Hyponatremia in Cirrhosis: Results of a Patient Population Survey

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Low serum sodium concentration is an independent predictor of mortality in patients with cirrhosis, but its prevalence and clinical significance is unclear. To evaluate prospectively the prevalence of low serum sodium concentration and the association between serum sodium levels and severity of ascites and complications of cirrhosis, prospective data were collected on 997 consecutive patients from 28 centers in Europe, North and South America, and Asia for a period of 28 days. The prevalence of low serum sodium concentration as defined by a serum sodium concentration ≤135 mmol/L, ≤130 mmol/L, ≤125 mmol/L, and ≤120 mmol/L was 49.4%, 21.6%, 5.7%, and 1.2%, respectively. The prevalence of low serum sodium levels (<135 mmol/L) was high in both inpatients and outpatients (57% and 40%, respectively). The existence of serum sodium <135 mmol/L was associated with severe ascites, as indicated by high prevalence of refractory ascites, large fluid accumulation rate, frequent use of large-volume paracentesis, and impaired renal function, compared with normal serum sodium levels. Moreover, low serum sodium levels were also associated with greater frequency of hepatic encephalopathy, spontaneous bacterial peritonitis, and hepatorenal syndrome, but not gastrointestinal bleeding. Patients with serum sodium <130 mmol/L had the greatest frequency of these complications, but the frequency was also increased in patients with mild reduction in serum sodium levels (131-135 mmol/L). In conclusion, low serum sodium levels in cirrhosis are associated with severe ascites and high frequency of hepatic encephalopathy, spontaneous bacterial peritonitis, and hepatorenal syndrome. (HEPATOLOGY **2006;44:1535-1542.**)

Impairment in body water homeostasis is a common feature of advanced cirrhosis.[1-3] This is characterized by a higher rate of renal retention of water in relation to sodium due to a reduction in solute-free water clearance. The consequent inability to adjust the amount of water excreted in the urine to the amount of water ingested leads to dilutional hyponatremia. In recent years, great advances have been made in the knowledge of the pathogenesis of reduced solute-free water clearance in patients with advanced cirrhosis. The inability to excrete an adequate amount of solute-free water in the urine is related to several factors, the most important of which is increased vasopressin release. A reduction of effective circulating volume due to arterial splanchnic vasodilation is considered the afferent factor leading to a baroreceptor-mediated nonosmotic stimulation of vasopressin release in cirrhosis.[4] Additional factors in the pathogenesis of hyponatremia in cirrhosis are thought to be reduced production of solute-free water due to a reduced sodium delivery to the distal tubule as a consequence of reduction of glomerular filtration rate and/or increase of sodium reabsorption in the proximal tubule.[4-7]

Several studies in large cohorts of patients with cirrhosis have shown that the renal ability to excrete free water, as assessed either by measuring solute-free water clearance or serum sodium concentration, shows an excellent correlation with survival. Patients with hyponatremia have a poor survival compared with that of patients without hyponatremia.[8-10] Moreover, recent studies have shown that serum sodium concentration correlates with survival in patients with cirrhosis awaiting liver transplantation, and the suggestion has been made that serum sodium could be

Abbreviations: CRF, case report form; CAPPS, Cirrhotic Ascites Patient Population Survey.

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added to the calculation of model for end-stage liver disease score to improve the accuracy of this scoring system in organ allocation for liver transplantation.[11-14] In contrast with the large amount of information that has been accumulated on the value of serum sodium in the prediction of prognosis, little is known regarding the clinical significance of the presence of hyponatremia, particularly the relationship between serum sodium levels and characteristics of ascites and development of complications of cirrhosis. Therefore, the aim of the present study was to assess the prevalence of low serum sodium levels and to determine the association between serum sodium levels and the characteristics of ascites and occurrence of other complications of cirrhosis by means of a prospective epidemiological study in a large series of patients with cirrhosis-related ascites.

Patients and Methods

Study Population. The study involved the prospective collection of data on patients from 28 hospital hepatology departments in Europe, North and South America, and Asia. For a period of 28 days at each center, consecutive patients with cirrhosis and ascites attending the hepatology outpatient clinics or under the care of hepatologists as inpatients were included in the study. The data collection was performed between March 2003 and August 2003 and was planned to include a minimum of 500 patients. The recording of consecutive inpatients or outpatients at each center was designed to avoid any bias due to selection of patients. Patients were included in the study according to the following criteria: (1) diagnosis of cirrhosis of the liver diagnosed either by histology or a combination of clinical, biochemical, and ultrasonographic findings; and (2) presence of ascites determined via paracentesis or ultrasonography. Data recorded were those routinely collected for the management of cirrhosis and ascites, and no investigations or interventions were performed expressly for the purpose of the study. Data on each patient were recorded at a single time point (1) when the patient came to an outpatient visit, (2) on admission as an inpatient, or (3) at the start of the study if the patient was already hospitalized. No patient was included more than once, and no follow-up of the patients was performed. The study was approved by the institutional review board of each participating hospital.

Data Collection. The method for data collection used in the prospective survey provided a case report form (CRF) that included five major sections. The first section included demographics and the status of the patients at the time of inclusion (inpatient or outpatient) as well as etiology, severity, and duration of cirrhosis. The severity of liver disease was assessed using the Child-Pugh score. Model for end-stage liver disease score could not be calculated, because measurement of international normalized ratio was not routinely performed in all participating centers. Duration of cirrhosis was estimated in years since diagnosis. In the second section of the CRF, several questions about the description and classification of ascites were included. Refractory and recidivant ascites were defined according to International Ascites Club criteria[15]: refractory ascites was defined as being nonresponsive to diuretics and not treatable with diuretics; recidivant ascites was defined as recurring at least 3 times per year despite treatment with diuretics and a low-sodium diet. In patients with neither refractory nor recidivant ascites, ascites was graded as moderate or tense. In addition, two more questions about (1) current body weight (kg) and (2) change in body weight (kg) and time interval since last visit (in weeks) were included in this section. In the third section of the CRF, several questions about the management of ascites were included. The patients were classified as those who were on diuretic treatment at time of inclusion and those who were not. The patients on diuretic treatment were then classified according to the number of diuretics that they were taking. The following information was then collected in patients on current diuretic treatment: (1) dose of spironolactone (mg/d), (2) dose of furosemide (mg/d), and (3) other diuretic agents and doses (mg/d). The following information on therapeutic paracentesis was collected: (1) repeated use of paracentesis, (2) time interval between the last two paracenteses (weeks), and (3) volume of ascites removed at the last paracentesis (liters). Any surgical or interventional procedures were recorded under the following categories: (1) previous insertion of transjugular intrahepatic portal systemic shunt and (2) previous insertion of peritoneovenous shunt. In the fourth section of the CRF, several questions were included about the occurrence of complications of cirrhosis other than ascites, such as: spontaneous bacterial peritonitis, gastrointestinal bleeding, hepatic encephalopathy, and hepatorenal syndrome, in the 4 weeks prior to the inclusion in the study. In the fifth and last section of the CRF, the most recently available results of the following tests: serum sodium, serum creatinine, serum bilirubin, serum albumin, prothrombin time, 24-hour urine volume, urine sodium concentration (24-hour or spot urine sodium concentration) were requested.

Data Quality Assurance. Management of clinical data was performed according to the following rules and procedures. Data entry, verification, and validation were performed using standard computer software (Clintrial); data were stored in an Oracle database on a Digital VMS computer. A double-entry method was used to ensure that

Table 1. Participating Countries and Centers and Number of Cases Documented

Geographical Area	No. of Countries	No. of Centers	No. of Documented Cases
Western Europe	5	11	560
Central Europe	3	6	111
North America	2	5	200
South America	1	2	74
Asia	3	4	52
Total	14	28	997

the data (except comments) were transferred accurately from the CRFs to the database. Moreover, every modification in the database could be traced using an audit trail. A data checking plan was established to define all automatic validation checks, as well as supplemental manual checks, to ensure data quality. All discrepancies were researched until resolved.

Statistical Methods. Results are expressed as the mean ± SD. Association of serum sodium with several variables—including patient characteristics, management of ascites, and complications of cirrhosis—was tested using ANOVA for continuous variables and chi-square test or Fisher exact test when appropriate for nominal variables. Patients were divided into three groups according to serum sodium concentration as follows: (1) serum sodium ≤130 mmol/L, (2) serum sodium between 131 mmol/L and 135 mmol/L, and (3) serum sodium >135 mmol/L. The cutoff level of 130 mmol/L was chosen because it is widely accepted to define hyponatremia in patients with cirrhosis, while the level of 135 mmol/L is the lower normal value.[4] *P* values of less than .05 were considered statistically significant.

Results

Number of Patients Documented and Completeness of Data. Data were obtained from 28 centers on 997 patients. The participating countries and centers and the number of cases documented are shown in Table 1. Responses to questions on demographics, classification of ascites, current medical therapy for ascites, use of therapeutic paracentesis, other interventions or surgical procedures, laboratory values, and recent complications of cirrhosis were obtained in 95% to 100% of the cases. Responses on weight change and time elapsing since the previous consultation were obtained in 60% of the cases. Serum sodium values were missing in 14 of the 997 patients included, thus statistical analyses relative to serum sodium refer to 983 patients.

Demographics and Features of Liver Disease. The survey population included 650 males (65.2%) and 347 females (34.8%). The mean age of the patients was 58.7 years with a range of 14 to 87. Inpatients accounted for 529 of the cases (53.1%), and 468 were outpatients (46.9%). The proportion of patients who were being treated as inpatients ranged from 34.5% in North America to 61.6% in Western Europe ($P < .001$). Cirrhosis was alcohol-related in 501 patients (50.3%), hepatitis C–related in 323 patients (32.4%), and hepatitis B–related in 98 patients (9.8%). These categories were not mutually exclusive, and 78 patients (7.8%) had two or three etiologies listed. Patients in Central Europe were more likely to have alcohol abuse as an etiology of cirrhosis (73% vs. 39%-46% in other regions) ($P < .001$), whereas hepatitis C was most common in Western Europe (37% vs. 6%-28% in other regions) ($P < .001$). The time since diagnosis of cirrhosis was given for 931 patients and ranged from 1 to 35 years. Child-Pugh class was given for 964 patients; most of these patients were in class B (n = 479) or class C (n = 414). As expected, inpatients had a higher Child-Pugh score (57.3% in class C) compared with 27.0% of outpatients ($P < .001$). There was no difference in age distribution, male/female ratio, and Child-Pugh classification among the different geographical regions.

The majority of patients (833/997 [83.6%]) were receiving one or more diuretic agents (Table 2). The most common diuretic used was spironolactone, in 755 patients (75.7%), which was given in the majority of cases at daily doses of 100 mg or 200 mg. The second most commonly used diuretic agent was furosemide in 659 patients (66.1%) given in doses of 40 mg or 80 mg/d. Six hundred thirty-six patients were taking two or three diuretic agents concomitantly, the most frequent combination being spironolactone and furosemide (n = 590). Large-volume paracentesis had been performed on more than one occasion in 417/992 patients (42.1%), while transjugular intrahepatic portal systemic shunt had been performed in 70 patients (7.0%) and peritoneovenous shunting had been performed in 12 patients (1.2%).

Table 2. Diuretic Therapy in Patients Included in the Study

Spironolactone plus furosemide	590
Spironolactone alone	124
Furosemide alone	64
Spironolactone plus other diuretics*	41
Other diuretics (alone or in combination)†	14
No diuretics	164

*Other diuretics included torasemide (n = 20), metolazone (n = 14), hydrochlorothiazide (n = 8), ethacrynic acid (n = 2), xipamide (n = 2), bumetanide (n = 1), and potassium canrenoate (n = 1). Some patients were taking three different diuretics.

†Amiloride, furosemide, ethacrynic acid.

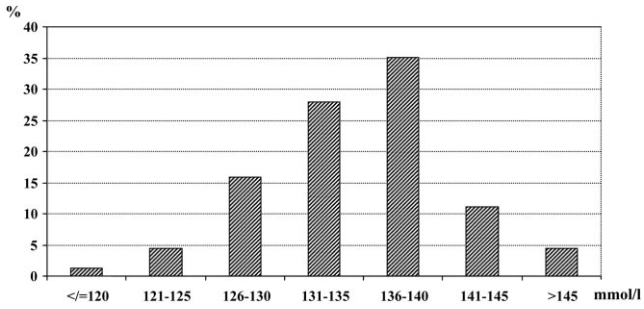

Fig. 1. Distribution of serum sodium in patients with cirrhosis-related ascites. The normal laboratory range is 136-145 mmol/L.

Association of Serum Sodium Values With Patient Characteristics, Features of Ascites and Renal Function, and Complications of Cirrhosis. Figure 1 shows the distribution of values of serum sodium in the entire population of patients. In total, 486/983 patients (49.4%) had values below the normal range (135 mmol/L) and 211/983 patients (21.6%) had values ≤130 mmol/L, which is the cutoff value widely used to define hyponatremia.[4] A serum sodium level below the normal range was observed in 57.4% of inpatients and in 40.2% of outpatients. The prevalence of a serum sodium ≤130 mmol/L was also higher in inpatients than in outpatients (28.0% vs. 13.8 %; $P < .001$). There were also some geographical variations in the proportion of patients with low serum sodium concentrations. In particular, patients from Asia and South America had a lower incidence of hyponatremia compared with that of patients from other geographical areas.

To assess the association between serum sodium and patient characteristics and complications of cirrhosis, the patients were divided into three groups according to serum sodium values. Serum sodium values were not associated with age, sex, or etiology of cirrhosis but were strongly associated with the severity of cirrhosis as assessed via Child-Pugh class (Table 3). In addition, there was a clear association between serum sodium levels and specific features of ascites and renal function (Table 4). The presence of low serum sodium values was associated with a higher prevalence of refractory ascites, greater fluid accumulation (as estimated via changes in body weight during the previous month), greater likelihood of undergoing paracentesis, and impaired renal function (as estimated via serum creatinine concentration). The mean values of serum creatinine in patients with serum sodium ≤130 mmol/L, 131-135 mmol/L, and >135 mmol/L were 130.0 ± 104.8 μmol/L, 114.4 ± 74.7 μmol/L, and 107.8 ± 72.9 μmol/L, respectively ($P = .004$). The number of patients not receiving diuretics was higher in the group of patients with serum sodium ≤130 mmol/L (60 patients, 28.4%) compared with the other two groups (>135 mmol/L: 69 patients, 13.9%; 131-135 mmol/L: 33 patients, 12%) ($P < .001$ for all).

Finally, the possible association between serum sodium concentration and complications of cirrhosis that had occurred within a 4-week period of the index visit was also assessed (Fig. 2 and Table 5). There was a clear inverse relationship between serum sodium levels and frequency of hepatic encephalopathy, spontaneous bacterial peritonitis, and hepatorenal syndrome. Patients with serum sodium ≤130 mmol/L had a much greater frequency of these complications compared with that of patients with normal serum sodium concentration. Moreover, patients with serum sodium concentration between 131 and 135 mmol/L had a frequency of complications lower than that of patients with serum sodium concentration ≤130 mmol/L but higher than that of patients with normal serum sodium levels. By contrast, the frequency of gastrointestinal bleeding was similar among groups, indicating a lack of association between serum sodium values and this major complication of portal hypertension.

Table 3. Characteristics of Patients Included in the Study Classified According to Serum Sodium Concentration

	>135 mmol/L (n = 497)	131–135 mmol/L (n=275)	≤130 mmol/L (n = 211)	*P* Value
Sex				
Female	191	92	59	NS
Male	306	183	152	NS
Age (yr)	59.3 ± 11.5	57.6 ± 11.1	58.9 ± 11.3	NS
Etiology of cirrhosis				
Alcoholic	245	136	115	
Nonalcoholic	252	139	96	NS
Child-Pugh class				
A	53	14	2	
B	280	120	75	
C	155	130	126	<.001

Abbreviation: NS, not significant.

Table 4. Characteristics and Management of Ascites and Serum Creatinine Concentration of Patients Included in the Study Classified According to Serum Sodium Concentration

	>135 mmol/L (n = 497)	131–135 mmol/L (n = 275)	≤130 mmol/L (n = 211)	*P* Value
Classification of ascites				
Number of patients	496	271	211	<.001
Refractory	65 (13.1)	50 (18.5)	62 (29.4)	
Recidivant	72 (14.5)	30 (13.7)	36 (17.1)	
Other	359 (72.4)	184 (67.9)	113 (53.6)	
Weight change since last visit				
Number of patients	287	164	125	<.001
>+1 kg/wk	41 (14.3)	44 (26.8)	51 (40.8)	
+/−1 kg/wk	234 (81.5)	105 (64.0)	65 (52.0)	
<−1 kg/wk	12 (4.2)	15 (9.1)	9 (7.2)	
Therapeutic paracentesis				
Number of patients	164	113	117	<.001
Yes	172 (34.9)	120 (43.6)	121 (57.9)	
No	321 (65.1)	155 (56.4)	88 (42.1)	
Interval between the last two paracentesis (wk)	6.4 ± 7.3	5.7 ± 7.6	3.7 ± 4.0	.003
Serum creatinine				
Number of patients	497	274	210	.005
Normal (≤108 μmol/L)	357 (71.8)	182 (66.4)	125 (59.5)	
Increased (>108 μmol/L)	140 (28.2)	92 (33.6)	85 (40.5)	

Discussion

This study represents the largest investigation reported thus far assessing serum sodium concentration in patients with cirrhosis and the association between serum sodium levels and the occurrence of major complications of cirrhosis. The results indicate that a large proportion of patients with cirrhosis have abnormal values of serum sodium concentration. In fact, almost one half (49.4%) of patients with cirrhosis had values of serum sodium concentration below the normal range (≤135 mmol/L) and one fifth (21.6%) had values ≤130 mmol/L. Values below 125 mmol/L were uncommon. Low serum sodium levels were not associated with age, sex, or etiology of cirrhosis but were more frequent in patients with severe liver failure (55% of patients belonged to Child-Pugh class C). Nevertheless, it should be pointed out that low serum sodium levels were also found in patients with moderate liver failure (Child-Pugh B or even Child-Pugh A). As expected, the prevalence of low serum sodium levels was very high in inpatients (57%), but it was also marked in outpatients (40%). The frequency of serum sodium ≤130 mmol/L in inpatients was 28%, a figure similar to that reported in previous studies including a lower number of patients compared with the current investigation.[3,16-18] Moreover, our study shows that the occurrence of low serum sodium levels is greater than previously reported, because a further 29% of inpatients had a mild reduction in serum sodium levels (between 131 and 135 mmol/L). Corresponding figures in outpatients were 14% and 26%, respectively.

Although it is generally believed that the existence of a serum sodium concentration ≤130 mmol/L is associated with difficult-to-treat ascites, few studies have been reported that specifically analyze the relationship between serum sodium levels and responsiveness of ascites to diuretic therapy. Arroyo et al.[3] reported that the presence of serum sodium ≤130 mmol/L was associated with lower glomerular filtration rate and solute-free clearance and a

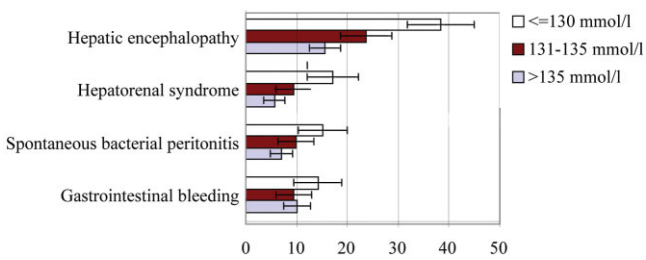

Fig. 2. Percentage of patients (±95% CI) with complications of cirrhosis within a 4-week period of the index visit classified according to serum sodium concentration.

Table 5. Odds Ratios for Different Complications of Cirrhosis in Patients With Serum Sodium Concentration Between 131 and 135 mmol/L and Patients With Serum Sodium Concentration Equal to or Lower Than 130 mmol/L

	131–135 mmol/L (95% CI)	≤130 mmol/L (95% CI)
Hepatic encephalopathy	1.69 (1.16–2.45)	3.40 (2.35–4.92)
Hepatorenal syndrome	1.75 (1.00–3.05)	3.45 (2.04–5.82)
Spontaneous bacterial peritonitis	1.44 (0.85–2.43)	2.36 (1.41–3.93)
Gastrointestinal bleeding	0.93 (0.56–1.54)	1.48 (0.91–2.41)

NOTE. The group of patients with serum sodium >135 mmol/L was used as a reference.

poorer response to diuretics compared with patients with serum sodium >130 mmol/L. Subsequent studies by Bernardi et al.[19] and Angeli et al.[20] showed that patients who do not respond to diuretics have lower serum sodium concentration compared with patients who respond to diuretics. The results of the current study confirm and extend these observations by showing that patients with serum sodium concentration ≤130 mmol/L have a higher frequency of refractory ascites, lower response in terms of change in body weight, higher requirement of large-volume paracentesis to manage their ascites, and a shorter interval between paracentesis. Moreover, the results show that patients with serum sodium between 131 and 135 mmol/L have signs of poor ascites response compared with patients with normal serum sodium concentration, although to a lesser extent than patients meeting the classical definition of hyponatremia (serum sodium ≤130 mmol/L).

Another significant finding was that serum sodium levels were strongly associated with the occurrence of some of the major complications of cirrhosis within a 4-week period of the inclusion of the patient in the study. In fact, the frequency of hepatic encephalopathy, hepatorenal syndrome, and spontaneous bacterial peritonitis were associated with serum sodium levels in such a way that patients with serum sodium ≤130 mmol/L had a significantly greater frequency of these complications compared with patients with normal serum sodium concentration. Patients with serum sodium between 131 and 135 mmol/L had a lower frequency of complications compared with patients with serum sodium ≤130 mmol/L, but higher than that of patients with normal serum sodium concentration (Fig. 2 and Table 5). Interestingly, there was no significant association between gastrointestinal bleeding and serum sodium levels. These higher frequency of complications may account at least in part for the poor survival reported for patients with low serum sodium concentration.[8-14] Although the results do not make it possible to prove the existence of a causal link between low serum sodium levels and these three major complications of cirrhosis, they suggest the possibility of a potentially negative impact of low serum sodium levels—even a mild reduction—on the clinical course of cirrhosis. Moreover, the results suggest that serum sodium levels should be closely monitored in patients experiencing these complications.

More than one third (38%) of the patients with serum sodium ≤130 mmol/L had an episode of hepatic encephalopathy within the previous month, compared with one fourth (24%) of patients with serum sodium between 131 and 135 mmol/L and only 15% of patients with normal serum sodium levels (Fig. 2 and Table 5). Although this association between hepatic encephalopathy and low serum sodium levels may be explained only on the basis of more severe liver failure among patients with serum sodium ≤130 mmol/L, there is also the possibility that the two events may be pathophysiologically linked. In fact, it has been demonstrated that low serum sodium levels in patients with cirrhosis are associated with a remarkable reduction in the cerebral concentration of organic osmolytes that probably reflect compensatory osmoregulatory mechanisms against cell swelling triggered by a combination of high intracellular glutamine, as a consequence of hyperammonemia, and low extracellular sodium.[21-23] In experimental models of acute liver failure, the presence of hyponatremia is associated with larger brain swelling compared with normal serum sodium concentration.[24] Finally, in patients with acute liver failure and grade IV hepatic encephalopathy, the administration of hypertonic saline to increase serum sodium concentration reduces the incidence and severity of intracranial hypertension compared with a control group of patients receiving the standard of care.[25]

Hepatorenal syndrome was also strongly associated with low serum sodium concentration in our series (17% in patients with serum sodium ≤130 mmol/L compared with 10% in patients with serum sodium 130-135 mmol/L and only 6% in patients with normal serum sodium concentration) (Fig. 2 and Table 5). This association may be explained by the fact that hepatorenal syndrome is frequently associated with an impaired excretion of solute-free water, so that the majority of patients with hepatorenal syndrome have a concomitant reduction of serum sodium concentration.[26,27] Alternatively, it has been shown that hyponatremia is a major risk factor for the development of hepatorenal syndrome in patients with ascites.[28] This increased risk of hepatorenal syndrome may be related to a more severe circulatory dysfunction of patients with hyponatremia compared with patients without hyponatremia.[4]

Finally, our data also indicate the existence of an association between spontaneous bacterial peritonitis and low serum sodium levels (Fig. 2 and Table 5). This association probably reflects the impairment in effective circulating blood volume that occurs in patients with cirrhosis in the setting of spontaneous bacterial peritonitis and may lead to hepatorenal syndrome in some patients, while others may develop only hyponatremia.[29-31] Hyponatremia has also been reported in the setting of sepsis unrelated to spontaneous bacterial peritonitis.[32] These findings indicate that close monitoring of serum creatinine and serum sodium concen-

tration should be performed in patients with cirrhosis throughout the course of a bacterial infection. Alternatively, the results may also suggest that patients with hyponatremia are a high-risk group for the development of spontaneous bacterial peritonitis in cirrhosis.

In conclusion, the results of this large observational study indicate that low serum sodium levels are a common feature in patients with cirrhosis, both inpatients as well as outpatients. The existence of serum sodium concentration <135 mmol/L is associated with a poor control of ascites and greater frequency of hepatic encephalopathy, hepatorenal syndrome, and spontaneous bacterial peritonitis compared with patients with serum sodium concentration within the normal range (>135 mmol/L). Patients with a serum sodium concentration <130 mmol/L are those with the greatest frequency of severe ascites and associated complications. Nevertheless, even patients with a mild reduction in serum sodium concentration should be considered a high-risk population because of their more severe ascites and greater frequency of major complications of cirrhosis compared with patients with normal serum sodium concentration.

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References

1. Hecker R, Sherlock S. Electrolyte and circulatory changes in terminal liver failure. Lancet 1956;271:1121-1125.
2. Shear L, Hall PW 3rd, Gabuzda GJ. Renal failure in patients with cirrhosis of the liver. II. Factors influencing maximal urinary flow rate. Am J Med 1965;39:199-209.
3. Arroyo V, Rodes J, Gutierrez-Lizarraga MA. Prognostic value of spontaneous hyponatremia in cirrhosis with ascites. Dig Dis Sci 1976;21:249-256.
4. Ginès P, Berl T, Bernardi M, Bichet DG, Hamon G, Jimenez W, et al. Hyponatremia in cirrhosis: from pathogenesis to treatment. HEPATOLOGY 1998;8:851-864.
5. Bichet D, Szatalowicz V, Chaimovitz C, Schrier RW. Role of vasopressin in abnormal water excretion in cirrhotic patients. Ann Intern Med 1982; 96:423-427.
6. Epstein M. Derangements of renal water handling in liver disease. Gastroenterology 1985;89:1415-1425.
7. Schrier RW, Arroyo V, Bernardi M, Epstein M, Henriksen JH, Rodes J, et al. Peripheral arteriolar vasodilation hypothesis: a proposal for the initiation of renal sodium and water retention in cirrhosis. HEPATOLOGY 1988; 8:1151-1157.
8. Llach J, Ginès P, Arroyo V, Rimola A, Tito L, Badalamenti S, et al. Prognostic value of arterial pressure, endogenous vasoactive systems, and renal function in cirrhotic patients admitted to the hospital for the treatment of ascites. Gastroenterology 1988;94:482-487.
9. Cosby RL, Yee B, Schrier RW. New classification with prognostic value in cirrhotic patients. Miner Electrolyte Metab 1989;15:261-266.
10. Fernandez-Esparrach G, Sanchez-Fueyo A, Ginès P, Uriz J, Quinto L, Ventura PJ, et al. A prognostic model for predicting survival in cirrhosis with ascites. J Hepatol 2001;34:46-52.
11. Heuman DM, Abou-assi SG, Habib A, Williams LM, Stravitz RT, Sanyal AJ, et al. Persistent ascites and low serum sodium identify patients with cirrhosis and low MELD scores who are at risk for early death. HEPATOLOGY 2004;40:802-810.
12. Biggins SW, Rodriguez HJ, Bacchetti P, Bass NM, Roberts JP, Terrault NA. Serum sodium predicts mortality in patients listed for liver transplantation. HEPATOLOGY 2005;41:32-39.
13. Ruf AE, Kremers WK, Chavez LL, Descalzi VI, Podesta LG, Villamil FG. Addition of serum sodium into the MELD score predicts waiting list mortality better than MELD alone. Liver Transpl 2005;11:336-343.
14. Biggins SW, Kim WR, Terrault NA, Saab S, Balan V, Schiano T, et al. Evidence-based incorporation of serum sodium concentration into MELD. Gastroenterology 2006;130:1652-1660.
15. Arroyo V, Ginès P, Gerbes AL, Dudley FJ, Gentilini P, Laffi G, et al. Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. HEPATOLOGY 1996;23:164-176.
16. Borroni G, Maggi A, Sangiovanni A, Cazzaniga M, Salerno F. Clinical relevance of hyponatraemia for the hospital outcome of cirrhotic patients. Digest Liver Dis 2000;32:605-610.
17. Porcel A, Diaz F, Rendom P, Macias M, Martin-Herrera L, Giron-Gonzalez J. Dilutional hyponatremia in patients with cirrhosis and ascites. Arch Intern Med 2002;162:323-328.
18. Arroyo V. Milestones in liver disease: Hecker R, Sherlock S. Electrolyte and circulatory changes in terminal liver failure (Lancet 1956;2:1221-1225). J Hepatol 2002;36:315-320.
19. Bernardi M, Laffi G, Salvagnini M, Azzena G, Bonato S, Marra F, et al. Efficacy and safety of the stepped care medical treatment of ascites in liver cirrhosis: a randomized controlled clinical trial comparing two diets with different sodium content. Liver 1993;13:156-162.
20. Angeli P, Pria MD, De Bei E, Albino G, Caregaro L, Merkel C, et al. Randomized clinical study of the efficacy of amiloride and potassium canrenoate in nonazotemic cirrhotic patients with ascites. HEPATOLOGY 1994; 19:72-79.
21. Haussinger D, Laubenberger J, vom Dahl S, Ernst T, Bayer S, Langer M, et al. Proton magnetic resonance spectroscopy studies on human brain myo-inositol in hypo-osmolarity and hepatic encephalopathy. Gastroenterology 1994;107:1475-1480.
22. Restuccia T, Gomez-Anson B, Guevara M, Alessandria C, Torre A, Alayrach ME, et al. Effects of dilutional hyponatremia on brain organic osmolytes and water content in patients with cirrhosis. HEPATOLOGY 2004; 39:1613-1622.
23. Häussinger D. Low grade cerebral edema and the pathogenesis of hepatic encephalopathy in cirrhosis. HEPATOLOGY 2006;43:1187-1190.
24. Cordoba J, Gottstein J, Blei AT. Chronic hyponatremia exacerbates ammonia-induced brain edema in rats after portacaval anastomosis. J Hepatol 1998;29:589-594.

25. Murphy N, Auzinger G, Bernel W, Wendon J. The effect of hypertonic sodium chloride on intracranial pressure in patients with acute liver failure. HEPATOLOGY 2004;39:464-470.
26. Ginès P, Guevara M, Arroyo V, Rodes J. Hepatorenal syndrome. Lancet 2003;362:1819-1827.
27. Alessandria C, Ozdogan O, Guevara M, Restuccia T, Jimenez W, Arroyo V, et al. MELD score and clinical type predict prognosis in hepatorenal syndrome: relevance to liver transplantation. HEPATOLOGY 2005;41:1282-1289.
28. Gines A, Escorsell A, Ginès P, Salo J, Jimenez W, Inglada L, et al. Incidence, predictive factors and prognosis of the hepatorenal syndrome in cirrhosis with ascites. Gastroenterology 1993;105:229-236.
29. Ruiz del Arbol L, Urman J, Fernandez J, Gonzalez M, Navasa M, Monescillo A, et al. Systemic, renal and hepatic haemodynamic derangement in cirrhotic patients with spontaneous bacterial peritonitis. HEPATOLOGY 2003;38:1210-1218.
30. Ruiz del Arbol L, Monescillo A, Arocena C, Valer P, Gines P, Moreira V, et al. Circulatory function and hepatorenal syndrome in cirrhosis. HEPATOLOGY 2005;42:439-447.
31. Angeli P, Guarda S, Fasolato S, Miola E, Craighero R, Del Piccolo F, 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.
32. Terra C, Guevara M, Torre A, Gilabert R, Fernández J, Martín-Llahí M, et al. Renal failure in cirrosis and sepsis unrelated to spontaneous bacterial peritonitis. Value of MELD score. Gastroenterology 2006;129:1944-1953.