

# Predictive Factors of Mortality Due to Polymicrobial Peritonitis With *Candida* Isolation in Peritoneal Fluid in Critically Ill Patients

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**Background:** *Candida* peritonitis (CP) is generally considered to be a severe disease, but its impact on outcome in critically ill patients remains unknown.

**Hypothesis:** The predictive factors of mortality due to CP can be determined by study of a population of patients with CP.

**Design:** A retrospective review of a prospective surgical intensive care unit (ICU) database of patients (January 1, 1994, through December 31, 2000).

**Setting:** University hospital in Paris, France.

**Patients:** Eighty-three patients with generalized CP.

**Main Outcome Measures:** Demographic and microbiologic data and outcome were collected, and nonsurvivors were compared with survivors.

**Results:** Overall ICU mortality due to CP was 43 (52%) of 83 patients. In a stepwise multivariate logistic regression, the following 4 variables were independently associated with mortality: APACHE II (Acute Physiology and Chronic Health Evaluation II) score on admission of at least 17 (odds ratio [OR], 28.4; 95% confidence interval [CI], 5.7-142.5;  $P < .001$ ), respiratory failure on admission (OR, 10.6; 95% CI, 2.2-51.2;  $P = .003$ ), upper gastrointestinal tract site of peritonitis (OR, 7.7; 95% CI, 1.7-34.7;  $P = .007$ ), and results of direct examination of peritoneal fluid that were positive for *Candida* (OR, 4.7; 95% CI, 1.2-19.7;  $P = .002$ ).

**Conclusions:** These results confirm the severity of CP in ICU patients and emphasize the prognostic value of direct examination of peritoneal fluid for *Candida* in this context.

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**F**UNGAL ISOLATES in the intensive care unit (ICU) represent almost 17% of all nosocomial infections, but only half of these patients receive antifungal therapy in current practice.<sup>1</sup> Mortality due to severe intra-abdominal infection remains as high as 40%, despite improvement in intensive care.<sup>2</sup> Mortality related to candidemia has been clearly established,<sup>3</sup> but the pathogenicity of yeasts in peritoneal fluid remains unclear.<sup>4</sup> In 3 series performed on a limited number of patients, overall mortality due to yeast peritonitis was as high as 62% to 75%.<sup>2,5,6</sup> Practice guidelines for the treatment of candidiasis have also been recently published.<sup>7</sup> In intra-abdominal infections, antifungal therapy has been recommended for peritoneal catheter dialysis infections, peritonitis related to intra-abdominal leakage of fecal material, and surgical repair and drainage.<sup>4,7</sup>

Studies concerning yeast peritonitis have included only limited numbers of pa-

tients, and none of these studies compared patients with and without isolation of *Candida* from peritoneal fluid.<sup>5,6,8-11</sup> These studies were only descriptive. Numerous predisposing factors for fungal infection have been reported, such as immunosuppression, alcohol consumption, diabetes, total parenteral nutrition, and previous antimicrobial therapy.<sup>5,6,8-11</sup> In most studies of yeast peritonitis, half of

## See Invited Critique at end of article

the patients also had extra-abdominal yeast infection that appeared to be a possible confounding factor.<sup>8-10</sup> Furthermore, in some studies, patients with infected pancreatitis were pooled with those with peritonitis, although these patient subpopulations were not always comparable.<sup>5,6</sup> Therefore, predictive factors of mortality for patients with a diagnosis of yeast peritonitis have not yet been clearly established.

The aim of this study was to determine the predictive factors of mortality of polymicrobial peritonitis with *Candida* isolation in critically ill patients.

## METHODS

### SELECTION OF PATIENTS

We conducted a retrospective study of all adult patients with a diagnosis of peritonitis requiring admission to a surgical ICU from January 1, 1994, through December 31, 2000. All consecutive patients with a diagnosis of peritonitis were prospectively included in a database, and their medical charts were reviewed retrospectively. Peritonitis was diagnosed on the basis of macroscopic findings and positive culture of the peritoneal fluid collected during operation. The inclusion criterion for this study was a culture positive for *Candida* in peritoneal fluid obtained during surgery. The exclusion criteria consisted of acute infected pancreatitis, acute perforation due to trauma of less than 6 hours, and primary peritonitis, such as dialysis catheter infection and ascites infection. Patients who underwent several laparotomies were included only once, for the laparotomy before admission to the ICU.

### MICROBIOLOGY AND ANTIBIOTIC THERAPY

We performed direct examination of peritoneal fluid, including tests for the presence of *Candida*, for all patients. After drying and fixing a smear of the sample on a glass slide, we performed a gram stain and examined the slide by means of light microscopy (original magnification  $\times 1000$ ). The entire slide was examined for bacilli, cocci, and *Candida*. Empirical antimicrobial therapy was begun intraoperatively and adapted as soon as possible according to identification and results of susceptibility testing ( $\leq 48$  hours). The recommended protocol for community-acquired peritonitis was a combination of amoxicillin sodium and clavulanic acid potassium plus gentamicin sulfate or a combination of piperacillin sodium and tazobactam sodium. No protocol was available for postoperative peritonitis, and the choice of treatment was left to the physician's discretion according to previous microbiologic results, when available. Antibiotic susceptibility testing was performed by the disk diffusion method, and cutoff points were defined by the Antibiotic Susceptibility Testing Committee of the Société Française de Microbiologie.<sup>12</sup> The hospital Mycology Department performed *Candida* identification and susceptibility testing. Blood cultures for bacteremia or fungemia screening were collected at least 3 times a day for 48 hours perioperatively. A strain was considered to be multiresistant when it was resistant to at least 2 classes of antibiotics that were usually effective on the strain. Empirical antimicrobial therapy was considered inappropriate when it did not target at least 1 of the bacteria isolated, except for *Candida*.<sup>2</sup> The coverage of yeast was not taken into account for the adequacy of empirical antimicrobial therapy. No protocol was available for the treatment of *Candida*, and treatment was left to the discretion of the physician in charge of the patient.

### SURGERY

All patients underwent laparotomy performed by the same surgical team (including D.C. and J.P.M.). Briefly, after peritoneal fluid sampling for microbiology, abundant peritoneal lavage was performed with sterile isotonic sodium chloride solution (10-20 L). When possible, a stoma was performed rather than a primary anastomosis. None of the wounds was left open. Mesh was not used to close wounds, and the abdomen was never irrigated after surgery.

## DATA COLLECTION

We reviewed all patient medical charts. The following demographic data and severity scores were recorded on admission to the ICU: APACHE II (Acute Physiology and Chronic Health Evaluation II) score,<sup>13</sup> Simplified Acute Physiology Score version II (SAPS II),<sup>14</sup> and organ system failure (OSF) score.<sup>15</sup> The OSF score was defined as cardiovascular failure (ie, heart rate  $< 54$  beats/min, systolic blood pressure  $< 60$  mm Hg, ventricular tachycardia or fibrillation, and/or arterial pH  $\leq 7.27$  with PaCO<sub>2</sub>  $\leq 49$  mm Hg); respiratory failure (ie, respiratory rate  $< 5$  or  $> 49$ /min, PaCO<sub>2</sub>  $\geq 50$  mm Hg, and/or alveolar arterial oxygen delivery  $> 350$  mm Hg); renal failure (ie, oliguria  $< 479$  mL per day or  $< 159$  mL per 8 hours, serum urea nitrogen level  $> 100.8$  mg/dL [ $> 36$  mmol/L], and/or serum creatinine level  $> 3.5$  mg/dL [ $> 310$   $\mu$ mol/L]); hematologic failure (ie, white blood cell count  $< 1000$  cells/ $\mu$ L, platelet count  $< 20000$  cells/ $\mu$ L, and/or hematocrit level  $< 20\%$ ); and neurologic failure (ie, Glasgow Coma Scale  $< 6$  without any sedation).<sup>15</sup> Underlying diseases were classified according to the criteria of McCabe and Jackson.<sup>16</sup> Patients were considered immunocompromized if they had received long-term treatment with corticosteroids, if they had cancer or hematologic disease, or if they had undergone previous anticancer radiotherapy or chemotherapy.<sup>13</sup> The type (community-acquired or postoperative), etiology, and primary site (upper or lower gastrointestinal tract) of the infection responsible for peritonitis were recorded. The mesocolon was considered the barrier between the upper and lower gastrointestinal tracts. Main laboratory characteristics and previous ongoing antimicrobial therapy were recorded. Antimicrobial therapy was considered to be ongoing when it had been prescribed 48 hours before the operation. Identification of pathogens in peritoneal fluid and blood cultures and results of antimicrobial susceptibility tests were recorded. Patient outcome was recorded as the number of and time to repeat laparotomies (when necessary), duration of mechanical ventilation, ICU length of stay, and ICU mortality.

### STATISTICAL ANALYSIS

Results are expressed as mean  $\pm$  SD or proportions. Nonsurvivors were compared with survivors. Univariate analysis was performed using Mann-Whitney and  $\chi^2$  tests with the Yates correction. Stepwise multiple logistic regression was performed (backward Wald model) by entering into the model the significant or relevant variables obtained from univariate analysis. The median value of the population was used as the cutoff for quantitative variables. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated.  $P < .05$  was considered significant.

## RESULTS

During the study period, 271 patients with peritonitis were admitted to the ICU. Their mean SAPS II was  $45 \pm 18$ . One hundred twenty patients (44%) died in the ICU. During the same period, the overall ICU mortality rate was 24%. Among the 271 patients, 83 with *Candida* peritonitis were included in the present study. Mortality among the 188 patients without *Candida* peritonitis was 41%. The mean SAPS II of patients with *Candida* peritonitis was  $45 \pm 16$ , and 43 patients died (52%; 95% CI, 41.3%-62.7%). In this study population, observed mortality was significantly higher than the mortality predicted by the SAPS II (34.8%).

The main patient characteristics on admission are summarized in **Table 1**. Compared with survivors, non-

**Table 1. Main Characteristics on Admission According to Outcome\***

Characteristic	Nonsurvivors (n = 43)	Survivors (n = 40)	P Value
Age, mean ± SD, y	69 ± 17	59 ± 16	.007
Female	26 (60)	26 (65)	.67
Immunocompromised	25 (58)	28 (70)	.26
McCabe fatal†	14 (33)	9 (23)	.31
SAPS II, mean ± SD	52 ± 16	37 ± 12	<.001
APACHE II score, mean ± SD	23 ± 7	14 ± 5	<.001
OSF score, mean ± SD	1.8 ± 1.1	1 ± 1	.002
Cardiovascular failure	34 (79)	23 (58)	.03
Respiratory failure	18 (42)	5 (13)	.003
Renal failure	22 (51)	12 (30)	.06
Type of infection			
Community acquired	17 (40)	13 (33)	.51
Postoperative	26 (60)	27 (68)	
Ongoing antimicrobial therapy	17 (40)	18 (45)	.61

\*Unless otherwise indicated, data are given as number (percentage). SAPS II indicates Simplified Acute Physiology Score version II; APACHE II, Acute Physiology and Chronic Health Evaluation II; and OSF, organ system failure.

†Defined by the criteria of McCabe and Jackson.<sup>16</sup>

**Table 2. Site and Main Causes of Peritonitis According to Outcome\***

	Nonsurvivors (n = 43)	Survivors (N = 40)	P Value
Origin of peritonitis			
Upper gastrointestinal tract	22 (51)	10 (25)	.01
Biliary tract	20 (47)	9 (23)	
Stomach or duodenum	2 (5)	1 (3)	
Lower intestinal tract	21 (49)	30 (75)	
Small bowel	9 (21)	10 (25)	
Colon	12 (28)	20 (50)	
Main causes of peritonitis			
Perforation	22 (51)	23 (58)	.41
Anastomosis leak	14 (33)	8 (20)	
Miscellaneous	5 (12)	4 (10)	
Unknown cause	2 (5)	5 (13)	

\*Data are expressed as number (percentage) of patients. Percentages have been rounded and may not sum to totals.

survivors were significantly older and had higher severity scores and a higher incidence of organ failure on admission. No difference in mortality was observed between community-acquired and postoperative peritonitis. The primary site and main causes of peritonitis are shown in **Table 2**. No difference was observed within groups. Microbiologic characteristics of peritoneal fluid are presented in **Table 3**. No difference in pathogens was observed between nonsurvivors and survivors. The main yeast isolated was *Candida albicans* (74%), followed by *Candida glabrata* (17%). No modification of sensitivity to fluconazole was observed for *C albicans* strains. The following miscellaneous strains (9%) were also isolated: *Candida inconspicua*, *Candida parapsilosis*, *Candida tropicalis*, *Candida zeylanoides*, and *Geotrichum candidum*. All the stains isolated were susceptible to fluconazole. Only 8 patients had a monomicrobial inoculum to *Candida* in the peritoneal fluid (7 with *C albicans* and 1 with *C*

**Table 3. Microbiologic Characteristics of Peritoneal Fluid According to Patient Outcome\***

Pathogens (n = 295)	Nonsurvivors (n = 143)	Survivors (n = 152)	P Value
Gram-negative bacilli	45 (31)	47 (31)	.92
Enterobacteriaceae	20 (14)	21 (14)	
<i>Klebsiella</i> species	13 (9)	16 (11)	
Nonfermenting bacilli	7 (5)	9 (6)	
Miscellaneous	5 (3)	1 (1)	
Gram-positive cocci	42 (29)	42 (28)	.74
Staphylococci	8 (6)	11 (7)	
Enterococci	24 (17)	23 (15)	
Streptococci	10 (7)	8 (5)	
Anaerobes	15 (10)	19 (13)	
<i>Bacteroides</i> species	8 (6)	11 (7)	.59
<i>Clostridium</i> species	6 (4)	5 (3)	
Miscellaneous	1 (1)	3 (2)	
Yeasts	41 (29)	44 (29)	.96
<i>Candida albicans</i>	31 (22)	33 (21)	
<i>Candida glabrata</i>	7 (5)	7 (5)	
Miscellaneous	3 (2)	5 (3)	

\*Data are expressed as number (percentage) of isolates. Percentages have been rounded and may not sum to totals.

**Table 4. Main Patient Characteristics After Laparotomy According to Outcome\***

	Nonsurvivors (n = 43)	Survivors (n = 40)	P Value
Multiresistant strains	18 (42)	11 (28)	.17
DE results positive for <i>Candida</i>	22 (51)	8 (20)	.003
Adequate empirical ATB	25 (58)	32 (80)	.03
Empirical antifungal treatment	16 (37)	15 (38)	.98
Definitive antifungal treatment	35 (81)	32 (80)	.87
Duration of ATB, mean ± SD, d	13 ± 8	14 ± 4	.34
Repeat laparotomy	29 (67)	15 (38)	.006
No. of repeat relaparotomies, mean ± SD	2.5 ± 2	1.7 ± 1	.18
Time to repeat laparotomy, mean ± SD, d	4.9 ± 4	3.5 ± 2	.38
Duration of MV, mean ± SD, d	19 ± 22	12 ± 11	.04
ICU length of stay, mean ± SD, d	19 ± 22	17 ± 14	.93

\*Unless otherwise indicated, data are expressed as number (percentage) of patients. DE indicates direct examination; ATB, antibiotic treatment excluding antifungal treatment; MV, mechanical ventilation; and ICU, intensive care unit.

*glabrata*). The mean number of bacteria isolated with *Candida* was 2.6 ± 1.7, with no difference between nonsurvivors and survivors (*P* = .65). Twenty-two cases of bacteremia were observed in nonsurvivors compared with 12 in survivors (*P* = .06). However, 9 cases of candidemia (*C albicans*) were observed in 5 nonsurvivors compared with no cases in survivors (*P* = .04). Main patient characteristics after laparotomy for peritonitis and patient outcomes are shown in **Table 4**. Direct examination of peritoneal fluid yielded results that were positive for *Candida* and inappropriate empirical antimicrobial therapy occurred more frequently in nonsurvivors. This group more frequently required repeat laparotomy, and the duration of mechanical ventilation in the ICU was

**Table 5. Independent Risk Factors Associated With ICU Mortality in Patients With *Candida* Peritonitis\***

Variable	$\beta$ (SD)†	Odds Ratio (95% CI)	P Value
APACHE II score >17	3.35 (0.82)	28.4 (5.7-142.5)	<.001
Respiratory failure	2.36 (0.80)	10.6 (2.2-51.2)	.003
Upper gastrointestinal tract origin	2.05 (0.76)	7.8 (1.7-34.7)	.007
Results of DE positive for <i>Candida</i>	1.56 (0.73)	4.7 (1.2-19.7)	.02
Constant	-3.79 (0.91)	...	<.001

\*Determined using model  $\chi^2_4 = 48.97$ ;  $P < .001$ . The correlation matrix did not demonstrate collinearity between variables. CI indicates confidence interval. Other abbreviations are explained in the first footnotes to Tables 1 and 4.

†Regression coefficient of the parameter in the logistic regression model.

**Table 6. Comparison of Patients According to the Results of Direct Examination of Peritoneal Fluid for *Candida*\***

	Direct Examination Results		P Value
	Positive (n = 30)	Negative (n = 53)	
Age, mean $\pm$ SD, y	68 $\pm$ 16	62 $\pm$ 17	.11
Female	22 (73)	30 (57)	.13
SAPS II, mean $\pm$ SD	46 $\pm$ 16	44 $\pm$ 17	.59
APACHE II score, mean $\pm$ SD	20 $\pm$ 7	18 $\pm$ 7	.24
Upper gastrointestinal tract origin	17 (57)	15 (28)	.01
Postoperative peritonitis	19 (63)	34 (64)	.94
Perioperative candidemia	4 (13)	1 (2)	.05
Repeat laparotomy	21 (70)	23 (43)	.02
Duration of MV for survivors, mean $\pm$ SD, d	15 $\pm$ 13	11 $\pm$ 10	.47
ICU length of stay for survivors, mean $\pm$ SD, d	22 $\pm$ 16	16 $\pm$ 13	.32
ICU mortality	22 (73)	21 (40)	.003

\*Unless otherwise indicated, data are expressed as number (percentages) of patients. Abbreviations are explained in the first footnotes to Tables 1 and 4.

longer than in survivors. Antifungal treatment consisted of fluconazole for empirical treatment (28/31 [90%]) and definitive treatment (57/67 [85%]) in the same proportion in both groups. Conventional amphotericin B was used in the other cases. No difference was observed in the numbers of patients receiving empirical and definitive antifungal treatment between survivors and nonsurvivors.

The following variables were entered in the multivariate analysis model: age of 64 years or older, APACHE II score of at least 17, SAPS II of at least 44, OSF score of at least 2, respiratory failure, cardiovascular failure, upper gastrointestinal tract origin of peritonitis, inappropriate empirical antimicrobial therapy, repeat laparotomy, and results of direct examination positive for *Candida*. The following 4 factors were found to be independently associated with death in *Candida* peritonitis (**Table 5**): APACHE II score of at least 17, respiratory failure, upper gastrointestinal tract origin of peritonitis,

and results of direct examination of peritoneal fluid positive for *Candida*.

Finally, comparison of the patients in whom a direct examination yielded positive findings for *Candida* and those with negative findings is summarized in **Table 6**. Patients with a positive finding for *Candida* had similar severity scores, but more frequently presented with an upper gastrointestinal tract origin of peritonitis and a higher rate of perioperative candidemia and more frequently required repeat laparotomy. A trend toward a higher number of bacterial isolates in the group with direct examination findings that were negative for *Candida* compared with the group with positive findings was observed ( $2.2 \pm 1.8$  vs  $2.1 \pm 1.6$  bacterial isolates;  $P = .06$ ).

## COMMENT

This study was performed in a large number of critically ill patients with abdominal candidiasis. The main original finding is the following 4 factors that were found to be independently associated with mortality in patients with *Candida* peritonitis: APACHE II score of at least 17, respiratory failure on admission, upper gastrointestinal tract origin of peritonitis, and findings of a direct examination of peritoneal fluid that were positive for *Candida*.

The retrospective design of the study may have influenced our results, although the patients were consecutively included in a prospective ICU database. However, it has been recently suggested that the results of observational studies do not systematically overestimate the magnitude of the effects of treatment compared with those of randomized, controlled trials on the same topic.<sup>17</sup> Basically, during the 5-year survey, the same surgical and ICU teams cared for the patients. However, the quantification of peritoneal lavage could not be performed in the design of this study. Mortality rates reported by previous studies focusing on fungal peritonitis ranged from 25% to 70% according to the definitions of peritoneal infection.<sup>5,6,8,9,11</sup> The mortality rate observed in the present study was consistent with that reported in those studies, as *Candida* isolation in peritoneal fluid was associated with an increased mortality in 100 patients with postoperative peritonitis (32%-61%).<sup>2</sup> Furthermore, the mortality rate in tertiary peritonitis with most *Candida* isolates has been reported to be as high as 70%.<sup>18</sup> In the present study, the lack of guidelines for initiating antifungal therapy may have biased the results on mortality rates in the 2 subpopulations if those patients who survived had been more frequently treated with fluconazole than nonsurvivors. This is very unlikely, as these rates did not differ between survivors and nonsurvivors. Furthermore, a higher proportion of patients received antifungal treatment than that recommended by recently published guidelines.<sup>7</sup> An argument can be made for the low rate of amphotericin B use. However, none of the strains of yeast isolated was resistant to fluconazole in this study. The lack of a control group without antifungal treatment may be of importance to compare mortality rates in *Candida* peritonitis, but this comparison was not possible in this retrospective study because a high proportion of patients were treated. Finally, the

technique used for direct examination should be discussed. None of the direct examination methods used for *Candida* detection has been standardized. As with all other direct stains, the sensitivity of detection is limited by the amount of material that can be reviewed on a slide, and, when only a small number of organisms are present, they may not be seen. However, this could explain a possible relationship between the magnitude of the inoculum and the rate of positive findings for *Candida* on direct examinations. All patients with candidemia died in this study, despite adequate antifungal treatment with fluconazole (all of the strains were *C. albicans*). Amphotericin B was not used for treatment because no evidence has been found in the literature that amphotericin B is better than fluconazole for the treatment of candidemia.<sup>19-22</sup>

The APACHE II score, the strongest variable associated with mortality in yeast peritonitis, has been used and validated in large surgical cohorts, especially for intra-abdominal infections.<sup>2,23-28</sup> A cutoff score of greater than 15 has been proposed to differentiate patients with a high risk for mortality from those with a low risk.<sup>24</sup> This value is similar to the cutoff of greater than 17 used in this study. Three studies focusing on predictive factors of mortality in peritonitis found the APACHE II score to be independently associated with mortality,<sup>2,27,29</sup> but none of these studies specifically focused on yeast peritonitis. The SAPS II was not independently associated with mortality when compared with the APACHE II score in this study. This could be related to the lower power of the SAPS II to predict mortality in patients with intra-abdominal infections, as the SAPS II has been essentially validated in medical patients in the ICU.

Among the various forms of organ failure, only respiratory failure was independently associated with mortality in this study. It has been suggested that respiratory failure alone does not necessarily indicate a poor prognosis, as the effects of respiratory failure can be compensated by the use of mechanical ventilation.<sup>24</sup> However, in the study by Koperna and Schulz,<sup>24</sup> only 4 patients (4%) presented with respiratory failure compared with 28% in this study. A recent study has shown that respiratory failure was the main organ failure associated with mortality in peritonitis.<sup>30</sup> Respiratory failure does not predispose to prolonged ICU and total hospital stays.<sup>30</sup> Septic shock is usually reported to be the main predictor of mortality in critically ill patients with peritonitis.<sup>2,25</sup> We found a high rate of cardiovascular failure (69%) in both groups in our study, which could minimize differences in mortality rates. This high rate of septic shock has not been reported in other series focusing on yeast peritonitis, probably because of the particularly high severity scores of our patients in comparison with those of previous studies. More than an isolated organ failure, the combination of several organ failures has been correlated with mortality in peritonitis.<sup>24</sup> Renal failure requiring dialysis is reported to be a major organ failure associated with mortality in peritonitis in general<sup>24</sup> and yeast peritonitis in particular,<sup>11</sup> but this correlation was not found in this study.

The upper gastrointestinal tract origin of peritonitis was the third factor independently associated with mortality in this study. This finding has been previously suggested in several studies, including cases of severe

peritonitis,<sup>23,25</sup> but not in all studies.<sup>26,27</sup> This factor could be explained by the large rate of postoperative peritonitis (64%) in our population. In these surgical settings, it is difficult to eradicate the source of sepsis in patients with leaking upper gastrointestinal tract anastomoses (similar to colonic resection and exteriorization), which may explain why their survival rate remains poor.<sup>25</sup> The impact of upper gastrointestinal tract perforation on mortality in the population with *Candida* peritonitis has never been previously addressed. The study that included the greatest number of patients (n=56) had the highest mortality rate (70%),<sup>11</sup> which could explain why no difference in mortality was observed between the upper and lower gastrointestinal tract origins of peritonitis.

Positive findings for *Candida* in the direct examination of peritoneal fluid was the last independent predictive factor of mortality in this study. The difference between infection and colonization when *Candida* is present in the peritoneal fluid is still a subject of controversy.<sup>4,7,31</sup> Quantification of *Candida* in the peritoneal fluid has been proposed as a tool to differentiate infection from colonization during peritonitis.<sup>6</sup> In a prospective study of 49 patients, moderate and heavy growths of *Candida* in peritoneal fluid were more frequently observed in the infection group (53%), compared with low growth in the colonization group (13%). However, a major flaw of that study was the inclusion of 90% of patients with pancreatitis in the infection group vs only 10% in the colonization group, as *Candida* has been reported to be one of the major pathogens isolated from infected pancreatitis.<sup>32</sup> Moreover, in the study by Calandra et al,<sup>6</sup> *Candida* was cultured from an intraoperative specimen in only 57% of patients. Another approach to quantification of the inoculum is the presence of *Candida* on direct examination of peritoneal fluid.<sup>33</sup> The presence of *Candida* on direct examination of peritoneal fluid may reflect the magnitude of the *Candida* inoculum, as we found that positive direct examination was independently associated with mortality. A limitation of direct examination could be the difficulty of identifying *Candida*. The difference in the rate of positive results found by trained microbiologists or mycologists compared with results of routine on-duty direct examination remains to be evaluated. Candidemia rates ranged from 0% to 32% during *Candida* intra-abdominal infections.<sup>5,6,8,11</sup> We found a 6% rate in our study, which was significantly associated with mortality on univariate analysis. Furthermore, 4 (80%) of 5 patients with candidemia had positive findings for *Candida* on a direct examination of peritoneal fluid. An upper gastrointestinal tract origin of peritonitis has been associated with yeast isolation in a few studies, particularly for the biliary tract, which was the leading origin of peritonitis in this study.<sup>34,35</sup> These 2 studies emphasized the high rate of candidemia and mortality associated with biliary tract infection. These results are in accordance with our findings. Treated or perforated peptic ulcers have also been associated with yeast isolation rates of 9% to 75%.<sup>36,37</sup> This rate could be related to modification of pH by antacid treatment of the ulcer.<sup>38</sup> In the present study, patients with direct examination of peritoneal fluid positive for *Candida* also presented with the highest rate of repeat laparotomy. Similarly, the in-

creased ICU mortality observed in the group with *Candida*-positive findings on direct examination could not be explained by differences in severity scores such as SAPS II or APACHE II score that were equivalent in the 2 groups in this study, as mortality predicted by the SAPS II did not differ from the mortality observed in the group of patients with negative findings on direct examination (33% vs 39%; 95% CI, 26%-52%), but it was significantly higher in the group with *Candida*-positive findings on direct examination (37% vs 73%; 95% CI, 57%-89%). These findings suggest the impact of the positive findings on the prognosis of *Candida* peritonitis.

## CONCLUSIONS

The following 4 factors were independently associated with mortality due to *Candida* peritonitis: APACHE II score and respiratory failure, which indicate severity on admission to the ICU; upper gastrointestinal tract origin of peritonitis; and results of direct examination of peritoneal fluid that are positive for *Candida*. Although the pathogenicity of *Candida* was not investigated, our data suggest that the magnitude of the *Candida* inoculum is associated with mortality. This study raises the question concerning early antifungal treatment when direct examination of peritoneal fluid is positive vs delayed treatment when cultures are positive. This question needs to be validated in prospective controlled trials.

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