# Analysis of variables predictive of severity in biliary peritonitis



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OBJECTIVE: To analyze clinical and laboratory findings in order to find variables predictive of severity of Biliary Peritonitis (BP). METHODS: Physical findings, course of illness, imaging and laboratory data were evaluated in 22 patients with BP, and statistically analysed to assess their prognostic significance.

RESULTS: Serious illness and worse outcome were associated with: age > 60 years (P=0.034), long time between onset of symptoms and treatment (P=0.025), fever > 38°C (P=0.009), WBC count > 17.000 cell/mm<sup>3</sup> (P=0.043), diffuse abdominal pain (P=0.034), and infected bile (P=0.048).

CONCLUSIONS: Most patients become severely ill due to supervening infection, while early bile drainage avoids serious complications. In addition, abdominal pain, fever and WBC count are also predictive of severity of BP.

KEY WORDS: Abdominal pain, Bile drainage, Biliary peritonitis, Infected bile, Severity prognosis

## Introduction

The term "Biliary Peritonitis" (BP) includes a wide spectrum of different clinical situations.

Clinical experience and previous researches have not shown any relationship between early onset of clinical findings and prognosis, therefore it is difficult to identify clinical signs predictive of the severity of prognosis of BP <sup>1,2</sup> In fact, a number of patients who become severely ill never show any obvious abdominal sign(s) <sup>3</sup>. Peritoneal signs alone are not reliable to predict severity and outcome of BP due to delay of their onset, which contributes to increase both mortality (8-40%) and morbidity (20-30%) <sup>4-6</sup>. Purpose of the present study was

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to retrospectively perform a statistical analysis of demographic, clinical, and laboratory findings in a cohort of patients with BP, in order to identify any possible factors predictive of severity and of a poor prognosis.

## Material and Methods

One thousand two hundred and forty four patients with acute peritonitis were admitted to the Department of Surgery "P. Valdoni", University of Rome "Sapienza" Medical School, Rome, Italy, between January 1990 and December 2004. Of these, 22 patients (1.8%) had BP and their medical records were reviewed.

All cases of bile collection in the abdominal cavity were classified as BP. Diagnosis was based on medical history and clinical findings supported by US evidence of abdominal fluid collection.

The reviewed variables included demography, pre- and post-operative physical signs and symptoms, and laboratory results (hematology, diagnostic imaging, pathology and microbiology).

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Therefore, we considered: age; gender; time between onset of symptoms and drainage; abdominal pain (diffuse or localized); occurrence of nausea, vomiting, jaundice; peritoneal signs (abdominal tenderness and rebound); fever; WBC count; serum level of bilirubin (total and conjugated), ALP; volume of bile collection, and bile microbiology analysis.

Data recorded were evaluated at the admission of patients to the hospital.

Treatment strategies, length of hospital stay, morbidity and mortality rates were also evaluated.

All patients received intravenous fluids, analgesics and antibiotics; nasogastric decompression was routinely employed.

Drainage of abdominal bile collection was the first step in the management of these patients. Subsequently, the underlying cause for bile leakage was sought in each case and tailored different therapeutic measures. Surgery was performed on 17 patients (77.3%), and interventional radiology techniques in 5 (22.7%). Patients were divided in two groups: group A (patients with BP, but no serious complications and a benign outcome), group B (patients with BP, who had a severe progression of the condition and eventually died).

#### Statistical analysis

Variables were submitted to univariate analysis to evaluate the prognostic relevance of collated data.

Data in the records regarding laboratory findings, age and fever were compiled using continue and class values.

The results are presented as means with standard deviation (SD) for normally distributed data, or medians with percentiles for non-normal distributions. Differences between groups were assessed by two-sided unpaired and paired t-test as appropriate for continuous data, and by analysis of frequency distribution (c<sup>2</sup> statistics) for categorical data.

Statistical analysis was performed using SPSS 9 statistical software and a probability value of less than 0.05 was considered significant.

# Results

Seventeen patients were assigned to group A, 5 to group B.

Overall mortality was 5 patients (22.7%) and morbidity 6 (27.3%).

In our experience, BP followed acute cholecystitis in 12 cases (54.5%), hepatobiliary surgery in 7 cases (31.8%), and abdominal trauma in 3 cases (13.6%) (Table I).

Mean overall age of the studied population was 62 years (range=19/82 years); 10 of these were males and 12 females. Thirteen patients (59.1%) were over 60 years.

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TABLE I - Causes of BP in the studied population.

## Patients Etiology of BP

1. L_A	Perforation of calculous gallbladder
2. C_S	Post-cholecystectomy injury
3. M_S	Liver Trauma
4. V_F	Acute cholecystitis with empiema
5. L_D	Perforation of calculous gallbladder
6. M_C	Perforation of biliary system due to liver neoplasia
7. G_B	Perforation of calculous gallbladder and gallstone ileus
8. D_V	Acute calculous cholecystitis
9. N_D	Acute acalculous cholecystitis
10. C_T	Perforation of calculous gallbladder
11. B_D	Traumatic injury of gallbladder and liver
12. B_B	Post-cholecystectomy injury
13. L_D	Perforation of calculous gallbladder
14. Q_R	Perforation of calculous gallbladder
15. R_T	Right liver resection
16. G_T	Post-cholecystectomy injury
17. S_Z	Liver trauma
18. F_L	Post-embolization of liver lesion
19. D_M	Post-cholecystectomy injury
20. G_A	Perforation of calculous gallbladder
21. D_D	Post-cholecystectomy injury
22. A_C	Perforation of calculous gallbladder

Time between onset of symptoms and drainage ranged from 2 to 17 days (mean=7 days); length of hospital stay ranged between 7-70 days (mean=24 days).

Statistical relevance and differences by groups for these variables are reported in Table II.

Diffuse abdominal pain was present in 8/17 cases (47.1%) of group A and in 5/5 cases (100%) of group B (P=0.034); 9/17 cases of group A (52.9%) vs no patients of group B reported abdominal pain localized to the right upper quadrant (RUQ) (P=n. s.). Nausea and vomiting were detected in 7 (41.2%) and in 6 (35.3%) patients of group A, and in 4 (80.0%) and 3 (60.0%) individuals of group B (P=n. s.). No statistical differences in peritoneal signs (e.g. abdominal tenderness, rebound, etc.) were noted in group A compared to group B (group A= 4/17 or 23.5% patients vs group B=2/5 or 40.0%; P=n. s.). Jaundice was recorded in 29.4 % in group A (5/17 patients), and in 40.0% of group B (2/5) (P=n. s.) (Table III). Fever, ranging from 37 to 39.5 °C (mean=37.8 °C), was overall recorded in 77.3%, and a temperature >38 °C was detected in 17.6% of patients of group A (3/17 patients) and in 80% of patients of group B (4/5 patients)(P=0.009).

Mean serum levels of ALP was 272 U/L, bilirubin (total and conjugated) 2.05 mg/dl and 1.10 mg/dl respectively. Mean overall WBC count was 16,420 cells/mm<sup>3</sup> (range 8,520-34,200 cells/mm<sup>3</sup>); WBC>17,000 cell/mm<sup>3</sup> was found in 9 cases belonging to both groups.

No statistical differences were observed with regard to ALP and bilirubin levels (P=n.s.), while WBC count >17,000 cell/mm<sup>3</sup> was found in 29.4% of group A and 80% of group B (P=0.043) (Table IV)

	Group A (No.=17)	Group B (No.=5)	Р
Age, mean ± SD ( years ) Age > 60 years, % (No.) Gender: Male, % (No.)	$58 \pm 20$ 47.1 (8) 35.3 (6) 64.7 (11)	$74 \pm 8$ 100 (5) 80.0 (4) 20.0 (1)	n.s. 0.034 n.s.
Time between onset of symptoms and drainage ± SD (days)	4 ± 2	12 ± 5	0.025

TABLE II - Demographic characteristics in the two study groups.

TABLE III - Clinical findings in the two groups.

	Group A (No=17)	Group B (No=5)	Р
Abdominal pain, % (No.)			
– Diffuse	47.1% (8)	100% (5)	0.034
- Localized in RUQ	52.9% (9)	0.0% (0)	n.s.
Nausea, % (No.)	41.2% (7)	80.0% (4)	n.s.
Vomiting, % (No.)	35.3% (6)	60.0% (3)	n.s.
Peritoneal signs, % (No.)	23.5% (4)	40.0% (2)	n.s.
Jaundice, % (No.)	29.4% (5)	40.0% (2)	n.s.
Fever > 38 °C, % (No.)	17.6 % (3)	80.0% (4)	0.009

TABLE IV - Laboratory values in the two study groups

	Group A (No.=17)	Group B (No.=5)	Р	
WBC, mean $\pm$ SD (x10 <sup>3</sup> cells/mm <sup>3</sup> )	15.2 ± 6.2	20.3 ± 5.1	n.s.	
WBC > 17000 cells/mm <sup>3</sup> , % (No.)	29.4%(5)	80.0% (4)	0.043	
Tot. Bilirubin, mean ± SD (mg/dl)	$2.14 \pm 2.06$	$1.71 \pm 0.60$	n.s.	
Conj. Bilirubin, mean ± SD (mg/dl)	$1.17 \pm 1.64$	$0.90 \pm 0.037$	n.s.	
ALP, mean $\pm$ SD (U/L)	231.8 ± 111.7	435.5 ± 150.6	n.s.	
Bile volume, mean ± SD (ml)	1680 ± 899	785 ± 500	n.s.	
Infected bile, % (No.)	52.9%(9)	100% (5)	0.048	

Bile volume ricovered at laparotomy in the 17 patients who received surgery ranged between 500 and 3,000 ml (mean=1,200 ml). Microbiology analysis of bile collection drained showed an overall infection rate of 63.6%. Enterococcus Faecalis (33%) and Escherichia Coli (29%) were the bacteria most frequently detected.

Infected bile was observed in 9/17 cases of group A and in 5/5 cases of group B (P=0.048); no significant differences of bile volumes were found in the two groups (P=n.s.) (Table I).

## Discussion

Collection of bile in the peritoneal cavity is unusual, representing only 2% of all peritonitis <sup>7-9</sup>, and it can be related to a number of causes, such as: acute cholecystitis (33-65%), abdominal trauma (16-33%), complications of abdominal surgery (23-41%) (cholecystectomy 60-79%, hepatic resections, 3.5–12%, liver transplantations, 7-13%) <sup>5,10-17</sup>. With regard to acute cholecystitis, free perforation is found only in 1-2% of patients, quite commonly early in the condition when gangrene develops before adhesions seal the gallbladder. Preoperative diagnosis is achieved in less than 50% of such cases <sup>18</sup>. The above reported inconsistent rates mainly depend on different definitions of BP given by different Authors. Some consider BP only those cases with collection of infected bile in the abdomen, and severe peritoneal signs and symptoms <sup>3,5,19</sup>, defining "bile ascites" the presence of bile in the abdomen. Other authors define as BP all abdominal bile collections, regardless of whether this is infected or not, or if there are peritoneal signs, as even sterile bile causes an inflammatory reaction on the peritoneal lining, with damage of the mesothelium and of the capillary endothelium <sup>4,20</sup>. Therefore, in the present study, we defined as BP all bile collections in the abdominal cavity.

In our series, peritoneal signs could be found only in 27.3% of cases, while abdominal pain, nausea and vomiting were common occurrences. As suggested by previous researches <sup>2,21,22</sup>. we noted that the presence of bile does not necessarily produce a clear clinical picture, and most patients with BP initially complain only of mild, vague, and non-specific abdominal symptoms. In these instances, bile collection remains unsuspected with delay in diagnosis, failure of treatment, and poor outcome. In contrast, only few patients with signs of peritonitis become critically ill and develop serious complications. Therefore, it is difficult to reliably predict the course of BP and to establish the outcome of these patients.

Our research confirmed that advanced age (> 60 years) is one of the main risk factors. Tokunaga <sup>23</sup>. reported that advanced age is related to septic complications, gangrenous changes and positive bile cultures. Medical conditions (e.g. diabetes mellitus, vascular or renal failure and immunodeficiency) common in elderly people contribute to promote sepsis.

Other studies 20-25 showed that morbidity and mortality increase in patients with diffuse abdominal pain, fever >38 °C and WBC count >18,000 cell/mm<sup>3</sup>. Even if these figures do not permit to achieve early diagnosis of BP, our study suggests that they are useful indexes to evaluate step by step the course of disease more than other laboratory findings, such as bilirubine and ALP <sup>24,25</sup>. Evidence shown that most patients become severely ill due to supervening infection, and length of time that bile remains in the abdomen is associated to a poorer prognosis. In our research, delayed drainage of bile was associated with higher incidence of severe illness, as normally sterile bile in the abdominal cavity eventually becomes infected with positive cultures <sup>26</sup>. Researches carried out on animals have shown: 1) bile salts constitute the toxic component of bile, 2) large amounts of bile in the abdomen can be rapidly lethal, and 3) mortality is greater if the bile is infected 27. Therefore, patients who initially do not show infected bile should nonetheless be promptly treated, as they would ultimately develop a timerelated septic process.

In conclusion, we recommended high index of suspicion for all patients in whom a BP could be justified, especially with advanced age (>60 years), and even in presence of mild clinical signs, as absence of peritonitis is common but does not imply a less severe disease. Early use of diagnostic imaging is recommended, and as soon as collection of bile is ascertained, this should immediately be drained in order to avoid serious complications. Besides, abdominal pain, fever and WBC count represent useful indexes to follow the course of the disease and to prevent ominous complications.

#### Riassunto

Lo scopo dello studio è stato quello di analizzare dati clinici e reperti di laboratorio in grado di definire fine i individuare le variabili di previsione prognostica grave della peritonite biliare.

Su 22 pazienti affetti da peritonite biliare sono stati valutati i reperti fisici, l'evoluzione della malattia, i referti di imaging ed i dati di laboratorio, analizzandoli statisticamente per definire il loro significato prognostico.

La gravità della malattia e l'evoluzione peggiore sono risultati associati con l'età > 60 anni (P=0.034), la lunghezza dell'intervallo tra l'inizio dei sintomi ed il trattamento (P=0.025), la temperatura febbrile >  $38^{\circ}$ C (P=0.009), la conta dei globuli bianchi >  $17.000 / \text{mm}^3$ (P=0,043), il dolore addominale diffuso (P=0.034) e la bile infetta (P=0.048).

La maggior parte dei pazienti si aggrava per sopravvenute superinfezioni, mentre il precoce drenaggio della bile evita complicazioni gravi. Inoltre il dolore addominale, la febbre e la conta die globuli bianchi sono altrettanti elementi di gravità della peritonite biliare.

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