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Risk Factors Recurrence of Spontaneous Ascitic Fluid Infection (Slai) in Cirrhotic Patients

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Abstract

Introduction: After an episode of spontaneous infection of ascitic fluid (ISLA). The recurrence of ISLA at one year is greater than 70%. We studied the risk factors associated with the occurrence of recurrence. Patients and methods: this was a retrospective, descriptive and analytical study of patient files, hospitalized in the department for 12 months, the choice of the sample was of convenience. Results: We have 1347 patient files collected including 389 cases of cirrhosis. We had 37 files of cirrhotic patients with ISLA including 28 cures without recurrence of ISLA, 08 files of patients with recurrence of ISLA and 03 excluded, *i.e.* a hospital prevalence of recurrence of 0.6% and a prevalence in cirrhotic patients of 23.5%. The most common antecedents were: hospital contact recent (35.3%), the concept of iterative ascites punctures (32.3%), the presence of HCC (29.4%), hepatic encephalopathy (20.6%) and digestive hemorrhage (14.7%). In univariate analysis, recent digestive bleeding was associated with an increased risk of recurrence (OR 7.2, 95% CI 0.96 - 67.1). HBV (62.5%) is the main etiology of cirrhosis. The PNN rate at 250 - 499 mm^3 (62.5%), the protein level <10 g/l (50%), the platelet level <200 G/mm^3 (75%). Patients on secondary prophylaxis with NORFLOXACIN were 25%. Recurrence of ISLA was treated with CEFTRIAXONE 2 g/24 hours. Conclusion: Recurrence of ISLA is serious, the predictive factors for recurrence are, hospital contact recent, the concept of iterative ascites punctures, the presence of HCC, the presence of hepatic encephalopathy and digestive bleeding.

Keywords

Antibiotic, Cirrhosis, Risk factors, Spontaneous Ascitic Fluid Infection, Recurrence

1. Introduction

Spontaneous ascitic fluid infection (SLAI) is a common complication during cirrhosis and is associated with a poor prognosis [1]. It is defined by the presence of a polynuclear neutrophil count (PNN) greater than 250/mm3 in the ascitic fluid, in the absence of digestive perforation and an intra-abdominal infectious focus [2]. Ascitic fluid infection is an extremely serious complication, occurring in approximately 20 to 30% of cirrhotic patients, especially when the protein level in the ascitic fluid is less than 10 g/l [3]-[5]. Hospital mortality varies from 10 to 50% [6]

This infection has a poor prognosis, because it is responsible for a worsening of hepatocellular insufficiency, a deterioration of renal function and an increase in portal pressure with a high risk of rupture of esophageal varices [3] [7]. The management of ISLA has been significantly improved over the last 30 years, reducing hospital mortality from 90% to approximately 20% [8].

After an episode of ISLA the risk of recurrence is high in the absence of prophylaxis [2]. The recurrence of ISLA at one year is greater than 70%, which justifies, on the one hand, that we consider secondary prophylaxis and on the other hand, that we discuss a possible liver transplant due to the significant mortality [2].

Prevention of recurrence of ISLA currently relies on antibiotic prophylaxis with quinolones. The administration of norfloxacin at a rate of 400 mg/day orally is effective in preventing the recurrence of ISLA [9]. Indeed, it has been demonstrated that the recurrence at one year was 20% in subjects treated with Norfloxacin versus 68% in the placebo group. It is therefore recommended to start secondary prophylaxis with norfloxacin after the first episode of ISLA [9].

Worldwide, there are few publications on the recurrence of ISLA. Moreover, the predictive factors for the recurrence of ISLA in cirrhotic patients are still poorly understood.

In sub-Saharan Africa, work relating to the recurrence of ISLA in cirrhotic patients is rare; in Côte d'Ivoire, although decompensated cirrhotic patients are frequently hospitalized, no study is available to our knowledge to date [10] [11] hence the interest of our study which aims to determine the factors of risk of recurrence of ISLA in cirrhotic patients hospitalized in our department.

2. Materials and Methods

This is a retrospective, descriptive and analytical study covering all the files of patients hospitalized in the hepato-gastroenterology department of the Hospital

and University Center (CHU) of Cocody; going from January 1, 2021 to December 31, 2022, *i.e.* 12 months, the choice of the sample was of convenience. Included in this study: the files of known cirrhotic patients with a recurrence of ISLA (cirrhotic patient having presented a first episode of ISLA diagnosed, treated then cured in the department who subsequently presents a new rise in the level of polynuclear neutrophils greater than 250/mm^3 in the ascites fluid after initial control). Not included were cirrhotic patients with recurrence of ISLA whose files were incomplete (unavailability of data on cirrhosis and its complications before recurrence of ISLA, elements of the management and cure of the 1st episode of ISLA). ISLA, data on the complications of cirrhosis during recurrence and data on the management of recurrence). The main endpoint for recovery from the first episode of ISLA was a neutrophil count below 250/mm^3 at control. Mortality was not assessed in this study because of the retrospective nature and the fact that the department only had two intensive care beds; requiring the admission of these bedridden patients to the intensive care unit. Recent Hospital contact was defined as a hospital stay in the last three months before the ISLA recurrence episode.

➢ Sociodemographic parameters

- Age
- Sex

➢ Clinical parameters

These are clinical data collected in hospitalization using medical records before and during the recurrence of ISLA:

- Before the recurrence of ISLA: notion of portal thrombosis, HCC, hepatorenal syndrome, hepatic encephalopathy, digestive bleeding, recent hospital contact.
- Time between 1st episode of ISLA and recurrence of ISLA.
- During recurrence: concept of recent digestive bleeding, refractory ascites, portal thrombosis, HCC, hepatorenal syndrome (HRS), hepatic encephalopathy, infection urinary.
- Other data collected: etiology of cirrhosis, HIV status.

➢ Biological parameters

- During the 1st episode of ISLA:

-Blood platelet level (NFS)

-Analysis of ascites fluid including a cytological examination (leukocyte count: PNN and lymphocytes) and chemical (dosage of protein levels) as part of the diagnosis of the 1st ISLA.

- After treatment of the 1st episode of ISLA:

-Blood platelet level (NFS)

-Analysis of ascites fluid including a cytological examination (leukocyte count: PNN and lymphocytes) and chemical (dosage of protein levels) as part of the evaluation of the healing of the 1st ISLA.

- During ISLA recurrence:

-Blood platelet level (NFS).

-Analysis of ascitic fluid including a cytological examination (leukocyte count: PNN and lymphocytes) and chemical examination (measurement of protein levels) as part of the diagnosis of recurrent ISLA.

- Other assessments:

-Biological parameters for assessing the severity of cirrhosis by the CHILD-PUGH Score before and during recurrence of ISLA.

o Prothrombin level (PT)

o Total bilirubinemia

o The protodogram: Albumin, total proteins

- Serum creatinine before and during ISLA recurrence
- Alpha feto-protein level before and during ISLA recurrence
- Viral markers: viral hepatitis B (HBV), C (HCV), D (HDV)
- Retroviral serology HIV
- Cytobacteriological examination of urine (ECBU)

➢ Radiological parameters

- Abdominal ultrasound or abdominal scanner: to assess the intra-abdominal organs; especially look for hepatic dysmorphia, signs of PH, a nodule suspicious for hepatocellular carcinoma (HCC) and/or the kinetics of HCC "Wash out"; appreciate the abundance of ascites. For the diagnosis of HCC, it was retained on the basis of CT and/or ultrasound with elevation of alpha feto-protein (AFP).

➢ Risk factors

The following elements were considered as risk factors for the recurrence of ISLA in cirrhotic patients:

- A high neutrophil count in ascites during the first episode of ISLA.
- A low concentration of ascites in proteins < 10 g.
- A history of ISLA.
- Hepatic encephalopathy.
- A urinary infection is diagnosed before the occurrence of ISLA recurrence.
- The absence of antibiotic prophylaxis secondary to nofloxacin after the first episode of ISLA.
- Blood platelet level < or = 100,000/mm^3.

➢ Prognosis: assess by the CHILD-PUGH score (before ISLA recurrence and during ISLA recurrence)

➢ Treatment:

- The notion of etiological treatment of cirrhosis (antiviral or other) before recurrence.
- The concept of iterative ascites punctures before recurrence.
- Use of antibiotics alone or in combination with human albumin during the first episode of ISLA.
- Use of secondary antibiotic prophylaxis after the first episode of ISLA.
- The concept of taking medication before the occurrence of recurrence of ISLA: Beta-blockers, diuretics, proton pump inhibitors, antiviral treatment,

traditional therapy.

- The evaluation of the management of the 1st ISLA.

Data collection, entry and analysis:

- Data collection was carried out using a survey form established for this purpose.
- Descriptive statistics (age, age class, numbers and percentages) were carried out using EPI-INFO V.7.
- The explanatory variables for the univariate analysis included demographic characteristics, history, biological parameters and medications used before the occurrence of recurrence.
- The data were analyzed with R SOFTWARE VERSION 3 AND EXCEL 2007 SOFTWARE for producing graphs. A difference was considered statistically significant for a p-value ≤ 0.05.

3. Results

During our study, we collected 1347 files of patients hospitalized in the department, including 389 cases of cirrhosis files. 37 files of cirrhotic patients with ISLA including 28 cures without recurrence of ISLA, 08 files of patients with recurrence of ISLA and 03 exclusions (01 incomplete file and 02 cures not evaluated); either:

-a hospital prevalence of ISLA recurrence in our study of 0.6%.

-a prevalence of recurrence of ISLA in cirrhotic patients in our series of 23.5%.

The sex ratio was 2.7 in the population of cirrhotics with cured ISLA while in the population of cirrhotics with recurrence of ISLA it was 7 in favor of men.

The most represented age group was that of 40 - 59 years, in our series (55.8%) general population and in cirrhotics with recurrence of ISLA (56%).

The time of occurrence of the recidivist of ISLA was: 75% (n = 6) of recurrences appeared less than a month after healing of the1stISLA and 25% (n = 2) between one and three months.

Table 1. Distribution of patients according to history before the occurrence of recurrence of ISLA.

		Population with cured ISLA (N = 34)		Population with recurrence of ISLA (n = 8)	
Settings		not	%	not	%
Etiology of cirrhosis	HBV	21	61.8%	5	62.5%
	HBV/HCV	1	2.9%	0	0%
	HCV	4	11.8%	2	25%
	others	8	23.5%	1	12.5%
Antiviral treatment	No	29	91.2%	7	87.5%
	Yes	5	8.8%	1	12.5%
Child score	B	28	82.4%	4	50%
	VS	6	17.6%	4	50%

Continued

Portal thrombosis	No	30	88.2%	7	87.5%
	Yes	4	11.8%	1	12.5%
CHC	No	24	70.6	3	37.5%
	Yes	10	29.4%	5	62.5%
SHR	No	31	91.2%	8	100%
	Yes	3	8.8%	0	0%
Hepatic encephalopathy	No	27	82.4%	5	50%
	Yes	7	17.6%	3	50%
Digestive hemorrhages	No	29	85.3%	5	62.5%
	Yes	5	14.7%	3	37.5%
Iterative punctures	No	23	67.7%	5	62.5%
	Yes	11	32.3%	3	37.5%
Recent hospital contact	No	22	67.6%	5	62.5%
	Yes	12	32.4%	3	37.5%

Table 2. Distribution of patients according to biological parameters during the 1st ISLA.

		Total population (N = 34)		Repeat offender population (n = 8)	
Settings		not	%	not	%
PNN in LA	250 - 499 m^3	15	44.1%	2	25%
	500 - 749 m^3	12	35.3%	5	62.5%
	750 - 999 m^3	1	3%	0	0%
	>1000 m^3	6	17.6%	1	12.5%
Proteins in LA	<10 g	7	20.6%	2	25%
	10 - 15 g	8	23.5%	2	25%
	>15 g	19	55.9%	4	50%
Platelets	<100 G	10	29.4%	4	50%
	100 - 200 G	11	32.4%	2	25%
	>200 G	13	38.2%	2	25%

During the 1st ILSA, the most frequent biological parameters were:

- LA cytology: PNN rate at 250 - 499 mm^3 (44.1%)
- Chemistry of LA: Protein level. >15 g/l (61.7%)
- Blood platelet level > 200 G/mm^3 (38.2%)

After healing from the first ILSA, the most frequent biological parameters were:

- LA cytology: PNN rate < 50 mm^3 (50%)
- Chemistry of LA: Protein level between 10 - 15 g/l (38.2%)
- Blood platelet level between 100 G/mm^3 - 200 G/mm^3 (53%)

The antibiotic therapy most used in the management of the 1st episode of ISLA was based on Ceftriaxone (94.1%) and Quinolones (5.9%), the same is true for the management of ISLA recurrence (100%).

Table 3. Distribution of patients according to current treatment at the occurrence of ISLA recurrence.

		Population with cured ISLA (N = 34)		Population with recurrence of ISLA (n = 8)	
Settings		not	%	not	%
Beta-blockers	No	34	100%	8	100%
	Yes	0	0%	0	0%
Diuretics	No	31	91.2%	7	87.5%
	Yes	3	8.8%	1	12.5
PPI	No	34	100%	7	87.5%
	Yes	0	0%	1	12.5%
Prevention (Norfloxacin)	No	34	100%	6	75%
	Yes	0	0%	2	25%
Traditional therapy	No	31	91.2%	7	87.5%
	Yes	3	8.8%	1	12.5%
Antiviral	No	29	85.3%	7	87.5%
	Yes	05	14.7%	1	12.5

Table 4. Distribution of patients according to current treatment at the occurrence of ISLA recurrence.

		Population with cured ISLA (N = 34)		Population with recurrence of ISLA (n = 8)	
Settings		not	%	not	%
Beta-blockers	No	34	100%	8	100%
	Yes	0	0%	0	0%
Diuretics	No	31	91.2%	7	87.5%
	Yes	3	8.8%	1	12.5
PPI	No	34	100%	7	87.5%
	Yes	0	0%	1	12.5%
Prevention (Norfloxacin)	No	34	100%	6	75%
	Yes	0	0%	2	25%
Traditional therapy	No	31	91.2%	7	87.5%
	Yes	3	8.8%	1	12.5%
Antiviral	No	29	85.3%	7	87.5%
	Yes	05	14.7%	1	12.5

Table 5. Univariate analysis of predictive factors for ISLA recurrence based on history before recurrence.

Variables	Odds Ratio	95% CI	p-value
Etiology cirrhosis			
Other	1		
HVB	2.18	0.27 - 46.0	0.5
HCV	7	0.44 - 211.3	0.18
Antiviral TT			
No	1		

Continued

Yes	0.78	0.03 - 6.51	0.84
Score ofCHILD			
B	1		
VS	0	N/A	0.99
Portal thrombosis			
No	1		
Yes	1.09	0.05 - 10.24	0.94
Hepatocellular carcinoma			
No	1		
Yes	1.62	0.27 - 8.62	0.56
Hepatorenal syndrome			
No	1		
Yes	0	N/A	0.99
Hepatic encephalopathy			
No	1		
Yes	3.3	0.51 - 20.41	0.18
Gastrointestinal bleeding			
No	1		
Yes	7.2	0.96 - 67.1	0.05
Puncture iterative			
No	1		
Yes	1.35	0.23 - 6.99	0.72
Recent hospital contact			
No	1		
Yes	1.13	0.19 - 5.77	0.88

A low concentration of proteins in ascites < 10 g was noted.

4. Discussion

Given the small number of files of cirrhotic patients with recurrence of ISLA, we did not address confounding factors or potential biases in the design of this retrospective study.

The absence of performing ascitoculture and standard bacteriology which would have made it possible to identify the most frequent germs in our department during ISLA recurrences constitutes the main limitation of this study. This study nevertheless made it possible to determine the prevalence and identify the risk factors for the occurrence of recurrence of ISLA. The prevalence of ISLA recurrence in cirrhotic patients in our series was 23.5%. Our results are lower than those of SAJJAD JAMID *et al*. [12] in Pakistan; CHIEN-HAO HUANG *et al*. [13] in China; PANOTPOL TERMSINSUK *et al*. [14] in Thailand; TITÓ L *et al*. [15] in Spain who reported respective prevalences of ISLA recurrence of 34%; 40.8%; 69% and 69.8%. This difference could be explained by the large number of incomplete files in our series. The results of our work are superimposable to those reported by SEBÁSTIAN *et al*. [16] in Argentina who reported a prevalence of ISLA recurrence of 20% - 26%. Our data are similar to those of GINES P *et al*. [9] in Spain who reported a prevalence of ISLA recurrence of 20% in cir-

rhotic patients. The sex ratio was 2.7 in the general population and 7 in the population of cirrhotics with recurrent ISLA. These results are superior to those of SAJJAD JAMIL *et al*. [12] in Pakistan who reported a sex ratio of 1.66 in the series and a sex ratio of 0.9 in the cirrhotic population. The most represented age group was that of 40 - 59 years, in our series (55.8%) general population and in cirrhotics with recurrence of ISLA (56%). Our results are superimposable to those of SAJJAD JAMIL *et al*. [12] in Pakistan where age < 55 years was found in 62.4% of the general population and in 74% of the cirrhotic population. In univariate analysis we found no significant links between the different demographic characteristics of the population and the occurrence of ISLA recurrence. This is the case for numerous other studies, notably those of SAJJAD JAMIL *et al*. [12] in Pakistan; PANOTPOL TERMSINSUK *et al*. [14] in Thailand; L TITÓ *et al*. [15] in Spain. The most common antecedents before the occurrence of ISLA recurrence were: hospital contact recent (35.3%), the concept of iterative ascites punctures (32.3%), has the presence of HCC (29.4%) and the presence of hepatic encephalopathy in 20.6% of cases (**Table 1**). In Pakistan SAJJAD JAMID *et al*. [12] mentioned there presence of hepatic encephalopathy (45.9%) and has the presence of HCC (24.2%). Our results are similar to those reported by SAJJAD JAMID *et al*. [12]. The significant links found with the occurrence of a recurrence of ISLA were the presence of hepatic encephalopathy (p = 0.03) and urinary infection (OR = 2.24; 95%. CI = 0.99 - 5.09. The most common etiology of cirrhosis was HBV (61.8%), followed by undetermined etiology's (11.8%), HCV (12.5%) and HBV/HCV (2.9%). The most common etiology of cirrhosis in the population with recurrence of ISLA was HBV (62.5%) (**Table 1**). Our results are similar to those of DIALLO MS *et al*. [17] who reported HBV cirrhosis as the main cause (57.14). In Pakistan SAJJAD JAMID *et al*. [12] found the HCV (55.4%), HBV (24.8%), HCV/HBV (9.6%). This could be explained by the high endemicity of HBV and HCV in Africa and Asia where the prevalence is around 2 to 6% depending on the country [10]-[12] [18].

The low protein concentration < 10 g was reported by GUARNER *et al*. [4] and TITÓ L *et al*. [15] (**Table 2**). PANOTPOL TERMSINSUK *et al*. [14] reported as a risk factor associated with the occurrence of recurrence of ISLA the rate of blood platelets < or = 100,000/mm^3. We have 75% of patients with recurrence of ISLA who had not received secondary prophylaxis with NORFLOXACIN. Our results are close to those of GINES P *et al*. [9] who reported a recurrence at one year of 20% in subjects treated with NORFLOXACIN compared to 68% in the placebo group (**Table 5**). The antibiotic therapy most used in the management of the 1st episode of ISLA (94.1%) and in the management of ISLA recurrence (100%) was based on CEFTRIAXONE. Furthermore, the duration of antibiotic therapy in the management of the 1st episode of ISLA and that of the recurrence of ISLA was mostly < 10 days. These treatments were in accordance with those of the consensus conferences and the recommendations of certain learned societies (European and North American) which recommend the em-

pirical use of antibiotics from the third-generation cephalosporin class as first-line treatment; an alternative represented by the Amoxicillin-clavulanic acid association or the use of Quinolones such as NORFLOXACIN or OFLOXACIN or Ciprofloxacin [2] [19]-[21].

As for DIALLO MS *et al*. [10], they reported as main risk factors for the occurrence of ISLA in cirrhotic patients: digestive bleeding (17.86%) (**Table 5**), protein level in ascitic fluid < 15 g/l (60.71%); thrombocytopenia < 98,000/mm^3 (42.86%) (**Table 2**); recent puncture of ascitic fluid (35.71%) (**Table 5**); bilirubin level > 30 mg/l (50%) and serum creatinine > 12 mg/l (25%).

This lack of relationship could be explained by the small size of our sample, which could affect the power of the statistical tests.

In addition, all patients who had a digestive hemorrhage or a protein level below 15 g/l were systematically placed on prophylactic antibiotic therapy and this practice, it should be noted, is in accordance with international recommendations [3] [19] [22].

NAUSBAUM JB [2]; DEVER JP *et al*. [23] had described as the main risk factors involved in the occurrence of ISLA: severe hepatocellular insufficiency at Child's stage C (**Table 5**), a low ascites protein concentration < 15 g/l (x 10 the risk); hyperbilirubinemia >30 mg/l; thrombocytopenia < 98,000/mm^3.

Human albumin was little used in the management of the 1st episode of ISLA (6.25%) and in the management of the recurrence of ISLA it had not been used. This could be explained on the one hand by the limited financial means of patients who were mainly middle class and on the other hand by the absence of subsidies and health insurance. In univariate analysis, we did not find significant links between treatment carried out at the 1st ISLA and the occurrence of a recurrence of ISLA (**Table 3**; **Table 4**). It appears from these studies that the risk factors statistically linked to ISLA vary greatly from one study to another. Many authors do not find a statistically significant link between these parameters and the occurrence of ISLA but recommend antibiotic prophylaxis given its severity and poor prognosis [2] [19] [24] [25].

5. Conclusion

This study allowed us to identify the main risk factors linked to the occurrence of recurrence of ISLA. However, this did not make it possible to identify the germs responsible for the recurrence of ISLA, hence the interest in a multicenter prospective cohort taking into account the search for germs. Despite recent developments in antiviral therapies, the treatment of viral hepatitis B and C remains expensive and difficult to access for the population of our country. Universal vaccination against HBV is the option to promote.

Ethics approval

Declaration for Human Rights

The hospital has consented to the use of data from patients who have been

consulted in the department. This study was approved by the hospital ethics committee and the principles of the Declaration of Helsinki were followed.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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