Renal Failure and Bacterial Infections in Patients with Cirrhosis: Epidemiology and Clinical Features

Silvano Fasolato,[1] Paolo Angeli,[1] Lucia Dallagnese,[1] Giulio Maresio,[1] Erika Zola,[1] Elena Mazza,[1] Freddy Salinas,[2] Silvio Donà,[3] Stefano Fagiuoli,[2] Antonietta Sticca,[1] Giacomo Zanus,[2] Umberto Cillo,[2] Ilaria Frasson,[1] Carla Destro,[4] and Angelo Gatta[1]

The aim of the study was to investigate the prevalence and clinical course of renal failure that was induced by the various types of bacterial infections in patients with cirrhosis and ascites. Three hundred and nine patients, who were consecutively admitted to the 3 major hospitals of Padova, Italy, during the first 6 months of 2005, were studied prospectively. Of these, 233 patients (75.4%) had evidence of ascites. In 104 patients with cirrhosis and ascites (44.6%) a bacterial infection was diagnosed. A bacterial infection-induced renal failure was observed in 35 of 104 patients (33.6%). The prevalence of renal failure was higher in biliary or gastrointestinal tract infections and in spontaneous bacterial peritonitis (SBP) and in than in other types of infections. In addition, the progressive form of renal failure was only precipitated by biliary or gastrointestinal tract infections, SBP, and urinary tract infections (UTI). In a multivariate analysis only MELD score ($P = 0.001$), the peak count of neutrophil leukocyte in blood ($P = 0.04$), and the lack of resolution of infection ($P = 0.03$) had an independent predictive value on the occurrence of renal failure. _Conclusion:_ The results of the study show that the development of bacterial-induced renal failure in patients with cirrhosis and ascites is related to the MELD score, and to both the severity and the lack of resolution of the infection. A progressive form of renal failure occurs only as a consequence of biliary or gastrointestinal tract infections, SBP, and UTI. (HEPATOLOGY 2007;45:223-229.)

Bacterial infection represents one of the most frequent complications in patients with cirrhosis and ascites, as a result of multiple abnormalities in the defensive mechanisms against bacteria.[1-4] Previous studies have revealed that the most common bacterial infections in patients with cirrhosis are urinary tract infections (UTI), pneumonia, and spontaneous bacterial peritonitis (SBP).[5-8] In spite of this order of prevalence, the role of bacterial infections in the pathogenesis of renal failure has been assessed mainly in patients with SBP.[9-11] Follo et al.

estimated that approximately one-third of patients with SBP develop renal failure despite the resolution of the infection.[9] This figure has been confirmed in other studies.[10,11] In most patients, SBP-induced renal failure follows a rapidly progressive course and meets all the criteria for the diagnosis of type 1 hepatorenal syndrome (HRS).[11] SBP-induced renal failure is associated with an in-hospital mortality rate ranging from 40%-78%.[10,11]

The pathogenesis of SBP-induced renal failure is related to the worsening of the circulatory dysfunction that characterizes cirrhosis with ascites.[12] In patients with cirrhosis and ascites, there is a marked reduction of effective circulating volume due to splanchnic arterial vasodilation.[13-16] The occurrence of renal failure in patients with SBP is associated with a further reduction of the effective circulating volume which is due to a further reduction of the resistance in the splanchnic circulation and to a fall in cardiac output.[12] This occurs in the context of further increased serum levels of cytokines (TNFα, interleukin-6) of nitric oxide and other endogenous vasodilators.[14-16]

Because the release of cytokines and vasodilators is a well-known feature of all bacterial infections and not only of SBP, it may be hypothesized that renal failure in pa-

tients with cirrhosis and ascites may be induced also by bacterial infections other than SBP.[17,18]

Up to now, the occurrence of renal failure in patients with cirrhosis and bacterial infections other than SBP has been investigated in only 1 study. This study showed that renal failure developed in 29 of 106 patients, with cirrhosis and sepsis (27%) being reversible in 22 of them (78%). In 6 of 7 patients with the nonreversible form of renal failure, sepsis was not resolved by antibiotic treatment. The prevalence of renal failure according to the type of infection was as follows: culture-negative sepsis (66%), spontaneous bacteremia (45%), cellulitis (35%), pneumonia (29%), UTI (10%), and others (18%).[19] We did not take the relationship between the progressive type of renal failure and the type of bacterial infection into consideration.[19] Therefore, the aim of the study was to investigate the prevalence and the clinical course of renal failure which was induced by the various types of bacterial infections in patients with cirrhosis and ascites.

Patients and Methods

Patient Population. All patients with cirrhosis admitted to the units of all 3 major hospitals in Padova between January 2005 and June 2005 were included in the study and evaluated prospectively. The study was approved by the local institutional ethical committee, and informed consent was obtained by all the participants. The diagnosis of cirrhosis based on clinical and/or histological findings was considered reliable in 357 of the 392 patients who were admitted to the hospitals during this time. Moreover, 48 of 357 patients were excluded because they had suffered a recurrence of cirrhosis after liver orthotopic liver transplantation.

Seventy-six of the 309 (24.6%) patients who were included in the study had no evidence of ascites at admission and had no previous history of ascites or use of diuretics. Conversely, 233 patients (75.4%) showed evidence of ascites at admission.

Clinical Management. The clinical suspicion of bacterial infection included the following: symptoms and signs of infection; neutrophil leukocytosis defined by a neutrophil count in blood $>7.8 \times 10^9$/L, and leukocyturia and bacteriuria.

The diagnosis of bacterial infection was then confirmed by the following: (1) chest X-ray and/or CT indicative of pulmonary infiltrate; (2) ultrasonography and/or CT scan of the abdomen indicative of gallbladder wall inflammation; (3) count of polymorph nuclear leukocytes and culture of ascites; (4) urine and blood cultures; (5) cultures of other organic fluid or secretions when clinically indicated; (6) skin swab.

Then antibiotic therapy was administered in all patients with bacterial infection on an empirical basis as follows: (1) community-acquired pneumonia: a third-generation cephalosporin or amoxicillin clavulanic acid plus azithromycin;[20] (2) nosocomial pneumonia: a third-generation cephalosporin plus quinolone (levofloxacin or ciprofloxacin);[21,22] (3) spontaneous bacterial peritonitis: quinolone (in patients who were not on prophylaxis with norfloxacin) or third-generation cephalosporin (in patients who were on prophylaxis with norfloxacin);[11,23] (4) urinary tract infections (quinolone or third-generation cephalosporin);[24] (5) biliary or gastrointestinal tract infection (third-generation cephalosporin or piperacillin-tazobactam); (6) cellulitis (amoxicillin and clavulanic acid); and (7) no evidence of source of infections (third-generation cephalosporin).[25] The empiric antibiotic treatment was modified on the basis of the results of cultures and antibiotic susceptibility "in vitro". In patients with no improvement of clinical and laboratory signs of infection nor positive bacterial cultures the antibiotic treatment was changed after 48-72 hours on an empirical basis. In most of these patients imipemen or meropemen plus teicoplanin were used. During the period of treatment the antibiotic dosage was always adjusted according to the parameters of renal function. Patients were given intravenous fluid (dextrose 5% and/or saline) in order to maintain an adequate hydration status. In patients with cirrhosis and ascites, diuretics were withdrawn at diagnosis of bacterial infection. Prophylactic albumin was not given in patients with SBP to prevent renal failure.

Renal function was assessed by measuring serum creatinine and blood urea nitrogen (BUN) at admission and throughout the hospital stay. In patients with renal failure before the development of the bacterial infection the presence of parenchymal renal disease was ruled out by means of clinical history, measurement of urine protein, and renal ultrasound examination. In patients who had developed renal failure after the diagnosis of bacterial infection, further causes of impairment of renal function were carefully excluded.

Definitions. The types of infections were defined according to the following standard criteria: Pneumonia was diagnosed in the presence of infiltrates on chest x-ray with concurrent fever, cough, and neutrophil leukocytosis; spontaneous bacterial peritonitis was diagnosed in the presence of a neutrophil leukocyte count in the ascitic fluid >250 cells/mm^3 without any evidence of surgically treatable sources of infections; urinary tract infection was diagnosed when fever and urinary symptoms were associated with bacteriuria, leukocyturia, and positive urine culture; biliary tract infections were diagnosed in the presence of fever and/or abdominal pain, neutrophilic

Table 1. Types of Bacterial Infections in Cirrhotic Patients without and with Ascites

Type of Infections	Patients with Cirrhosis Without Ascites (n = 13)	Patients with Cirrhosis and Ascites (n = 104)
Pneumonia	4 (30.7%)	25 (24.0%)
Urinary tract infections	6 (46.2%)	44 (42.3%)
Spontaneous bacterial peritonitis	–	17 (16.3%)
Biliary tract or gastrointestinal tract infections	–	3 (2.9%)
Skin infections	1 (7.7%)	5 (4.8%)
Culture negative bacterial infections	1 (7.7%)	4 (3.8%)
Spontaneous bacteremia	1 (7.7%)	6 (5.8%)

leukocytosis and a compatible ultrasonographic or CT picture; gastrointestinal tract infection was diagnosed when vomiting, diarrhea, fever, and abdominal pain were associated with neutrophilic leukocytosis and positive stool culture; skin infection was diagnosed when fever and cellulitis were associated with neutrophilic leukocytosis; spontaneous bacteremia was defined in the presence of a positive blood culture without evident source of infection; and culture-negative bacterial infection was defined by the presence of fever, neutrophilic leukocytosis, and negative blood culture without evident source of infection.

The presence of systemic inflammatory response syndrome (SIRS) in patients with cirrhosis and bacterial infections was defined according to the criteria of the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference Committee.[26]

Bacterial infections were considered solved by the antibiotic treatment when all clinical signs of infection had disappeared, combined with the normalization of laboratory and radiological findings, and the disappearance of positive microbiological findings.

According to Terra et al.[19] renal failure was defined when serum creatinine and/or BUN are greater than 1.5 mg/dL and 30 mg/dL, respectively. Because no information about serum creatinine and BUN was available prior to hospital admission, renal failure was considered as being related to the bacterial infection when: (1) renal failure appeared after the diagnosis of infection; (2) a preexistent renal failure significantly worsened after the diagnosis of infection (implying an increase of more than 50% of the preinfection value of serum creatinine and/or BUN). Renal failure related to bacterial infection is also classified into 3 types: "reversible", when serum creatinine and BUN were back to normal range during hospitalization; "steady", when the impairment of renal function stabilized during hospitalization and "progressive", when serum creatinine and BUN progressively increased during hospitalization.

Statistical Analysis. Comparisons between groups were performed using the Chi-square test or Fischer's exact test for categorical data. Comparison between 2 groups was performed by Student t test for continuous data. Comparison between more than 2 groups was performed with ANOVA. Then, a post hoc analysis was performed by means of the test of Scheffè. Univariate analysis was used to identify factors predicting in-hospital mortality and the development of bacterial infection induced renal failure. Variables reaching statistical significance in univariate analysis were subsequently included in multivariate analysis by stepwise logistic regression in order to identify independent predictors of the endpoint. Then, the survival functions were plotted according to the median value of the independent predictor variables. Statistical analyses were performed using the Statistica 6.1 software (Copyright Stat Soft Inc., 1984-2004, Tulsa, OK). P values lower than 0.05 were considered significant.

Results

Characteristics of Patients. A bacterial infection was diagnosed in 104 of 233 (44.6%) patients with cirrhosis and ascites and in 13 of 76 (17.1 %) patients without ascites, respectively ($P < 0.0001$).

The types of bacterial infections in both groups of patients are shown in Table 1. In 6 of 13 (46.1%) patients without ascites and in 60 of 104 (57.7%) patients with ascites the diagnosis of bacterial infection was confirmed by a positive culture. Table 2 shows the features and aetiology of the different types of bacterial infections in patients with cirrhosis and ascites. Demographic and baseline clinical and laboratory features at admission in patients with cirrhosis and ascites without bacterial infection (Group 1), and in patients with cirrhosis, ascites and bacterial infection (Group 2) are shown in Table 3. Looking at the prevalence of bacterial infections in patients with cirrhosis and ascites according to gender, UTI were

Table 2. Characteristics of Bacterial Infections in Patients with Cirrhosis and Ascites

Type of Infection	Community/ Nosocomial Acquired Infection	Cultures+/ Cultures−	Gram+/ Gram−
Pneumonia	18/6	4/21	2/2
Urinary tract infections	26/18	40/4	10/30
Spontaneous bacterial peritonitis	14/3	7/10	3/4
Biliary or gastrointestinal tract infections	1/2	2/1	2/0
Skin	4/1	1/4	0/1
Culture negative bacterial infection	2/2	0/4	0/0
Spontaneous bacteremia	2/4	6/0	4/2

Table 3. Demographic, Clinical, and Biochemical Characteristics of Patients with Cirrhosis and Ascites with and without Infections at Admission

Parameter	With Infections ($n = 104$)	Without Infections ($n = 129$)	P Value
Age (years)	65.9 ± 1.4	62.9 ± 1.0	NS
Sex (male/female)	53/51	97/32	<0.00025
Etiology			
Alcohol	39	40	NS
Virus	48	59	
others	17	30	
History of cirrhosis (months)	71.6 ± 7.5	75.8 ± 8.6	NS
MAP (mm Hg)	93.0 ± 2.0	98.3 ± 1.6	<0.0005
Child-Pugh score	9.7 ± 0.2	8.5 ± 0.2	<0.05
MELD score	20.1 ± 0.8	16.1 ± 0.6	<0.0001
Albumin (g/L)	27.7 ± 0.6	29.6 ± 0.8	NS
Prothrombin time (%)	47.0 ± 1.5	53.6 ± 1.2	<0.001
Bilirubin (mg/dL)	5.3 ± 0.7	4.1 ± 0.6	NS
Serum creatinine (mg/dL)	1.8 ± 0.1	1.0 ± 0.1	0.0001
BUN (mg/dL)	36.1 ± 3.4	18.6 ± 0.9	<0.001
PMN count (cells/mm^3)	4480 ± 0.3	3900 ± 0.2	NS

NOTE. Data are presented as mean $\pm$ SE. NS = not significant.

more frequent in females than in males (42.3% versus 13.3%, $P < 0.05$). At admission, the difference in the leukocyte count in blood between the 2 groups did not reach statistical significance, but that difference became statistically significant as soon as the leukocyte count in blood at the diagnosis of bacterial infection was considered (4846 $\pm$ 343 cells/mm^3 in Group 1 versus 7972 $\pm$ 719 cells/mm^3 in Group 2, $P < 0.0001$). A SIRS was diagnosed in 37.9% of patients with ascites and bacterial infection. The resolution of the infection was obtained in 95 of 104 patients of Group 2 (91.3%). In 9 of 20 (45.0 %) patients with ascites and bacterial infection who died during hospitalization, bacterial infection was not resolved by the antibiotic treatment. Finally, the mean hospital stay in Group 2 was longer than in patients of Group 1 (14.7 $\pm$ 1.1 versus 8.4 $\pm$ 1.1 days, $P < 0.0001$).

Renal Failure. Taking into account all the cases of renal failure, renal failure was observed in 3 of 13 (23.1%) patients with cirrhosis and without ascites who developed a bacterial infection and in 62 of 104 (59.6 %) patients with cirrhosis and ascites who developed a bacterial infection, respectively. The difference in the prevalence of renal failure between the 2 groups of patients was statistically significant ($P < 0.025$).

The prevalence of bacterial infection-induced renal failure, was higher in patients with cirrhosis and ascites (33.6 %) than in those without ascites (7.6%, $P < 0.05$). In 16 of 35 patients with cirrhosis and ascites renal failure developed after the diagnosis of bacterial infection. In the remaining 19 patients a preexisting renal failure worsened after the onset of bacterial infection. Table 4 shows the

clinical and laboratory characteristics of renal function in patients who developed a bacterial-induced renal failure and in patients who did not.

The prevalence of bacterial infection-induced renal failure according to the type of bacterial infection is shown in Fig. 1. The prevalence of renal failure was higher in biliary or gastrointestinal tract infections and in SBP than in the other types of infections. In addition, the progressive form of bacterial infection-induced renal failure was observed only in biliary or gastrointestinal tract infections, SBP, and UTI. Considering the types of infections which induced a progressive form of renal failure as a whole, they showed a lower mean arterial pressure (90.89 $\pm$ 2.34 mm Hg) and a trend toward a higher value of MELD[27] (21.56 $\pm$ 1.00) as compared to pneumonia (97.76 $\pm$ 2.56 mm Hg, $P < 0.05$ and 16.68 $\pm$ 1.56, $P < 0.05$, respectively) and other infections (101.66 $\pm$ 2.44 mm Hg, $P < 0.05$ and 20.06 $\pm$ 1.13, $P =$ NS). As a consequence, patients who developed a progressive form of bacterial-induced renal failure had a lower MAP than patients who developed a non progressive form of bacterial infection-induced-renal failure (80.47 $\pm$ 2.48 versus 89.68 $\pm$ 2.4 mm Hg, $P < 0.025$). The individual clinical features of patients with cirrhosis and ascites who developed a progressive form of renal failure as a consequence of UTI are reported in Table 5. Renal failure can occur in these patients in spite of the resolution of the infection. All 15 patients with cirrhosis and ascites who developed a progressive form of bacterial infection-induced renal failure were checked for the diagnosis of type 1 hepatorenal syndrome according to the criteria which were proposed by the International Ascites Club in 1996.[28] All they met the criteria for type 1 HRS. In order to identify factors

Table 4. Clinical and Laboratory Characteristics of Patients with Cirrhosis and Ascites with and without Bacterial-Induced Renal Failure

Parameter	With Renal Failure ($n = 35$)	Without Renal Failure ($n = 69$)	P Value
Age (years)	67.5 ± 2.8	65.0 ± 1.6	NS
SIRS	20/35	18/69	<0.01
MAP (mm Hg)	85.4 ± 1.9	95.9 ± 1.9	<0.0001
Child-Pugh score	10.1 ± 0.4	9.5 ± 0.3	NS
MELD score	24.4 ± 6.0	16.1 ± 0.6	<0.0001
Albumin (g/L)	27.3 ± 1.2	27.8 ± 0.7	NS
Prothrombin time (%)	47.3 ± 2.9	46.9 ± 1.7	NS
Bilirubin (mg/dL)	6.7 ± 1.4	4.4 ± 0.7	NS
Serum creatinine (mg/dL)	3.1 ± 0.3	1.1 ± 0.1	<0.0001
BUN (mg/dL)	66.9 ± 7.6	20.6 ± 1.4	<0.001
Urine sodium (mEq/day)	19.4 ± 1.3	55.5 ± 6.7	<0.0001
Proteinuria (mg/day)	190.30 ± 12.5	NE	–

NOTE. Data are presented as mean $\pm$ SE. NE = not evaluated, NS = not significant.
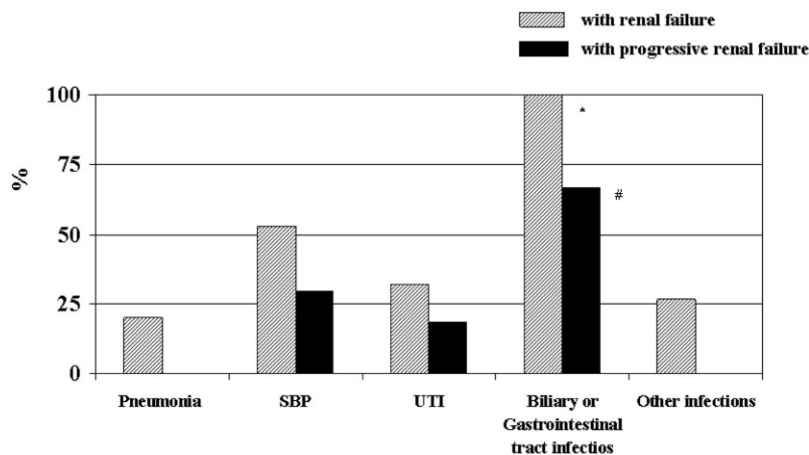
Fig. 1. Prevalence of bacterial-induced renal failure (gray bars) and of bacterial-induced progressive renal failure (black bars) in patients with cirrhosis according to the types of bacterial infections. $*P < 0.025$ (chi-square test for the distribution of bacterial infection-induced renal failure among the various types of bacterial infections.) $\#P < 0.0025$ (Chi-square test for the distribution of bacterial infection-induced progressive renal failure among the various types of bacterial infections.)

predicting bacterial infection-induced renal failure in patients with ascites and bacterial infection, variables obtained at the time of diagnosis of the infection were analyzed. In univariate analysis the variables with prognostic value were the following: MELD score ($P = 0.0003$), the peak count of neutrophil leukocyte in blood ($P = 0.001$), the presence of SIRS ($P = 0.008$), and the resolution of the bacterial infection ($P = 0.01$). In the multivariate analysis, only MELD score ($P = 0.001$), the peak count of neutrophil leukocyte in blood ($P = 0.04$), and the resolution of infection ($P = 0.03$) showed an independent prognostic value.

Mortality. Twenty of 104 (19.2%) patients with cirrhosis and ascites who developed a bacterial infection died during hospitalization. This mortality rate was higher than that observed in patients with cirrhosis and ascites without bacterial infections (10.1 %, $P < 0.05$). Causes

of death in patients with cirrhosis, ascites, and bacterial infection were renal failure in 8, gastrointestinal bleeding in 4, liver failure in 3, multiorgan failure in 3, and unknown in the remaining 2 patients. The mortality rate was higher in patients with cirrhosis and ascites who developed bacterial infection-induced renal failure than in those who did not (42.8% versus 7.24%, $P < 0.0001$).

In order to identify factors predicting mortality in patients with cirrhosis, ascites, and bacterial infection, variables obtained at the time of diagnosis of the infection were analyzed. In the univariate analysis, the variables with prognostic value were the following: MELD score ($P = 0.0006$), the presence of bacterial infection-induced renal failure ($P = 0.007$), the peak value of serum creatinine ($P = 0.004$), the peak count of neutrophil leukocyte in blood ($P = 0.002$) and the resolution of the bacterial infection ($P = 0.0001$). In the

Table 5. Individual Parameters in Patients with Cirrhosis and Ascites with Renal Failure Induced by UTI

UTI	Etiology	Clinical Symptoms	Type of Renal Failure	MELD Score	Child-Pugh Score	MAP (mm Hg)	Resolution of the Infection
Patient 1	*Escherichia c.*	dysuria, leukocyturia, bacteriuria	Reversible	18	11	93.33	Yes
Patient 2	*Escherichia c.*	fever, leukocyturia, bacteriuria	Steady	19	9	86.66	Yes
Patient 3	*Enterococcus f.*	dysuria, leukocyturia, bacteriuria	Reversible	15	9	85.00	Yes
Patient 4	*Escherichia. c.*	fever, leukocyturia, bacteriuria	Reversible	11	9	90.00	Yes
Patient 5	*Escherichia c, Candida sp*	fever, dysuria, leukocyturia, bacteriuria	Progressive	30	13	78.33	No
Patient 6	*Enterococcus f.*	fever, neutrophil leukocytosis, leukocyturia, bacteriuria	Progressive	30	12	75.00	Yes
Patient 7	*Escherichia c.*	fever, neutrophil leukocytosis, leukocyturia, bacteriuria	Progressive	17	10	86.66	Yes
Patient 8	*Escherichia c.*	dysuria, leukocyturia, bacteriuria	Reversible	14	9	86.66	Yes
Patient 9	*Escherichia c. Candida sp.*	fever, leukocyturia, bacteriuria	Progressive	26	11	86.66	Yes
Patient 10	*Acinetobacter f. Candida sp*	dysuria, neutrophil leukocytosis, leukocyturia, bacteriuria	Progressive	23	13	76.66	No
Patient 11	*Enterococcus f, Candida sp.*	fever, neutrophil leukocytosis, leukocyturia, bacteriuria	Reversible	11	8	103.33	Yes
Patient 12	*Enterococcus f., Candida a.*	fever, leukocyturia, bacteriuria	Progressive	14	9	78.33	Yes
Patient 13	*Pseudomonas a.*	dysuria, neutrophil leukocytosis, leukocyturia, bacteriuria	Progressive	31	14	86.66	No
Patient 14	*Coagulase-negative Staphylococcus, Candida a.*	dysuria, leukocyturia, bacteriuria	Progressive	21	11	80.00	Yes

multivariate analysis, only MELD score ($P = 0.002$) and the resolution of infection ($P = 0.04$) showed an independent prognostic value.

Discussion

This study confirms that bacterial infections represent a common complication in patients with cirrhosis and particularly in those with cirrhosis and ascites, regardless of the aetiology of the liver disease. It also shows that among patients with cirrhosis and ascites, females develop UTIs more frequently than males, thereby confirming previous observations.[29,30] In terms of prevalence, the study also confirms that UTI, pneumonia, and SBP represent the most common type of bacterial infection in patients with cirrhosis and ascites.[5,6,8,31] According to the criteria of the American College of Chest Physicians/Society of Critical Care Medicine[26] bacterial infection was associated with a diagnosis of SIRS, therefore defining a picture of sepsis, in 37.9% of cases. The development of bacterial infection in patients with cirrhosis and ascites is associated with higher in-hospital mortality as observed by Foreman et al.,[32] and a longer hospital stay. In keeping with Terra et al.,[19] the lack of resolution of the bacterial infection and MELD score, were the only predictors of death among a large series of parameters which were analyzed at the diagnosis of bacterial infection.

The main findings of the study deal with the relationship between bacterial infections and the development of renal failure and are as follows: (1) renal failure is a complication of almost all the types of bacterial infection, and not only of SBP in patients with cirrhosis and ascites, (2) the progressive form of renal failure is a complication only of biliary or gastrointestinal tract bacterial infections, SPB, and UTI; (3) the progressive form of renal failure in these infections occurs in many cases regardless of the resolution of the infection, and (4) the progressive form of renal failure meets the major diagnostic criteria of type 1 HRS, not only in SBP, but also in biliary or gastrointestinal tract infections and UTI. The prevalence of bacterial infection-induced renal failure in the current series was 33.6 %, relatively close to that observed previously in patients with cirrhosis and ascites and SBP,[9-11] and slightly higher than that observed by Terra et al. in patients with cirrhosis and with or without ascites as a result of bacterial infections not including SBP.[19] The prevalence of bacterial infection-induced renal failure in patients with cirrhosis and ascites was significantly higher compared with a 15.4% prevalence in patients with cirrhosis and without ascites, who developed a bacterial infection. The development of bacterial induced renal failure in patients with cirrhosis and ascites seems to be related to a higher MELD score, to a higher peak value of the count of neutrophil leukocytes in blood, and to the lack of resolution of infection in the current series. At a difference, the CTP score was not found to be an independent predictive factor of bacterial induced renal failure in patients with cirrhosis and ascites.

The independent predictive value of MELD score on the development of bacterial-induced renal failure is well in keeping with Sort et al.,[10] who showed that the independent predictors of the development of SPB-induced renal failure in patients with cirrhosis and ascites included serum bilirubin and serum creatinine levels, which are 2 of the 3 parameters on which the MELD score is based.

The independent predictive value of the severity of the bacterial infection, as reflected in the peak count of the neutrophil leukocytes in blood, is well in keeping with what was observed by Follo et al.[9] in patients with cirrhosis, ascites and SBP. Finally, the independent predictive value of the lack of resolution of bacterial infection on the development of renal failure patients with cirrhosis and ascites represents an original finding of the current study. Nevertheless, it should be outlined that Terra et al.[19] recently observed that the development of the non reversible form of renal failure in patients with cirrhosis, ascites and bacterial infection other than SBP was strongly associated with the lack of resolution of the infection.

Renal failure complicated all types of bacterial infections in patients with cirrhosis and ascites (Fig. 1), but the development of a progressive form of renal failure occurs only in SBP, UTI, and biliary or gastrointestinal tract infections. In contrast with Terra et al.[19] the development of a progressive form of renal failure occurs in many patients regardless of the resolution of the infection (Table 5). It should be also outlined that in patients bacterial-induced renal failure there was no evidence of renal damage because urine sodium was low and proteinuria was not clinically significant (Table 4). In addition all patients who developed the progressive form of renal failure met the International Ascites Club major criteria for the diagnosis of type 1 HRS.[32] Therefore, it appears that the existence of acute tubular necrosis as a cause of the progressive renal failure in these patients can be excluded, at least at the time of diagnosis. This observation together with the finding of a lower mean arterial pressure as compared to patients without bacterial-induced renal failure (Table 4) supports the concept that a renal vasoconstriction due to a more severe arterial underfilling was the main determinant of renal failure in patients with cirrhosis and bacterial infection. As a consequence, the study showed for the first time that a progressive form of renal failure with the features of type 1 HRS can be precipitated not only by SBP, but also by biliary or gastrointestinal tract bacterial infections and UTI. If this observation will

be confirmed by further studies in the near future, the prevention of bacterial infection-induced renal failure should not be limited to SBP, but also extended to these types of bacterial infection.

In conclusion, the results of the study show that bacterial infections frequently precipitate renal failure in patients with cirrhosis and ascites. The probability of developing bacterial infection-induced renal failure is related to the MELD score, the severity of the infection, and the lack of resolution of the infection. A progressive form of renal failure, which meets the diagnostic criteria of type 1 HRS, can be precipitated not only by SBP but, also by biliary or gastrointestinal tract bacterial infections and UTI.

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