Renal impairment after spontaneous bacterial peritonitis: Incidence and prognosis

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BACKGROUND/AIMS: Spontaneous bacterial peritonitis (SBP) is an important complication in cirrhotic patients. The aim of the present study was to assess the incidence, predictive factors and prognosis for renal impairment (RI) after SBP in cirrhotic patients from southern Brazil.

METHODS: Of the 1030 hospitalizations evaluated, 114 episodes of SBP were diagnosed in 94 patients (mean age 49 years; 76.59% men). SBP diagnosis was established when the ascitic fluid polymorphonuclear cell count was equal to or greater than 250 cells/mm^3. Five cases were excluded. The variables assessed as possible predictors of steady or progressive RI were blood urea nitrogen and creatinine levels before the diagnosis of SBP; type of infection, antibiotic prophylaxis, first episode or recurrent SBP, presence of gastrointestinal bleeding and hepatic encephalopathy during hospitalization, SBP resolution, Child-Pugh classification, levels of blood pressure, ascitic fluid and blood polymorphonuclear cell count, bacteriological data (positive and negative ascitic fluid culture), albumin, bilirubin, sodium and prothrombin time at the moment of diagnosis.

RESULTS: The incidence of SBP was 11.07%. In 61 (55.96%) episodes, SBP was associated with RI (transient in 57.37%; steady in 19.67%; and progressive in 22.95%). The mortality rate associated with progressive RI was 100%; 58.33% with steady RI; and 2.85% with transient RI. The mortality rate in patients with or without RI was 36.07% and 6.25%, respectively (P<0.001). The level of creatinine (greater than or equal to 1.3mg/dL) before the diagnosis of SBP and the rate of infection resolution were the only predictors of RI in the multivariate analysis.

CONCLUSIONS: RI after SBP is a common complication, and indicates a poor prognosis for this infection. High levels of creatinine before infection and the rate of infection resolution are independent predictors of RI.

Key Words: *Kidney failure; Liver cirrhosis; Spontaneous bacterial peritonitis*

La défaillance rénale après une péritonite bactérienne spontanée : L'incidence et le pronostic

HISTORIQUE ET OBJECTIFS : La péritonite bactérienne spontanée (PBS) est une complication importante chez les patients cirrhotiques. La présente étude vise à évaluer l'incidence, les facteurs prédictifs et le pronostic de défaillance rénale (DR) après une PBS chez des patients cirrhotiques du sud du Brésil.

MÉTHODOLOGIE : Sur les 1 030 hospitalisations évaluées, 114 épisodes de PBS ont été diagnostiqués chez 94 patients (âge moyen de 49 ans, 76,59 % de sexe masculin). Un diagnostic de PBS était posé lorsque la numération cellulaire polymorphonucléaire était égale ou supérieure à 250 cellules/mm^3. Cinq cas ont été exclus. Les variables évaluées comme prédicteurs possibles de DR stable ou évolutive étaient le taux d'azotémie et de créatinine avant le diagnostic de PBS, le type d'infection, la prophylaxie antibiotique, le premier épisode ou la récurrence de PBS, la présence d'hémorragie gastro-intestinale et d'encéphalopathie hépatique pendant l'hospitalisation, la résolution de la PBS, la classification Child-Pugh, la tension artérielle, le liquide d'ascite et la numération cellulaire polymorphonucléaire, les données bactériologiques (culture positive et négative du liquide d'ascite), l'albumine, la bilirubine, le sodium et le temps de prothrombine au moment du diagnostic.

RÉSULTATS : L'incidence de PBS était de 11,07 %. Dans 61 (55,96 %) épisodes, le PBS s'associait à une DR (transitoire dans 57,37 % des cas, stable dans 19,67 % des cas et évolutive dans 22,95 % des cas). Le taux de mortalité associé à une DR évolutive était de 100 %, mais de 58,33 % en cas de DR stable et de 2,85 % en cas de DR transitoire. Le taux de mortalité chez les patients présentant ou non une DR s'établissait à 36,07 % et à 6,25 %, respectivement (P<0,001). Le taux de créatinine (équivalant à 1,3 mg/dL) avant le diagnostic de PBS et le taux de résolution de l'infection étaient les seuls prédicteurs de DR dans le cadre de l'analyse multivariée.

CONCLUSIONS : La DR après une PBS est une complication courante indicatrice du mauvais pronostic de cette infection. Des taux élevés de créatinine avant l'infection et un taux de résolution de l'infection sont des prédicteurs indépendants de DR.

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Spontaneous bacterial peritonitis (SBP) is an important clinical complication affecting patients with cirrhosis and ascites (1-3). It is associated with a poor short term and long term prognosis, with an in-hospital mortality rate ranging from 20% to 40%, and a recurrence rate of 70% after one year (4-9).

Renal impairment (RI) after SBP has been described in 25% to 38% of the reported cases (10-12). It probably occurs as a result of an accentuation of the circulatory dysfunction (common in patients with cirrhosis and ascites) induced by the infection (13). Recently, RI has been shown to be the best predictor of in-hospital mortality in patients with SBP (10-14).

All studies on RI in patients with SBP published so far were performed in Barcelona, Spain (10-12,14). Therefore, we wanted to investigate whether similar results would be observed in others areas of the world, namely Brazil.

The aim of the present study was to assess the incidence, predictive factors and prognosis of RI after SBP in a population of cirrhotic patients in southern Brazil.

MATERIALS AND METHODS

All patients with cirrhosis and ascites admitted to Santa Casa de Misericórdia de Porto Alegre, Brazil, from January 1991 to June 2000 were evaluated. A total of 520 patients (1030 hospitalizations) with ascites secondary to cirrhosis were analyzed. One hundred and fourteen episodes of SPB were diagnosed in 94 patients. In this population the mean age was 49 years (range 15 to 95 years) and 76.59% were male.

Cirrhosis was confirmed by biopsy in 55 patients (48.25%), and by clinical, laboratory, endoscopic and ultrasonographic data in the remainder of the patients. Cirrhosis was caused by alcohol consumption associated with hepatitis C virus infection in 31 patients (32.98%); by alcohol consumption only in 27 patients (28.72%); by hepatitis C only in 18 patients (19.15%); and by hepatitis B only in 12 patients(12.76%). In one patient, it was caused by hepatitis B, hepatitis C and alcohol consumption; in two patients, it had an autoimmune etiology; and in three other patients it was cryptogenic.

Liver function was evaluated using the Child-Pugh classification (15).

Diagnostic paracentesis was carried out at hospital admission in every patient and during hospitalization whenever SBP was suspected. An established routine (16) was used for the determination of the levels of ascitic fluid total protein, albumin, amylase, lactic dehydrogenase activity, glucose, total and differential cell count and for cytopathological testing. For the bacteriological analysis, 10 mL samples of ascitic fluid were cultured in aerobic and anaerobic blood culture bottles at the patient's bedside.

In addition to paracentesis, blood was also drawn for the following analyses: complete blood count, levels of aminotransferases, bilirubin, alkaline phosphatase, albumin, blood urea nitrogen (BUN), creatinine, electrolytes and prothrombin time.

A diagnosis of SBP was established when the ascitic fluid polymorphonuclear cell count was equal to or greater than 250 cells/mm^3, independently of bacteriological results (17). Secondary peritonitis was ruled out based on the absence of clinical, laboratory and ultrasonographic data. SBP was considered community-acquired when the diagnosis was established within 48 h after admission and hospital-acquired if it was established after this period (18).

Information concerning antibiotic prophylaxis with norfloxacin before hospitalization was obtained from the patient or family. Treatment of SBP was initiated as soon as the diagnosis was made. The antibiotics used were cefotaxime or ceftriaxone IV for 10 days. The dosage was adjusted during the treatment according to kidney function or according to the in vitro susceptibility of the isolated organisms. The diuretic therapy was suspended at the moment of diagnosis.

TABLE 1
Data at diagnosis of 109 episodes of spontaneous bacterial peritonitis (SBP)

Data	Results
Community-acquired SBP n (%)	67 (61.4)
Hospital-acquired SBP n (%)	42 (38.5)
Antibiotic prophylaxis n (%)	25 (22.9)
Mean arterial pressure (mmHg)	78.5±16 6
Sodium (mmol/L)	131.9±6.9
Total bilirubin (mg/dL)	5.4±7.0
Prothrombin activity (%)	55.1±14.2
Albumin (g/dL)	2.3±0.5
Blood urea nitrogen (mg/dL)	75.2±67.9
Creatinine (mg/dL)	1.6±1.3

Data presented as mean ± SD

SBP-associated RI was defined as an increase in BUN or serum creatinine to levels greater than 45 mg/dL or 1.3 mg/dL (upper limit of normal), respectively, in patients with normal baseline values, or as a 50% increase in BUN or creatinine over baseline values in patients with pre-existing renal impairment. For cases of hospital-acquired SBP, the creatinine level on the day of admission was considered as baseline. For community-acquired cases, creatinine levels measured two to four weeks before admission (during clinic visits or previous hospitalizations) were taken as baseline (10).

RI was classified as progressive when BUN and creatinine levels increased progressively; as steady when the initial impairment in kidney function was stabilized during hospitalization; and as transient when BUN and creatinine levels returned to baseline values during hospitalization (10).

Five cases were excluded from the present analysis: three because of nephrotoxic drug use; one due to severe hypovolemia secondary to upper gastrointestinal bleeding a few hours before the diagnosis of SBP; and one because renal failure was caused by ureteral obstruction. Therefore, 109 episodes of SBP were included in the study.

The following variables were assessed as possible predictors of steady or progressive SBP-related RI: BUN and creatinine levels before the diagnosis of SBP, type of infection, antibiotic prophylaxis, first episode or recurrent SBP, presence of gastrointestinal bleeding and hepatic encephalopathy during hospitalization, SBP resolution, Child-Pugh classification, blood pressure levels, ascitic fluid and blood polymorphonuclear cell count, bacteriological data (positive and negative ascitic fluid culture), albumin, bilirubin, sodium and prothrombin time at the moment of diagnosis (10,11).

The Ethics Committee at Santa Casa de Misericórdia de Porto Alegre approved the study protocol.

Qualitative variables were analyzed using the χ^2 test and the relative risk analysis. Quantitative variables were compared using Student's *t* test. Variables reaching a statistical significance ($P<0.05$) in the univariate analysis were introduced into a multivariate model.

TABLE 2
Clinical characteristics of patients with or without renal impairment (RI)

Data	No RI	RI
Age	48.42±2.0	50.21±1.2
Sex (male) (n[%])	68 (76.4)	19 (76.0)
Hospital-acquired infection (n[%])	15 (31.2)	27 (44.26)
Prophylactic antibiotic (n[%])	14 (55.4)	11 (44)
Encephalopathy hepatic (n[%])	6 (24)	17 (19.50)
Systolic blood pressure (mmHg)	107.92±12.20	105.62±20.30
Diastolic blood pressure (mmHg)	66.15±9.35	64.33±12.80

Age and blood pressure data presented as mean ± SD

RESULTS

The occurrence of SBP was 11.07% (114 SBP episodes in 1030 admissions in patients with cirrhosis and ascites).

The clinical and laboratory data at the time of diagnosis of the 109 SBP episodes included in the study are presented in Table 1. As expected, the results of standard liver function tests (bilirubin, albumin, and prothrombin time) were markedly deteriorated, reflecting the poor hepatic function associated with SBP. According to the Child-Pugh classification, 2.6% of the patients were classified as Child A, 46.4% as Child B and 50.8% as Child C. Thirty-six patients (33%) had renal impairment at the moment of infection diagnosis.

Some clinical characteristics of patients with or without renal impairment are demonstrated in Table 2. They are similar in these two groups (P>0.05).

The overall hospital mortality was 22.9% (25 cases). Death was due to upper gastrointestinal bleeding in six patients, no response to antibiotic treatment in eight, renal failure in seven and liver failure in four patients.

RI occurred in 61 (55.9%) episodes. It was transient in 35 (57.3%), steady in 12 (19.6%), and progressive in 14 episodes (22.9%). When only stable and progressive RI were considered, the incidence of RI was 23.8% (26 episodes). RI was significantly associated to hospital mortality (36% versus 6.2%; P<0.001). Hospital mortality occurred in 100% of cases with progressive, in 58.3% of cases with steady and in only 2.8% of cases with transient RI.

The comparison between SBP episodes without RI and with steady or progressive RI revealed that seven of the 17 variables assessed were significant predictors of RI according to the univariate analysis: gastrointestinal bleeding during hospitalization (P=0.007); lack of infection resolution (P=0.001); prothrombin time (P=0.04), albumin (P=0.02), and sodium levels (P=0.03) at the time of diagnosis, BUN (P<0.001) and creatinine (P<0.001) levels before the diagnosis of SBP (Table 3). However, in multivariate analysis the only predictors of RI were the level of creatinine (greater than or equal to 1.3 mg/dL) before the diagnosis of infection and the rate of SBP resolution.

DISCUSSION

Four studies performed in Barcelona showed that RI after SBP constitutes an important predictor of mortality (10-12,14).

Follo et al (10), studying 252 SBP episodes in 197 patients, demonstrated that approximately 30% presented with RI, which was progressive in 42%, steady in 33% and transient in 25% of the cases. According to those authors, the predictors of RI in a multivariate analysis were levels of BUN and serum sodium before SBP diagnosis and neutrophil count in blood at the moment of diagnosis. When RI occurred, mortality was 54%; however, mortality was only 9% in cases without RI. On the other hand, transient RI was not associated with higher mortality. Only the development of RI and the level of creatinine before SBP were associated with higher mortality.

TABLE 3
Variables with significant predictive value for spontaneous bacterial peritonitis-renal impaired (SBP-RI) in univariated analysis

Variables	No SBP-RI	SBP-RI	P value
Prothrombin activity (%)	58.69±15.85	52.05±14.16	0.041
Albumin (mg/dL)	2.72±0.53	2.45±0.59	0.022
sodium (mmol/L)	135.04±6.36	132.20±5.60	0.034
BUN (mg/dL)	39.04±25.57	101.00±77.65	<0.001
Creatinine (mg/dL)	0.93±0.45	2.13±1.43	<0.001
GI bleeding (n[%])	16 (18.2)	11 (41)	0.007
No infection resolution (n[%])	3 (30)	7 (70)	0.001

Data presented as mean ± SD. BUN Blood urea nitrogen; GI Gastrointestinal

Toledo et al (12) analyzed the predictors of resolution and survival in SBP, and showed that RI was an important predictor of prognosis. RI was present in 38% of the cases. BUN at the time of diagnosis was an independent predictor of infection resolution and patient survival.

Another study (11), evaluating the correlation between RI and SBP prognosis, demonstrated a 25% incidence for RI. In that study, the factors associated with the development of RI were previous renal failure, high ascitic fluid cytokine levels and mean arterial pressure. Ten of the 13 patients (77%) who developed RI died during hospitalization, but only 39 (5%) of those without RI died.

Llovet et al (14) demonstrated that RI was one of the seven independent factors associated with poor prognosis of SBP.

The exact pathogenesis of this renal function impairment remains uncertain (19,20). Navasa et al (11), studying 52 patients with cirrhosis and SBP, observed high levels of cytokine (tumour necrosis factor and interleukin 6) in the serum and ascitic fluid of patients who later developed RI. Furthermore, those patients also had higher serum renin levels when compared with patients without RI. Thus, it is postulated that cytokines lead to nitric oxide release, which in turn results in arterial vasodilatation and hemodynamic alterations (reflected by higher renin levels) that may cause renal failure. Therefore, the occurrence and severity of RI after SBP may result from the combination of infection-induced circulatory failure and cirrhosis-related circulatory failure. This combined effect probably overcomes the compensatory action of renal vasodilators, leading to a decrease in renal perfusion and glomerular filtration rate. Sort et al (13) confirmed the importance of hemodynamic dysfunction in SBP patients in a randomized, prospective study in which survival was improved and the incidence of RI was decreased following administration of intravenous albumin.

No studies have addressed the development of RI after SBP in areas outside Spain. Despite the fact that etiology of liver disease is similar in Spain and Brazil, the degree of malnutrition, low socioeconomic status and racial differences found in Brazil when compared with Europe constitute important factors that could have influenced the results of this study, but did not.

The incidence of RI observed in the present study was slightly higher than that observed in the literature, although most authors do not consider cases of transient failure as cases of RI. When our cases of transient renal failure are excluded, the incidence drops to almost 24%, which is in agreement with the literature (10-12). The higher incidence of transient renal failure observed in our patients could be the result of a delay in hospitalization, which is a common fact in Brazilian public hospitals.

On the other hand, our study showed that RI after SBP is an important predictor of SBP prognosis also in Brazil, particularly in cases of steady and progressive renal failure. This finding is similar to that described by Follo et al (10).

A study performed by Sort et al (13) demonstrated that the administration of albumin (acting as a plasmatic expander) at the moment of SBP diagnosis prevented RI and reduced mortality in patients with SBP (13). Although these results are encouraging, this treatment is very expensive. On the other hand, our study confirmed the findings reported by two studies carried out in Barcelona (11,13), in that the level of creatinine before diagnosis is an important predictor of development of RI. Therefore, in order to reduce cost, we suggest that this particular group of patients be selected for treatment with albumin, but further studies are necessary in order to assess this point.

In addition, we demonstrated that the occurrence of SBP-RI is also associated with a failure of infection resolution. This is probably secondary to the persistence of bacteremia in these patients, which facilitates hemodynamic dysfunction as already described (11).

In conclusion, the present study confirms that RI is a common complication of SBP and an important predictor of mortality in distinct areas of the world.

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REFERENCES

1. Caly WR, Strauss E. A prospective study of bacterial infections in patients with cirrhosis. J Hepatol 1993;18:353-8.
2. Garcia-Tsao G. Spontaneous bacterial peritonitis. Gastroenterol Clin North Am 1992;21:257-75.
3. Wilcox CM, Dismukes WE. Spontaneous bacterial peritonitis. A review of pathogenesis, diagnosis and treatment. Medicine 1987;66:447-56.
4. Andreu M, Sola R, Silges-Serra A, et al. Risk factors for spontaneous bacterial peritonitis in cirrhotic patients with ascites. Gastroenterology 1993;104:1133-8.
5. Ariza J, Xiol X, Esteve M, et al. Aztreonam vs. cefotaxime in the treatment of gram-negative spontaneous peritonitis in cirrhotic patients. Hepatology 1991;4:91-8.
6. Fong TL, Akriavidis EA, Runyon BA, Reynolds TB. Polymorphonuclear cell count response and duration of antibiotic therapy in spontaneous bacterial peritonitis. Hepatology 1989;9:423-6.
7. Gilbert JA, Kamath PS. Spontaneous bacterial peritonitis: An update. Mayo Clin Proc 1995;70:365-70.
8. Grangé JD, Amiot X, Grangé V, et al. Amoxicillin clavulanic acid therapy of spontaneous bacterial peritonitis: A prospective study of twenty-seven cases in cirrhotic patients. Hepatology 1990;11:360-4.
9. Runyon BA. Spontaneous bacterial peritonitis: An explosion of information. Hepatology 1988;8:171-5.
10. 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;20:1495-501.
11. 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.
12. Toledo C, Salmeron JM, Rimola A, et al. Spontaneous bacterial peritonitis in cirrhosis: Predictive factors of infection, resolution and survival in patients with cefotaxime. Hepatology 1993;17:251-7.
13. 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.
14. Llovet JM, Planas R, Morrilas R, et al. Short-term prognosis of cirrhotics with spontaneous bacterial peritonitis: Multivariate study. Am J Gastroenterol 1993;88:388-92.
15. Pugh RNH, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus in bleeding oesophageal varices. Br J Surg 1973;60:648-52.
16. Mattos AA. Peritonite bacteriana espontânea e suas variantes: Epidemiologia, diagnóstico e história natural. GED 1994;13:97-108.
17. Rimola A, Garcia-Tsao G, Navasa M, et al. Diagnosis, treatment and prophylaxis of spontaneous bacterial peritonitis: A consensus document. J Hepatol 2000;32:142-53.
18. Ho H, Zuckerman MJ, Ho TK, Guerra LG, Verghese A, Casner PR. Prevalence of associated infections in community-acquired spontaneous bacterial peritonitis. Am J Gastroenterol 1996;91:735-42.
19. Arroyo V, Gines P, Gerber AL, et al. Definition of refractory ascites and hepatorenal syndrome in cirrhosis. Hepatology 1996;23:164-76.
20. Moore M, Wendon J, Frazer M, Karani J, Williams R, Badr K. Plasma endothelin immunoreactivity in liver disease and the hepatorenal syndrome. N Engl J Med 1992;27:1774-8.