had quantitatively prevailed in primary specimens of SP. In those patients, who developed TP further on, a shift towards Gram-negative flora was marked alongside higher incidence of *Candida albicans*.

**Table 1**

Microbial spectre of SP and TP upon index operation

Strain	SP, %	TP, %
<b>Gram-positive</b>		
<i>Staphylococcus epidermidis</i>	45,3	43,5
<i>Methicillin-sensitive Staphylococcus aureus</i>	15,6	12,1
<i>Methicillin-resistant Staphylococcus aureus</i>	1,2	2,4
<i>Enterococcus faecalis</i>	28,1	26,7
<i>Streptococcus pyogenes</i>	32,3	36,5
<i>Streptococcus viridans</i>	15,6	17,2
<b>Gram-negative</b>		
<i>Escherichia coli</i>	37,8	44,3
<i>Pseudomonas aeruginosa</i>	7,9	13,2
<i>Citrobacter Freundii</i>	31	28,7
<i>Klebsiella mobilis</i>	42,2	37,3
<i>Klebsiella pneumoniae</i>	4,1	5,5
<i>Proteus vulgaris</i>	11,9	10,1
<i>Acinetobacter spp.</i>	66,4	49,8
<i>Moraxella spp.</i>	12,5	9,7
<i>Serratia spp.</i>	9,8	11,2
<b>Fungi</b>		
<i>Candida albicans</i>	1,7	7,6
<i>Candida glabrata</i>	0	6,2
<i>Candida krusei</i>	0	5,5
<i>Candida tropicalis</i>	0	1,5
<i>Geotrichum candidum</i>	1,1	4,7

A detailed analysis of primary microbiograms had shown that the infection was presented by cultural associations. In SP group, 3 different microorganisms formed an association in 24,5 % of cases, 2 – in 70,1 % and only in 5,4 % it was monocultural. Microbial associations in the TP group were alike to those in SP group, but with a 23,1 % fraction of *Candida spp.*

Relaparotomy, regardless PRL or ODRL, was the indication for peritoneal exudate sampling. In case of PRL, volume of peritoneal fluid was scarce and so were the findings (positive growth – 51,4 %): a variety of coccal flora (88,3 % of cultures), associated with *E. coli* (14,3 % of cases). In contrast, specimens taken during ODRL presented a wider (89,5 %) range of microorganisms, incl. *E. coli*, *Klebsiella spp.*, *Proteus spp.* and *Enterobacter spp.*, associated with *Candida albicans* in 13,1 % of cases.

In 58,7 % of patients, TP was diagnosed on ODRL, in 15,4 % – on PRL. Intraoperative sampling was positive only in 13,7 %, from drainages – in 11,2 %. Cumulative microbial spectre of TP is shown in **Table 2**.

**Table 2**  
Microbial spectre of TP

Strain	%
<b>Gram-positive</b>	
<i>Staphylococcus epidermidis</i>	12,9
<i>Staphylococcus saprophyticus</i>	10
<i>Methicillin-sensitive Staphylococcus aureus</i>	7,4
<i>Methicillin-resistant Staphylococcus aureus</i>	34,4
<i>Enterococcus faecalis</i>	20,1
<i>Enterococcus faecium</i>	11,1
<i>Streptococcus pyogenes</i>	26,1
<i>Streptococcus viridans</i>	13,6
<b>Gram-negative</b>	
<i>Escherichia coli</i>	25,9
<i>Pseudomonas aeruginosa</i>	44,6
<i>Citrobacter Freundii</i>	28,7
<i>Klebsiella pneumoniae</i>	27,1
<i>Klebsiella oxytoca</i>	12,2
<i>Klebsiella mobilis</i>	43,5
<i>Proteus vulgaris</i>	24
<i>Proteus mirabilis</i>	11,2
<i>Acinetobacter Baumannii</i>	33,5
<i>Moraxella spp.</i>	15,1
<i>Serratia spp.</i>	9,4
<b>Fungi</b>	
<i>Candida albicans</i>	15,3
<i>Candida glabrata</i>	23,1
<i>Candida krusei</i>	26,4
<i>Candida tropicalis</i>	14,6
<i>Geotrichum candidum</i>	2,7

Among patients of TP group, whose peritoneal exudate gave growth to *Candida* spp. (90 % – non-albicans), 80 % died.

Initial blood sampling was successful in 41,2 % of SP cases, though being false-positive in 9,3 %. Pathogenic flora was verified in 35,4 % cases and was presented by *Streptococcus pyogenes* (23,4 %), *E. coli* (10,3 %), *Proteus vulgaris* (34,1 %) and *Acinetobacter Baumannii* (32,2 %), not influencing the previously applied antibiotherapy. Following the development of TP, hemocultures were positive in 15,1 %, presented mainly by *Proteus spp.* and non-albicans *Candida spp.*

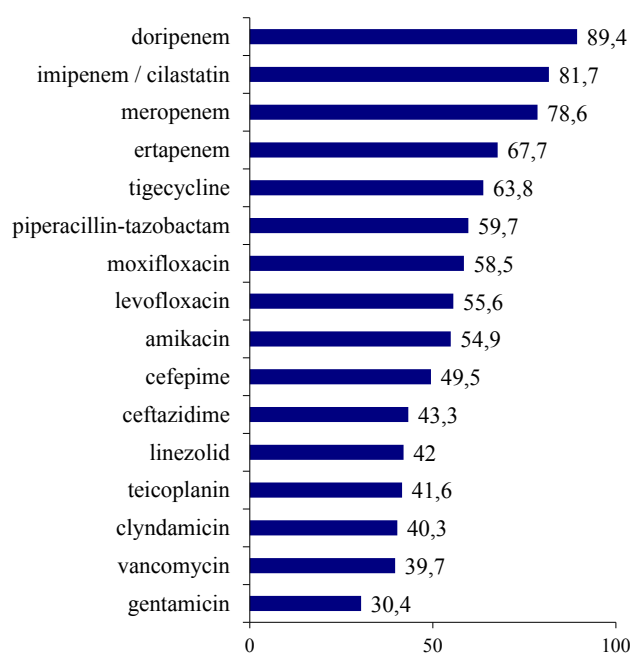
Taking into account a multifold amount of results, antibacterial susceptibility to chosen drugs in SP group is given as Expected clinical efficacy (ECE) ( $\geq 66$  % of cultures presented delayed growth  $\geq 20$  mm) in **Fig. 1**.

In SP group, caspofungin had shown the highest antifungal ECE (23 %). Voriconazole had ECE 22,8 %, fluconazole – 17,8 %.

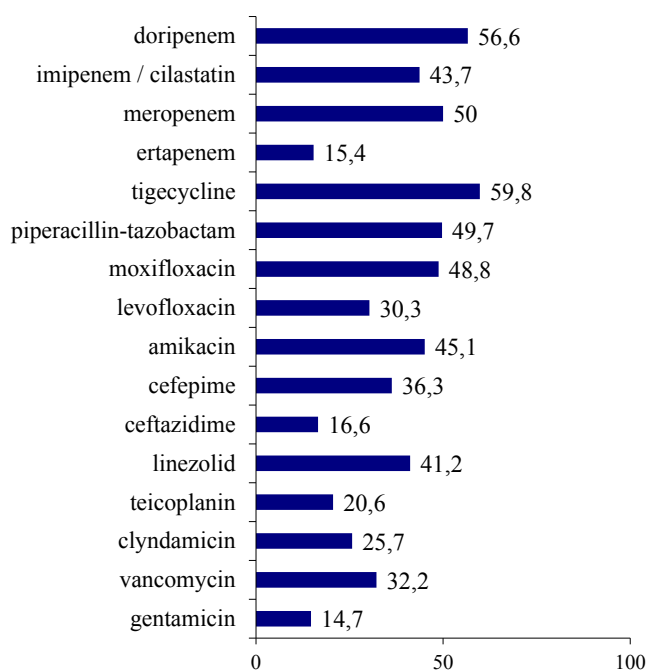
Expected clinical efficacy in TP group is shown in **Fig. 2**.

We had observed a substantial shift of *Candida* towards non-albicans subspecies, which in 68,2 % had exposed a good susceptibility to caspofungin (26,1 %) and voriconazole (18,3 %) and a rather poor one to fluconazole (9,5 %). Half of the TP group received 4 antimicrobials at once incl. 1 systemic antifungal agent.

Noteworthy peculiarities have also been marked upon analysis of ECE values depending on Gram-polarity of pathogens (**Table 3**). In most cases of TP, antibacterials showed lower ECE cf. to SP group.



**Fig. 1.** ECE – SP group ( % of sensitive cultures)



**Fig. 2.** ECE – TP group ( % of sensitive cultures)

Antibiotic resistance to  $\geq 2$  antibiotics was revealed in 35,3 % patients of SP group with prevalence of extended spectrum  $\beta$ -lactamase producing pathogens (*Enterobacteriaceae*, *Pseudomonas aeruginosa*). In TP group this parameter was 63,8 %: 2<sup>nd</sup> group carbapenem-resistant *Acinetobacter baumannii* (61,3 % of cultures), methicillin-resistant *Staphylococcus aureus* (32,1 %), fluconazole-resistant *Candida albicans* (58,3 %). In general, multi-drug resistant (MDR) pathogens comprised 28,7 % of cases in TP group and were represented mainly by *Acinetobacter spp.* and *Klebsiella spp.* with highest (39,8 %) sensitivity to doripenem.

Received results created the basis for introduction of changes in antimicrobial treatment (Table 4).

**Table 3**  
ECE depending on Gram-polarity (% of sensitive cultures)

Antibacterial drug	Gram-positive		Gram-negative	
	SP	TP	SP	TP
doripenem	80	68	92	81
imipenem / cilastatin	76	65	84	76
meronem	78	63	80	69
ertapenem	60	41	70	37
tigecycline	64	58	69	58
piperacillin-tazobactam	75	62	30	21
moxifloxacin	86	74	48	39
levofloxacin	50	59	65	48
amikacin	57	38	62	54
cefepime	30	42	55	31
ceftazidime	68	50	34	15
linezolid	50	41	11	10
teicoplanin	51	32	9	8
clindamycin	50	28	13	5
vancomycin	45	43	45	2
gentamicin	24	19	40	17

**Table 4**  
Characteristics of antimicrobial treatment in both groups

Type of antibiotic treatment	SP		TP	
de-escalation	14,3 %		0 %	
escalation	4,7 %		100 %	
combined	85,6 %	93,3 % – 2 agents,	100 %	73,1 % – 2 agents,
		6,7 % – 3 agents		16,6 % – 3 agents,
definitive	44,5 %		30 %	

It is worth of mentioning that several substrains of *Staphylococci* (TP group) demonstrated medium (33–66 %) susceptibility to fosfomycin. As well, we observed  $\geq 66$  % in vitro efficacy of co-trimoxazole towards certain strains of *Acinetobacter spp.* and *Citrobacter spp.* Similar in vitro data were obtained about activity of colistin towards *P. aeruginosa* and *E. coli*. Although, none of those were chosen for use in vivo due to known significant side effects, particularly toxicity and risk of further promotion of antibiotic resistance.

## 5. Discussion

Tertiary peritonitis was once called an “uncontrolled peritonitis”, manifesting itself as sepsis at the background of sterile peritoneum [13]. Hospital-acquired infections, concomitant diseases and immunosuppression are one of the most potent risk factors of mortality [14]. Failure of antibacterial therapy is considered to be one of the indications for hemoculturing, as *Candida spp.* are often suspected [9]. Severity of condition, causal pathogenic flora and prognosis differ substantially in septic patients of surgical department and ICU [15].

According to a recent study of O. van Ruler et al. [16], 70 % of peritoneal cultures of SP were polymicrobial, 19 % – monomicrobial and 11 % showed no microbial growth. Another group of authors observed 72 % cases of polymicrobial, 8–28 % monomicrobial cultures and up to 20 % of unsuccessful microbial sampling [17, 18]. These data partially coincide with ours, though percentages in TP group differ essentially.

Recent studies of microbial spectre of SP prove that it is mostly stable throughout years: *E. coli* – 50–100 %, *Streptococcus spp.* – 10–44 %, *P. aeruginosa* – 24,9 %, *S. aureus* – 16 % [19]. Severity of the patient's condition and difficulties of adequate “source control” upon index emergency operation often form the indication for relaparotomy – a known risk factor for further colonization of abdominal cavity by nosocomial pathogens [20]. This could explain why causal flo-



ra of TP is alike to that in SP, though has obvious qualitative and quantitative differences. Majority of modern works indicate on lower incidence of successful peritoneal sampling, a move towards Gram-positive flora and increasing content of fungi [21]. One study observed *E. coli* in 52 % cultivates of TP, *Klebsiella spp.* – 10 %, *Enterobacter spp.* – 19 %, *P. aeruginosa* 13 %, *Enterococcus faecalis* – 33 %, *Enterococcus faecium* – 8 % [22]. These findings also have similarities with our research, though, study duration could have led to changes both in spectre and antibiotic susceptibility over time. Diversities and sometimes discrepancies in microbial spectres of peritonites could be explained by differences in regional protocols/standards of antibiotic treatment and structure of morbidity of given population.

Yeast strains comprise 22–41 % in exudate of SP and 17 % of all nosocomial isolates in ICU [23]. Isolation of *Candida* from intra-abdominal cultures is successful in 57 % of cases and is associated with increased mortality [24]. In the structure of obtained fungal cultures during SP, *Candida albicans* was seen in 74 %, *Candida glabrata* – 17 %; remaining 9 % included: *Candida inconspicua*, *Candida parapsilosis*, *Candida tropicalis*, *Candida zeylanoides*, *Geotrichum candidum* [23]. In our research, in SP group we observed lesser percentage of *Candida albicans* and very moderate – of *Candida non-albicans* in comparison to TP group.

Prevalence of *Candida*, especially of its non-albicans strains, in peritoneal exudate on index operation hints upon compromised anti-infective defense and latent immunodeficiency as potent risk factors for development of TP. In case of candidous TP, mortality reaches 70 % [11]. Peritoneal sampling during TP had shown positive culturing of *albicans*-subspecies in 12 % of cases, *non-albicans*-subspecies – in 3 % [23]. In TP group, we had seen a remarkable shift of the ratio of “albicans/non-albicans” subspecies in favour of the latter.

Blood culture is a necessary method to control the spread of the infection to the systemic level. According to reports, it's successful in 9,2–21,2 % [25, 26]. Results of hemocultivation differ as well, probably depending on patient's general health condition, severity of surgical disease, characteristics of therapy and accuracy of cultivation. Leading Gram-positive pathogens in blood culture are *Staphylococcus spp.* (48,7 %) and *Enterococcus spp.* (12,8 %) [10]. Gram-negative pathogens were obtained from 25,7 % specimens and included *Klebsiella pneumoniae* (12,8 %), *Enterobacter cloacae* (2,6 %), *E. coli* (2,6 %), *Proteus vulgaris* (2,6 %); others (7,7 %) were: *P. aeruginosa* (2,6 %), *Acinetobacter baumannii* (2,6 %) and *Candida* (2,6 %) [10]. In our study, mostly Gram-positive coccal flora was found in blood of patients of SP group and only 2 pathogens in TP group, notably, *non-albicans Candida spp.*

International research data claim a vast range of hemocultivation of *Candida spp.* – 4–32 % [27]. Regardless of primary disease, Hung-Wei C. et al. [28] reported a shift from *Candida albicans* to *Candida non-albicans* subspecies in hemocultures, with *non-albicans* quotient equaling up to 63 %. Out results of hemocultivation in TP group were 90 % of non-albicans substrains.

Clinicians still deal with unclear previous history of antibiotic use and fungal status, which directly affect the results of antibacterial treatment. Normally, antibacterial therapy should start as pre-emptive, later on transforming into a definitive one. Nowadays, there are probably no borders for migration of resistant microflora and interchange of its defense mechanisms between species. Even if “source” and “damage control” principles had been maintained on the index procedure, inadequate antimicrobial therapy is the risk factor for pessimistic outcome [21].

Antimicrobial susceptibility data vary a lot due to the huge set of independent factors, including technique of sampling, quality of nutritional media, subjectivity of interpretation and actual antimicrobial protocols. In our study, 2<sup>nd</sup> group carbapenems showed the highest in vitro efficacy in both study groups, corresponding to data of other colleagues [29]. Other clinicians call to diminish/ignore the use of any generation cephalosporins due to serious drop of their efficacy with time and strong promotion of antibacterial resistance [26].

On one hand, antifungal therapy should be prescribed either to each critical patient or in case of positive fungal culture [8], on the other – empiric coverage of yeast in abdominal sepsis is not supported by present data because of high resistance of *Candida spp.* to fluconazole [27].

Finally, the “collateral damage” effect, alongside natural process of antibiotic resistance, became the main reason of emergence of MDR pathogens. Antibiotic resistance to  $\geq 2$  antibiotics

occurred in 64,9 % of cases of SP, presented mainly by extended spectrum  $\beta$ -lactamase-producing *Enterobacteriaceae spp.* and *P. aeruginosa* in 11,1 % and 11,9 % respectively [26]. In other works, fraction of nosocomial MDR reached 84,8 %, but just 14 % in case of TP [23]. Our findings of MDR pathogens make up for 35,3 % in SP group, and 28,7 % of strains in TP group.

All above emphasize the complexity of the problem of TP and the necessity of further in-depth investigation of its microbial spectre and antibiotic resistance in order to improve the approach to diagnostics and treatment results.

## 6. Conclusions

1. Tertiary peritonitis remains to be one of the most severe forms of abdominal sepsis with highest mortality.
2. Causing pathogenic flora in case of tertiary peritonitis is mainly Gram-negative and coccal with high rates of antibiotic resistance both in vitro and in vivo.
3. Fungi, presented predominantly by *Candida non-albicans* substrains, show an increasing content in peritoneal exudate and major effect upon mortality in tertiary peritonitis.
4. In case of tertiary peritonitis, a significant percent of peritoneal specimens do not provide any culture growth despite of observing stringent sampling, transportation and cultivation rules.
5. Antimicrobial therapy of tertiary peritonitis can never be standardized and should always be thoroughly based upon regular and proper peritoneal and blood sampling.

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