Prevalence and risk factor of renal dysfunction induced by bacterial infection other than spontaneous bacterial peritonitis in patients with cirrhosis

Khouloud Bouslama, Fatma Houissa, Radhouane Dabbeche, Slim Bouzaidi, Senda Trabelsi, Mohamed Salem, Taoufik Najjar

University Tunis El Manar, Faculty of Medicine of Tunis, Charles Nicolle Hospital, Hepatology and Gastroenterology department, Tunis, Tunisia

K. Bouslama, F. Houissa, R. Dabbeche, S. Bouzaidi, S. Trabelsi, M. Salem, T. Najjar

Prévalence et facteurs de risque de l'insuffisance rénale induite par une infection bactérienne autre que l'infection du liquide d'ascite chez les patients cirrhotiques

LA TUNISIE MEDICALE - 2013 ; Vol 91 (n°06) : 391-395

R É S U M É

Prérequis : La détérioration de la fonction rénale chez les cirrhotiques ayant une infection spontanée du liquide d'ascite (ILA) est un facteur prédictif de mortalité hospitalière. Cependant la signification clinique de l'insuffisance rénale (IR) au cours des infections bactériennes autres que l'ILA n'est pas connue.

But : Déterminer la prévalence et l'impact de l'insuffisance rénale chez les patients cirrhotiques ayant une infection autre que l'ILA.

Méthodes : Nous avons mené une étude rétrospective ayant colligé tous les patients cirrhotiques ayant une infection autres que l'ILA hospitalisés au service de gastroentérologie de l'hôpital Charles Nicolle.

Résultats : Quatre vingt deux patients ont été inclus dans ce travail. L'infection était urinaires dans 41.5% des cas, une pneumonie dans 34.1% des cas, une infection biliaire dans 3.7% des cas, une cellulite dans 6.1% des cas, une infection gastro-intestinale dans 4.9% des cas et une bactériémie dans 9.7% des cas. Une IR a été observée chez 40 patients (48,8%), 13 d'entre eux avaient une IR irréversible. En analyse uni et multivariée, le score de MELD initial,le taux de PNN, de bilirubine et la pression artérielle était des facteurs de risque de survenue d'IR.

Conclusion : La prévalence de l'IR chez les cirrhotiques ayant une infection bactérienne autre que l'ILA est élevée (48,8%) et sa survenue est corrélée à la sévérité de l'atteinte hépatique. Le caractère irréversible de l'IR a un impact péjoratif sur le pronostic de ces patients.

M o t s - c l é s

Cirrhose ; infection bactérienne ; insuffisance rénale

K. Bouslama, F. Houissa, R. Dabbeche, S. Bouzaidi, S. Trabelsi, M. Salem, T. Najjar

Prevalence and risk factor of renal dysfunction induced by bacterial infection other than spontaneous bacterial peritonitis in patients with cirrhosis

LA TUNISIE MEDICALE - 2013 ; Vol 91 (n°06) : 381-385

S U M M A R Y

Background: Deterioration of renal function in cirrhotic patients with spontaneous bacterial peritonitis (SBP) is a predictor for inhospital mortality. However, the clinical significance of renal dysfunction during bacterial infection other than SBP is unknown.

Aim: To investigate the prevalence and clinical significance of renal dysfunction due to bacterial infections other than SBP in patients with liver cirrhosis.

Methods: Retrospective data from in-patients with bacterial infections other than SBP were analyzed.

Results: Eighty-two patients were recruited for the analysis. Infection was located in urinary tract (41.5%), pneumonia (34.1%), biliary tract (3.7%), cellulitis (6.1%), gastrointestinal tract (4.9%) and bacteremia of unknown origin (9.7%). Renal dysfunction developed in 40 patients (48.8%), of which 13 patients had irreversible renal dysfunction. In the univariate and multivariate analysis, the initial MELD score, neutrophil count, bilirubin, and blood pressure were significant risk factors for renal dysfunction.

Conclusion: The prevalence of renal dysfunction during bacterial infection other than SBP in patients with liver cirrhosis was 48.8%, and its development was related to the severity of the liver disease. Occurrence of irreversible renal dysfunction seemed to affect the prognosis of these patients.

K e y - w o r d s Liver cirrhosis, Bacterial infection, Renal dysfunction

Bacterial infection is a complication that occurs at a higher incidence in patients with liver cirrhosis (1-4). In particular, cases in which renal dysfunction occurs during the course of bacterial infection have a poor prognosis, and renal dysfunction is a key indicator predicting death in patients with bacterial infection (1). Bacterial infections commonly observed in patients with liver cirrhosis are, in descending order of frequency, urinary tract infection, pneumonia, and spontaneous bacterial peritonitis (SBP) (5-8). Most of the studies concerned about the clinical significance of renal dysfunction in patients with SBP (9-11). In patients with bacterial infection other than SBP, despite its higher prevalence, the clinical significance of renal dysfunction which might have the same pathophysiology as SBP, has not been thoroughly examined.

The objectives of this study were to examine the prevalence of renal dysfunction in the presence of bacterial infections other than SBP and to evaluate risk factors, and prognosis for irreversible renal dysfunction.

PATIENTS AND METHODS

The current study included patients with liver cirrhosis resulted from bacterial infections other than SBP and who were hospitalized at our medical institution between 1st January 2000 and 30 December 2010. Diagnosis of liver cirrhosis was made based on clinical, radiological, or histopathological findings. Diagnostic criterias for each bacterial infection were as follows.

Pneumonia was diagnosed when chest X-ray abnormalities was accompanied by fever, coughing, and leukocytosis. Urinary tract infection was diagnosed when fever and recurrent urinary tract symptoms that were positive for bacteriuria by urine culture existed. Biliary tract infection was suggested when fever, abdominal pain, leukocytosis, coexisted with findings suggestive of biliary tract infection on ultrasonography or abdominal CT scans.

Gastrointestinal infection was defined as having vomiting, diarrhea, fever, abdominal pain, leukocytosis, and positive findings on a stool culture test. Cellulitis was defined as a skin infection, fever, and leukocytosis.

Bacteremia of unknown origin was defined as positive findings on a blood culture in the absence of other infectious causes (4, 8). For cases which had ascite, ascitic fluid culture and analysis were done to exclude SBP and culture-negative neutrocytic ascites. Renal dysfunction following bacterial infection was defined as >50% increase in serum creatinine level over the base line value with abnormal peak serum creatinine level (>1.5 mg/dL) after the bacterial infection was diagnosed (12). Reversible renal dysfunction was defined as return to that of the normal value in 2 weeks of treatment period after renal dysfunction occurred. For cases in which the serum creatinine levels did not return to that of the normal value in 2 weeks of treatment period or were persistently elevated, an irreversible renal dysfunction was diagnosed. The clinical characteristics and serum biochemistry findings, including age, gender, blood pressure, liver cirrhosis etiology, type of bacterial infection, Child-Pugh score, WBC count, prothrombin time, Model for End-Stage Liver Disease (MELD) score, and serum sodium, BUN, creatinine, bilirubin, and albumin concentrations during the course of bacterial infection, were retrospectively analyzed in all patients to determine risk factors for renal dysfunction.

The data are expressed as mean ± standard error (SE) or number and percentage. Continuous variables were analyzed using independent t-test, and discontinuous variables were analyzed with Pearson's chi-square or Fisher's exact test. Multivariate analysis was performed using a multiple logistic regression for variables with significant p-values in univariate analysis. All statistical analyses were performed with SPSS 16.0. A p value <0.05 was considered significant.

RESULTS

1. Patient characteristics and overall prevalence of renal dysfunction

The current study was conducted with 82 patients who were hospitalized at our medical institution due to liver cirrhosis accompanied by a bacterial infection other than SBP. The mean age was 62 years±10.6; the male-to-female ratio was 2.28. Causative factors for liver cirrhosis included chronic hepatitis C in 40, chronic hepatitis B in 18, NASH in 14 and unknown causes in nine.

There were 34 cases of urinary tract infection, 26 cases of pneumonia and 14 cases of gastrointestinal infection (Table 1). Renal dysfunction developed in 40 (48.7%) of the patients with liver cirrhosis who concurrently had a bacterial infection.

Table 1 : Baseline Characteristics of the 82 Patients with Bacterial Infection

Characteristic	value	(%)
AGE (years)	62 [30 - 82]	
Gender		
MASCULIN	57	69.51
FEMININ	25	30.48
Etiology		
HVB	18	21.95
HCV	40	48.78
NASH	14	17.07
INFECTION		
urinary tract infection	34	41.46
pulmonary infection	26	31.7
gastrointestinal	4	4.87

2. Risk factors for developing renal dysfunction:

The clinical characteristics of the 40 patients who had renal dysfunction occurred after diagnosis of bacterial infection and the 42 patients who did not had renal dysfunction were comparatively evaluated. The mean age was 62.18 ± 12.82 years in patients with renal dysfunction and 61.86 ± 12.88years in patients without renal dysfunction. There were no significant differences in gender, diastolic pressure, Child-Pugh score, cirrhosis etiology or type of bacterial infection between the two groups. However, there was significant difference in systolic pressure. Systolic and diastolic pressures were 113 ±

20.1mmHg and 58.2 ± 8.7 mmHg, respectively, in 40 patients who had renal dysfunction developed and 123.8 ± 12.4 mm Hg and 64.3 ± 11.5 mmHg, respectively, in 42 patients who did not have renal dysfunction (Table 2). There was no significant difference in serum sodium, albumin and prothrombin time during the course of bacterial infection between the two groups. However, in patients with renal dysfunction, the WBC count, serum bilirubin, serum creatinine, BUN and MELD score were significantly higher than those in patients without renal dysfunction (Table 2).

Table 2 : Comparison of Characteristics of Groups according to Development of Renal Dysfunction

Characteristic	Patients with renal dysfunction (n=40)	Patients without renal dysfunction (n=42)	P value
Age	62.18±12.82	61.86±12.88	0.91
Gender			0.37
Male	72.5	66.7	
Female	27.5	33.3	
Blood pressure mmHg			
Systolic	113±20.1	123.8±12.4	0.004
Diastolic	58.2±8.7	64.3±11.5	0.009
Etiology			0.46
HVB	25	19	0.51
HCV	45	52.4	0.50
NASH	12.5	21.4	0.29
unknown	15	7.1	0.25
secondary	2.5	0	0.31
alcoholic	0	0	
immune	0	0	
Infection			0.424
urinary	35	47.6	0.24
pneumonia	30	33.3	0.74
biliary	5	2.4	0.53
cellulitis	7.5	4.8	0.28
gastrointestinal	7.5	2.4	0.6
others	0	4.8	0.16
bacteremia	15	4.8	0.12
CHILD-Pugh			0.82
A	7.5	4.8	0.6
B	52.5	57.1	0.67
C	40	38.1	0.85
WBC count	8562.5±4543	4941.9±1784	<0.0001
Serum sodium	132.82±7.6	134.5±3.89	0.205
Bilirubin	109.62±138.74	54.6 ±39.57	0.016
Prothrombin time	50 ±17.2	47.26±11.35	0.38
BUN	14.2±8.1	5.69 ±2.97	< 0.0001
Creatinine	199.7±103.4	70.1 ±14.26	<0.0001
Albumin	26.12 ±3.83	26.19±2.3	0.92
Meld	28.25± 12.08	16.29±5.1	<0.0001

WBC count: white blood cell, Model for End-Stage Liver Disease (MELD) score. NASH: non alcoholic steatohepatitis; BUN: blood urea nitrogen; HVB: chronic hepatitis B; HCV: chronic hepatitis

A multiple logistic regression analysis was performed on systolic and diastolic pressure, WBC count, bilirubin level, and MELD score, which were all significant in the univariate analysis. The MELD score, WBC count and diastolic blood pressure ware significantly associated with the occurrence of renal dysfunction resulting from bacterial infection.

The prevalence of renal dysfunction in cases with a MELD score >20 was 7.39 times the prevalence in the other cases (OR= 7.39/ 95% confidence interval= 2.13-25.612/p=0.002) (Table 3).

Table 3 : Multiple Logistic Regression Analysis for the Variables Affecting Renal Dysfunction Development after Bacterial Infection

odds ratios	Odds Ratio (OR)	95% IC of Wald OR		P value
Systolic blood pressure	1.02	0.67	1.546	0.927
Distolic blood pressure	0.38	0.18	0.812	0.013
WBC	8.39	0.84	83.737	0.070
MELD score >=20	7.39	2.13	25.612	0.002
Bilirubin	1.00	0.99	1.006	0.594

3. Prevalence, risk factors, and prognosis of irreversible renal dysfunction:

Irreversible renal dysfunction occurred in 13 patients, representing 15.8% of the total number of patients and 32.5% of those who had renal dysfunction. When patients with irreversible renal dysfunction were compared with those without irreversible renal dysfunction (reversible renal dysfunction and no renal dysfunction), the MELD score, systolic and diastolic pressure; WNC count, BUN, creatinine level, albumin and urinary tract infection showed significant difference (Table 4). This was in disagreement with the results of the multivariate analysis in which only the MELD score and the diastolic blood pressure ware a significant risk factor for developing irreversible renal dysfunction (p=0.001 for the MELD SCORE and p=0.015 for diastolic blood pressure) (Table 5).

All the patients, who have developed irreversible renal dysfunction, died within three months. There were no significant differences in clinical characteristics and blood test results between patients who died and those who did not; only the MELD score was significantly different between the two groups (p=0.001).

DISCUSSION

Bacterial infection is one of the most common complications in patients with liver cirrhosis, and mortality has been higher (1-4). Urinary tract infection, pneumonia, and SBP are bacterial infections commonly seen in patients with liver cirrhosis (5-8). Studies concerning bacterial infection in patients with liver cirrhosis have focused mainly on those with SBP. Renal dysfunction is concurrently present in approximately one-third of SBP cases and is one of the most powerful indicators predicting death during the hospitalization (9). In patients with liver cirrhosis accompanied by ascites, there is a concurrent presence of circulatory dysfunction characterized by arterial dilatation, hypotension, increased cardiac output, and decreased

Table 4 : Comparison of Characteristics of Groups according to Development of Irreversible Renal Dysfunction

Characteristic	Patients without irreversible renal dysfunction (n= 69)	Patients with irreversible renal dysfunction (n= 13)	valeur = p
Age	62,26±12,71	60.69±13.54	0.51
Gender			0.52
Male	n=48	n=9	
Female	n=21	n=4	
Blood pressure mmHg			
Systolic	123±14.9	94.6±6.6	<0.0001
Diastolic	64.1 ±1.01	53.1 ±7.5	0.0007
Etiology			
HVB	15.1	2.9	0.46
HCV	33.7	6.3	0.54
NASH	11.8	2.2	0.45
unknown	7.6	1.4	0.63
secondary	0.8	0.2	0.16
alcoholic	0	0	
immune	0	0	
Infection			
urinary	28.6	5.4	0.02
pneumonia	21.9	4.1	0.33
biliary	2.5	0.5	0.41
cellulitis	4.2	0.8	0.99
gastrointestinal	3.4	0.6	0.51
others	1.7	0.3	0.99
bacteremia	6.7	1.3	0.11
CHILD-Pugh			
A	7.2	0	0.99
B	58	38.5	0.23
C	34.8	61.5	0.12
WBC count	6040±3116	10253±5397	0.005
Serum sodium	133.5±5.19	134.6±9.61	0.99
Bilirubin	59.62±60.67	197.23 ±186.98	0.04
Prothrombin time	49.2 ±14.47	45.62 ±14.71	0.63
BUN	7.62±3.98	21.62 ±9.55	< 0.0001
Creatinin	104.39±61.55	286.85 ±110.94	<0.0001
Albumin	26.48 ±3.06	24.46±3.01	0.01
MELD	19.54±8.6	35.85±12.06	<0.0001

Table 5 : Multiple Logistic Regression Analysis for the Variables Affecting Irreversible Renal Dysfunction after Bacterial Infection

Odds Ratios (OR)				
	OR	**IC 95% (OR)**		**P**
Systolic blood pressure	0.976	0.63	1.511	0.913
Diastolic blood pressure	0.381	0.174	0.832	0.015
WBC count > 10 000	9.792	0.949	101.054	0.055
MELD score >= 20	11.198	2.779	45.128	0.001
Bilirubin level	0.999	0.991	1.008	0.907
Urinary tract infection	0.46	0.139	1.526	0.205
ALBUMIN	1.223	0.995	1.504	0.056

effective circulating volume. In patients with liver cirrhosis and concurrent SBP, cytokine (TNF-alpha and IL-6) and nitric oxide levels are elevated, resulting in the dilatation of blood vessels and decreased renal blood flow. The deterioration of compensatory mechanisms leads to renal dysfunction (9, 13). It is well known that albumin infusion can prevent renal dysfunction and enhance survival in patients with liver cirrhosis and concurrent SBP (10,14). In all types of bacterial infection, the increased release of inflammatory cytokines and vasodilatory substances can lead to renal dysfunction and circulatory dysfunction. According to a recent study, there was a concurrent presence of bacterial infection, including SBP, in 44.6% of hospitalized patients with liver cirrhosis and ascites. Of these, 33.6% had renal dysfunction (15). Other studies have reported renal dysfunction in 26% of patients who concurrently had a bacterial infection other than SBP (16). In our series, in which SBP was excluded, renal dysfunction occurred in 10% of all patients, which is close to the prevalence of renal dysfunction previously reported in patients with liver cirrhosis and bacterial infection include SBP. In our study, type of bacterial infection were similar to the recent studies (5-8). Urinary tract infection was the most common, followed by pneumonia. In a recent study, renal dysfunction reportedly occurred more frequently in patients with biliary tract infection (15). However, we found no significant difference in the occurrence of renal dysfunction based on the type of infection. The improvement in infection is well-known independent risk factors for developing renal dysfunction in patients with liver

cirrhosis who concurrently have a bacterial infection (14).
The MELD score is the best prognostic marker of patients with cirrhosis and sepsis.16 Other study which have examined renal dysfunction after SBP, reported that blood urea nitrogen before peritonitis and band neutrophils count in blood at diagnosis were independent predictors for the development renal dysfunction (9). This is in agreement with the results of our study. But the most important risk factor identified for developing renal dysfunction and irreversible renal dysfunction was the MELD score, indicating that severe hepatic dysfunction is a risk factor for developing renal dysfunction in patients with liver cirrhosis and bacterial infection. Patients with liver cirrhosis in whom renal dysfunction occurred due to bacterial infections other than SBP had a poor prognosis; the hospitalization mortality rate is 42.8% (7.24% in cases without renal dysfunction) (15) and the 3-month mortality is 66% (13% in cases without renal dysfunction) (16). Particularly in cases with irreversible renal dysfunction, the 3-month mortality may reach 100%. In our series, the hospitalization mortality was 32.5% in patients who developed renal dysfunction, and all those who died during the hospitalization had developed irreversible renal dysfunction. The MELD score was a factor for predicting hospitalization death. In summary, renal dysfunction occurred in 48.8% of patients with liver cirrhosis who developed a bacterial infection other than SBP. The MELD score was the most important factor that independently predicted the occurrence of renal dysfunction and irreversible renal dysfunction. Patients with liver cirrhosis who concurrently had a bacterial infection and renal dysfunction had a poor prognosis. In particular, the prognosis was poor for those with irreversible renal dysfunction.
There were several limitations to the current study. This was retrospective in design and lacked data about the use of plasma expanders. Further studies are warranted to examine whether albumin treatment can prevent the occurrence of renal dysfunction and enhance survival in patients with bacterial infections other than SBP.

References

1. Navasa M, Rodes J. Bacterial infections in cirrhosis. Liver Int. 2004;24:277–80.
2. Garcia-Tsao G. Current management of the complications of cirrhosis and portal hypertension: variceal hemorrhage, ascites, and spontaneous bacterial peritonitis. Gastroenterology. 2001;120:726–48.
3. Bolognesi M, Merkel C, Bianco S, et al. Clinical significance of the evaluation of hepatic reticuloendothelial removal capacity in patients with cirrhosis. Hepatology. 1994;19:628–34.
4. Deschenes M, Villeneuve JP. Risk factors for the development of bacterial infections in hospitalized patients with cirrhosis. Am J Gastroenterol. 1999;94:2193–7.
5. Borzio M, Salerno F, Piantoni L, et al. Bacterial infection in patients with advanced cirrhosis: a multicentre prospective study. Dig Liver Dis. 2001;33:41–8.
6. Caly WR, Strauss E. A prospective study of bacterial infections in patients with cirrhosis. J Hepatol. 1993;18:353–8.
7. Rosa H, Silverio AO, Perini RF, Arruda CB. Bacterial infection in cirrhotic patients and its relationship with alcohol. Am J Gastroenterol. 2000;95:1290–3.
8. Yang YY, Lin HC. Bacterial infections in patients with cirrhosis. J Chin Med Assoc. 2005;68:447–51.
9. Follo A, Llovet JM, Navasa M, et al. Renal impairment after spontaneous bacterial peritonitis in cirrhosis: incidence, clinical course, predictive factors and prognosis. Hepatology. 1994;20:1495–1501.
10. Sort P, Navasa M, Arroyo V, et al. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. N Engl J Med. 1999;341:403–9.
11. Angeli P, Guarda S, Fasolato S, et al. Switch therapy with ciprofloxacin vs. intravenous ceftazidime in the treatment of spontaneous bacterial peritonitis in patients with cirrhosis: similar efficacy at lower cost. Aliment Pharmacol Ther. 2006;23:75–84.
12. Augoustides JG, Pochettino A, Ochroch EA, et al. Renal dysfunction after thoracic aortic surgery requiring deep hypothermic circulatory arrest: definition, incidence, and clinical predictors. J Cardiothorac Vasc Anesth. 2006;20:673–7.
13. Navasa M, Follo A, Filella X, et al. Tumor necrosis factor and interleukin-6 in spontaneous bacterial peritonitis in cirrhosis: relationship with the development of renal impairment and mortality. Hepatology. 1998;27:1227–32.
14. Tandon P, Garcia-Tsao G. Bacterial infections, sepsis, and multiorgan failure in cirrhosis. Semin Liver Dis. 2008;28:26–42.
15. Fasolato S, Angeli P, Dallagnese L, et al. Renal failure and bacterial infections in patients with cirrhosis: epidemiology and clinical features. Hepatology. 2007;45:223–9.
16. Terra C, Guevara M, Torre A, et al. Renal failure in patients with cirrhosis and sepsis unrelated to spontaneous bacterial peritonitis: value of MELD score. Gastroenterology. 2005;129:1944–53.