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A Predictive Model for Avoiding Follow-Up Paracentesis in Spontaneous Bacterial Peritonitis

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Keywords

Spontaneous bacterial peritonitis · Liver · Cirrhosis · Antibiotics · Paracentesis

Abstract

Background: Recent studies suggest that follow-up paracentesis (FuP) in cases of spontaneous bacterial peritonitis (SBP) should only be performed if there is a clinical and/or analytic worsening. We aimed to evaluate which patients with SBP would benefit from the FuP. ***Métodos:*** This retrospective study included consecutive patients diagnosed with SBP between January 2011 and June 2018 in our tertiary center. Clinical and analytical data were obtained at baseline and on the third day of antibiotic therapy. An adequate response on the third day of treatment was defined by a decrease of ≥25% in the neutrophil count of the ascitic fluid (AF). ***Results:*** Ninety-six episodes of PBE in 75 patients (79% male sex, mean age 61 ± 11 years old) were included. At admission, a higher serum neutrophil count ($p = 0.043$), a lower level of serum total proteins ($p = 0.040$), a positive culture in AF ($p < 0.001$) and a previous diagnosis of diabetes mellitus ($p = 0.035$) were related to inadequate response (IR). At day 3, acute kidney injury ($p = 0.023$), C-reactive protein >100 mg/L ($p < 0.001$), the presence of fever ($p = 0.047$) and abdominal pain ($p < 0.001$) were also associated with IR. In multivariate analysis, the presence of respiratory insufficiency (OR = 16.403; 95% CI: 2.315–116.222; $p = 0.005$) and abdominal pain (OR = 10.381; 95% CI: 1.807–59.626; $p = 0.009$) at admission, serum white blood cell count >9×10^9 (OR = 5.832; 95% CI: 1.275–26.669; $p = 0.023$), and CRP >100 mg/L (OR = 5.043; 95% CI: 1.267–20.076; $p = 0.022$) at day 3 of antibiotic therapy were predictors of IR. The predictive model presented good accuracy [AUROC of 0.893 ($p < 0.001$)] – a cutoff of 0.090 had a sensitivity, specificity, positive predictive value, and negative predictive value for IR of 97, 46, 83, and 77%, respectively. ***Conclusions:*** The performance of FuP on day 3 after the beginning of empiric therapy should be individualized, according to clinical and analytic variables of this predictive model.

Modelo preditivo para evitar a paracentese de seguimento na peritonite bacteriana espontânea

Palavras Chave

Peritonite bacteriana espontânea · Fígado · Cirrose hepatica · Antibioterapia · Paracentese

Resumo

Introdução: Estudos recentes têm sugerido a realização de paracentese de seguimento ao 3º dia, na peritonite

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bacteriana espontânea (PBE), apenas em doentes com agravamento clínico e/ou analítico. Este trabalho pretende avaliar quais os doentes em que a paracenteses ao 3º dia se mantém essencial. ***Methods:*** Estudo retrospetivo realizado em centro terciário, com inclusão dos doentes com PBE entre janeiro de 2011 e junho de 2018. Dados clínicos e analíticos foram obtidos à data de admissão e ao 3° dia de antibioterapia. A resposta terapêutica foi considerada adequada quando a contagem de neutrófilos no líquido ascítico era ≥25%. ***Resultados:*** Foram incluídos 96 episódios de PBE correspondentes a 75 doentes (79% homens, com idade media de 61 ± 11 anos). À admissão, a presença de diabetes *mellitus* ($p = 0.035$), uma maior contagem de neurófilos séricos ($p = 0.043$), nível inferior de proteínas séricas totais ($p = 0.040$) e positividade nas culturas de líquido ascítico total ($p < 0.001$) relacionaram-se com inadequada resposta (IR). Ao 3° dia de antibioterapia, a presença de lesão renal aguda ($p = 0.023$), proteína C reativa >100 mg/L ($p < 0.001$), febre ($p = 0.047$) e dor abdominal ($p < 0.001$) foram também associados a IR. Na análise multivariada, a presença de insuficiência respiratória (OR = 16.403; 95% CI: 2.315–116.222; $p = 0.005$) e dor abdominal (OR = 10.381; 95% CI: 1.807–59.626; $p = 0.009$) à admissão, contagem séria de leucócitos >9 $\times 10^9$ (OR = 5.832; 95% CI: 1.275–26.669; $p = 0.023$) e PCR >100 mg/L (OR = 5.043; 95% CI: 1.267–20.076; $p = 0.022$) ao 3° dia de antibioterapia foram preditores de IR. O modelo preditivo apresentado apresenta boa acuidade [AUROC de 0.893 ($p < 0.001$)] – para um *cutoff* de 0.090 tem uma sensibilidade, especificidade, valor preditivo positivo e valor preditivo negativo para IR de 97, 46, 83, e 77%, respetivamente. ***Conclusões:*** De acordo com o nosso modelo, a realização de paracenteses de seguimento ao 3 dia após início de antibioterapia empírica deverá ser individualizada, de segundo as variáveis clínicas e analíticas apresentadas.

Introduction

In its decompensated state or with portal hypertension, liver cirrhosis is associated with significant changes in the human immune system leading to a syndrome called cirrhosis-associated immune dysfunction [1]. This dysfunction, related to the increase in intestinal permeability, results in bacterial and endotoxin translocation to mesenteric lymph nodes and other external sites, causing infectious complications [2]. Spontaneous bacterial peritonitis (SBP) is one of the most frequent complications. The diagnosis of SBP is established when the polymorphonuclear (PMN) leukocyte count in the ascitic fluid (AF) is equal to or greater than 250 cells/mm, in the absence of intra-abdominal cause for infection (i.e., surgically treatable) [3, 4].

SBP has an estimated prevalence of 1.5–3.5% in ambulatory patients and up to 10% in hospitalized patients [5]. A prospective study reported a rate of 47% of bacterial infections in hospitalized cirrhotic patients, with 31% of these infections being SBP [6].

SBP is associated with higher mortality rates, ranging between 18 and 33% in some series [7]. Nonetheless, an early diagnosis, related to adequate therapy, allows a decrease in disease-related mortality [7].

Guidelines recommend that a diagnostic paracentesis should be performed at admission in cirrhotic patients with: (i) ascites (who require hospitalization); (ii) local or systemic symptoms (abdominal pain, tenderness, vomiting, diarrhea, hyper/hypothermia, tachycardia and/or tachypnea) (iii) signs of clinical deterioration such as hepatic encephalopathy, gastrointestinal bleeding or worsening of renal and/or liver function [8, 9].

Adequate handling of AF is required to increase the accuracy of SBP diagnosis. The injection of 1 mL of fluid into a purple-top ethylenediaminetetraacetic acid allows a more accurate cell count; moreover, a bedside injection of at least 10 mL into aerobic and anaerobic blood culture bottles increases the accuracy of positive cultures [10].

When the culture is positive (approximately 40% of cases), the most common pathogens include Gram-negative bacteria, mainly *Escherichia*, with *Escherichia coli* being the most prevalent [5, 10, 11]. Gram-positive cocci have previously accounted for less than 25% of SPB cases; however, there is a recent increased prevalence [12].

Antibiotic therapy should be initiated early to improve outcomes of disease [12]. Third-generation, broad-spectrum cephalosporins are the drugs of choice for community-acquired infections. Cefotaxime (2 g every 8 h) during 5 days is considered the gold-standard therapy [8, 9, 13]. Ceftriaxone (2 g/day for 5 days) is an acceptable alternative [14]. Albumin should be administered (1.5 g/kg at diagnosis and 1 g/kg on day 3) to avoid type 1 hepatorenal syndrome [may occur in approximately 30% of SBP patients (treated with antibiotics alone)] and improve survival [8].

European guidelines suggest a new paracentesis 48 h after the beginning of antibiotics to demonstrate SBP resolution (by a decrease in PMN cells >25%) and to adjust therapy if needed [8]. However, some recent studies consider that this procedure is unnecessary for all patients

and could be individualized according to the clinical and analytical course [9, 15].

With this study, the authors aim: (i) to determine the patients who may benefit from follow-up paracentesis according to clinical and analytical predictors of inadequate response on day 3 of treatment, and (ii) to create a predictor model of inadequate response to antibiotic therapy.

Material and Methods

We have performed a retrospective single-center study (in a tertiary center) including all consecutive adult patients admitted with SBP between January 2011 and June 2018. Patients who died from causes other than SBP during that period were excluded (Fig. 1).

Data from serum laboratory workup at admission and 48 h after the beginning of antibiotics included: blood count with platelets, cytocholestatic parameters, serum proteinogram, urea, creatinine, and C-reactive protein levels. Moreover, an initial AF evaluation was performed, simultaneously, with a differential count of fluid cells and microbiologic culture. Information regarding clinical aspects, namely abdominal pain and fever, were also collected. In all cases, antibiotics and albumin were initiated as soon as possible. Adequate antibiotic therapy response was considered when AF neutrophil count decreased more than 25% related to pretreatment value after 2 days of antibiotic treatment [8]. According to a Numerical Rating Scale, abdominal pain was felt when it was classified, by every patient, as 2 points [16]. Active alcohol consumption was defined as a consumption ≥20 g in women or 30 g in men. Hepatic encephalopathy was considered over 2 on the West Haven scale. Respiratory insufficiency was defined as PaO_2 <60 mm Hg. Acute kidney injury was defined according to the European Association for the Study of the Liver (EASL) criteria [8].

Statistical analysis was performed using SPSS v. 26 (IBM®, Armonk, NY, USA). Data were analyzed using a χ^2 test for categorical variables, independent-samples *t* test, and Mann-Whitney U nonparametric test for continuous variables. Multivariate analysis using binary logistic regression was used; the variables included as predictors were selected from univariate analysis if $p < 0.1$. Model discrimination was measured using the area under the receiver operating characteristic curve (AUROC), considering 95% confidence intervals (CIs). Statistical significance was considered if the *p* value was less than 0.05.

Results

General Characteristics and Demographics

We have included 96 episodes of SBP in 75 patients (79% male sex, mean age 61 ± 11 years old). Demographic data are shown in Table 1. The median time of admission was 11 days (IQR 8–19), the period corresponding to the hospital stay. In 53% of cases ($n = 51$), ceftriaxone (2 g) was used as initial therapy, and in 33% ($n = 32$) piperacillin-tazobactam (4.5 g), with renal adjustment if necessary. In 80% ($n = 77$) of cases, the etiology of cirrhosis was alcoholic, and 83% ($n = 72$) of patients had a Child-Pugh C disease stage. Nosocomial SBP occurred in 25% ($n = 24$) of the cases. Thirty percent of patients were on antibiotic prophylaxis with norfloxacin (400 mg/day), and 25% ($n = 24$) had a previous diagnosis of SBP. Sixteen percent were on rifaximin (550 mg, twice a day) at the time of SBP diagnosis.

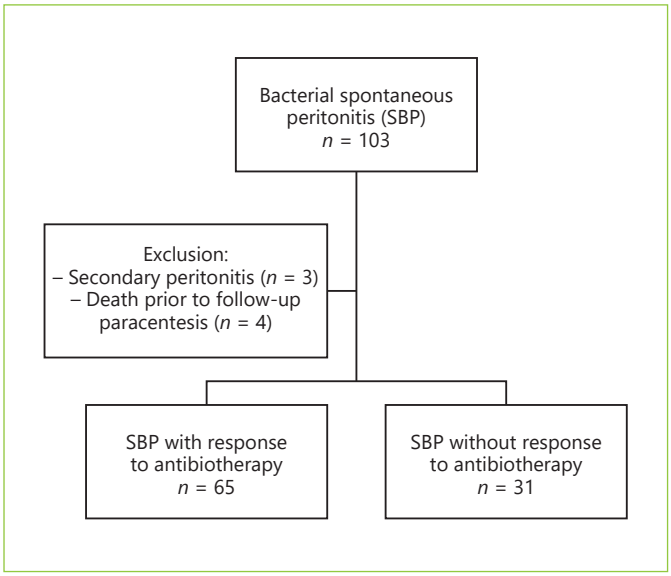

Fig. 1. Flow diagram of patient inclusion process.

Outcome

An inadequate response to antibiotic therapy was observed in 30% of cases ($n = 31$) and, according to its response, patients were divided into 2 groups: those who responded to antibiotic therapy (group 1, $n = 65$) and those without an adequate response (group 2, $n = 31$) (Table 1).

Twenty percent of patients died during admission (6 of them due to causes unrelated to peritonitis). Thirty-nine percent of patients had DM, and this pathology was more prevalent in group 2 ($p = 0.035$).

Admission

As we can observe in Table 1, a higher median count of serum neutrophils [9.16 (5.63–11.57) vs. 6.95 (3.75–9.40) × 10^9, $p = 0.043$], as well as a lower median of total proteins in AF [12 (9–16) vs. 18 (11–24) g/L, $p = 0.040$], were related to an inadequate response to therapy (group 2). Additionally, a positive microbiologic culture of AF ($p < 0.001$) was more frequently found in this group.

Table 1. Demographic, baseline and 48 h after antibiotic therapy data

	All patients ($N = 96$)	Response to antibiotherapy ($n = 65$)	Inadequate response to antibiotherapy ($n = 31$)	p value
Demographics				
Age, mean ± SD, years	61±11	60±10	63±12	0.251*
Gender, male, *n* (%)	76 (79)	48 (74)	28 (37)	0.063**
Smoking, *n* (%)	42 (44)	27 (64)	15 (36)	0.527**
Active alcohol consumption, *n* (%)	75 (78)	52 (80)	23 (74)	0.520**
Diabetes mellitus, *n* (%)	38 (40)	21 (32)	17 (55)	**0.035****
Etiology of CLD, *n* (%)				
Alcoholic	77 (80)	53 (82)	24 (77)	0.639**
Hepatitis C	11 (12)	6 (9)	5 (16)	0.321**
Alcoholic + HCV	9 (9)	4 (6)	5 (16)	0.143**
Child-Pugh, *n* (%)				
B	15 (17)	9 (15)	6 (21)	0.476**
C	72 (83)	50 (85)	22 (79)	
Hepatocellular carcinoma, *n* (%)	22 (23)	13 (20)	9 (29)	0.325**
Antibiotic SPB prophylaxis (norfloxacin), *n* (%)	25 (26)	18 (28)	7 (23)	0.594**
Time of admission, median (IQR), days	11 (8–18)	13 (11–20)	10 (9–12)	**0.029***
Previous decompensation(s)				
SBP, *n* (%)	24 (25)	15 (23)	9 (29)	0.529**
Ascites, *n* (%)	79 (82)	51 (79)	28 (90)	0.155**
Hepatic encephalopathy, *n* (%)	59 (62)	38 (59)	21 (68)	0.382**
Gastrointestinal variceal bleeding, *n* (%)	23 (24)	16 (25)	7 (23)	0.827**
Characteristics on admission				
Type of infection, nosocomial SBP, *n* (%)	24 (25)	17 (26)	7 (23)	0.705**
Hepatic encephalopathy, *n* (%)	29 (30)	13 (42)	16 (25)	0.084**
Acute kidney injury, *n* (%)	28 (31)	11 (37)	17 (28)	0.421**
Respiratory insufficiency, *n* (%)	10 (10)	4 (6)	6 (19)	0.072**
MELD, median (IQR), pts	16 (13–21)	16 (14–20)	15 (12–21)	0.415*
Albumin, median (IQR), g/L	26 (22–28)	25 (22–28)	26 (23–29)	0.586*
Serum WBC, median (IQR), $\times 10^9$	9.2 (5.8–12.4)	10.6 (6.8–12.8)	8.6 (5.1–11.7)	0.086*
Serum neutrophils, median (IQR), $\times 10^9$	7.51 (4.04–10.39)	6.95 (3.75–9.40)	9.16 (5.63–11.57)	**0.043***
Amount of PMN in ascitic fluid, median (IQR), /µL	2,508 (670–4,560)	3,076 (737–5,112)	1,579 (670–4,005)	0.521*
Amount of proteins in ascitic fluid, median (IQR), g/L	12 (10–20)	12 (9–16)	18 (11–24)	**0.040***
CRP, median (IQR), mg/L	81 (23–114)	80 (27–106)	91 (32–129)	0.684*
Positive ascitic fluid culture, *n* (%)	18 (19)	5 (8)	13 (42)	**<0.001****
Characteristics on day 3				
Acute kidney injury, *n* (%)	30 (33)	15 (25)	15 (48)	**0.023****
Abdominal pain, *n* (%)	22 (23)	7 (11)	15 (48)	**<0.001****
Fever, *n* (%)	12 (13)	5 (8)	7 (23)	**0.047****
WBC >9,000, *n* (%)	18 (19)	6 (9)	12 (39)	**<0.001****
CRP >100 mg/L, *n* (%)	28 (30)	11 (17)	17 (55)	**<0.001****

SD, standard deviation; CLD, chronic liver disease; SBP, spontaneous bacterial peritonitis; WBC, white blood cells; PMN, polymorphonuclears; CRP, C-reactive protein.

Day 3 after Antibiotic Therapy

On the 3rd day of therapy, it was observed that patients with an inadequate antibiotic response had higher counts of serum white blood cell count (WBC) $>9 \times 10^9$ ($p < 0.001$), C-reactive protein (CRP) >100 mg/L ($p < 0.001$), fever ($p = 0.047$) and abdominal pain ($p < 0.001$), than group 1.

Paired Analysis

In both groups, a decrease in the serum count of leucocytes, creatinine, CRP and PMN of AF was observed. However, this decrease was more significant in patients of group 1 for PMN of AF count and serum creatinine ($p < 0.001$ and $p = 0.033$, respectively) (Table 2).

Table 2. Variation of variables between admission and 3rd day

	Response to antibiotherapy ($n = 65$)	Inadequate response to antibiotherapy ($n = 31$)	p value
Δ absolute serum WBC, median (IQR), $\times 10^9$	–1.4 (–5.6 to 2.0)	–2.3 (–4.9 to –0.9)	0.071*
Δ absolute PMN of ascitic fluid, median (IQR), /μL	98 (–230 to 959)	–2,232 (–4574 to –490)	<0.001*
Δ CRP, median (IQR), mg/L	14 (–15.3 to 60.8)	–9.5 (–51.9 to 6.6)	0.085*
Δ serum creatinine, median (IQR), mg/dL	0.2 (–0.1 to 0.48)	–0.1 (–0.3 to 0.1)	0.033*

WBC, white blood cells; PMN, polymorphonuclears; CRP, C-reactive protein. * Mann-Whitney U test, $p = 0.05$.

Table 3. Multivariate logistic regression analysis

	Unadjusted OR (95% CI)	p value	Covariate adjusted OR (95% CI)	p value
Demographics				
Age	1.024 (0.983 to 1.067)	0.249	1.047 (0.983 to 1.116)	0.151
Gender				
Female	Ref.		Ref.	
Male	3.306 (0.889 to 12.286)	0.074	3.783 (0.593 to 24.140)	0.159
Smoking	1.319 (0.558 to 3.118)	0.528	–	–
Active alcohol consumption	0.719 (0.262 to 1.970)	0.521	–	–
Diabetes mellitus	2.544 (1.058 to 6.121)	**0.037**	1.806 (0.519 to 6.283)	0.353
Hepatocellular carcinoma	1.636 (0.611 to 4.383)	0.327	–	–
Antibiotic SPB prophylaxis (norfloxacin)	0.762 (0.280 to 2.074)	0.594	–	–
Rifaximin	0.670 (0.215 to 2.084)	0.489	–	–
Previous decompensation(s)				
SBP	1.364 (0.519 to 3.585)	0.529	–	–
Ascites	2.562 (0.678 to 9.682)	0.165	–	–
Hepatic encephalopathy	1.492 (0.606 to 3.671)	0.384	–	–
Gastrointestinal variceal bleeding	0.893 (0.324 to 2.461)	0.827	–	–
Characteristics on admission				
Type of infection			–	–
Community-acquired	Ref.			
Nosocomial	0.824 (0.301 to 2.255)	0.706		
Hepatic encephalopathy	2.212 (0.891 to 5.493)	0.087	1.404 (0.345 to 5.715)	0.635
Acute kidney injury	1.234 (0.501 to 3.039)	0.648	–	–
Respiratory insufficiency	3.660 (0.951 to 14.091)	0.059	16.403 (2.315 to 116.222)	**0.005**
Characteristics on day 3				
Acute kidney injury	2.875 (1.152 to 7.173)	**0.024**	1.549 (0.397 to 6.041)	0.529
Abdominal pain	7.768 (2.707 to 22.290)	**<0.001**	10.381 (1.807 to 59.626)	**0.009**
Fever	3.500 (1.011 to 12.112)	**0.048**	0.639 (0.085 to 4.801)	0.664
WBC >9,000	6.105 (2.015 to 18.498)	**0.001**	5.832 (1.275 to 26.669)	**0.023**
CRP >100 mg/L	5.851 (2.240 to 15.284)	**<0.001**	5.043 (1.267 to 20.076)	**0.022**

WBC, white blood cells; PMN, polymorphonuclears; CRP, C-reactive protein.

Predictors of Antibiotic Failure

In multivariate analysis, the presence of respiratory insufficiency (OR = 16.403; 95% CI: 2.315–116.222; $p = 0.005$) and abdominal pain (OR = 10.381; 95% CI: 1.807–59.626; $p = 0.009$) at admission, serum WBC ≥9 $\times 10^9$ (OR = 5.832; 95% CI: 1.275–26.669, $p = 0.023$) and CRP >100 mg/L (OR = 5.043; 95% CI: 1.267–20.076; $p = 0.022$) at day 3rd of antibiotic therapy were predictors of an inadequate response to antibiotics in SBP (Table 3).

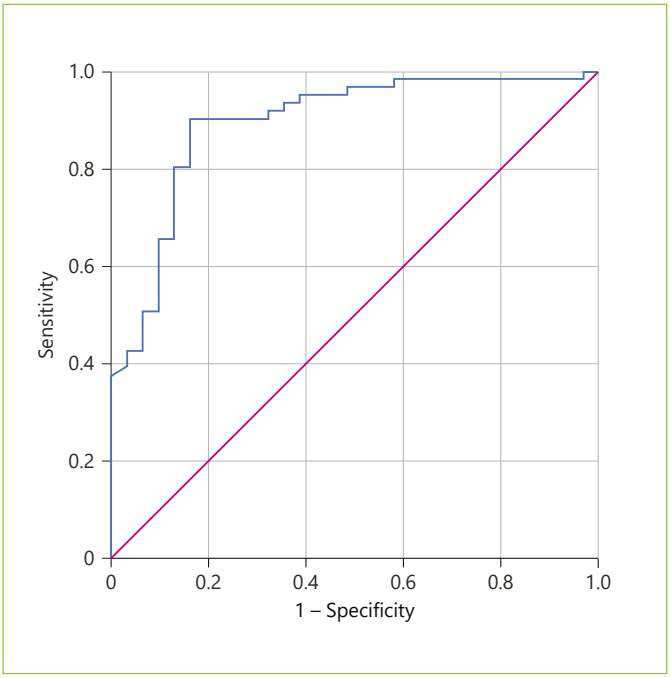

Fig. 2. ROC curve – accuracy of model in predicting inadequate response to antibiotic therapy.

A predictor model of inadequate response to therapy was created [–3.816 + (2.797 × respiratory insufficiency) + (2.340 × abdominal pain) + (1.763 × serum WBC >9 × 10^9) + (1.618 × CRP > 100)] with a good accuracy (AUROC 0.893, $p < 0.001$); for a cut-off of 0.090, this model has a sensitivity of 97% and a specificity of 46%, with a positive predictive value of 83% and a negative predictive value of 77% (Fig. 2).

Discussion

EASL guidelines recommend an assessment of AF through a paracentesis with cytological analysis of fluid at day 3 of antibiotics for all cases of SBP to monitor response and adjust therapy, if needed [8]. In fact, in clinical practice, an intermediate analysis of AF may play an important role, namely in matters of unfavorable clinical course. It allows therapy orientation in cases of non-response and can be a clue for a specific cause for the increased count of PMN.

However, our work meets other recent studies that suggest an individualized approach when following SBP cases [9]. Moreover, this is one of the first studies in the literature that link demographic and clinical factors to the convenience (or not) of an intermediate evaluation of AF by paracentesis. By evaluating clinical and analytical parameters in patients with SBP, we could depict some factors, both at admission and on day 3 after therapy, that can predict an inadequate response to antibiotics. Furthermore, as shown in Table 2, the behavior of clinical and analytical variables between admission and patient's reevaluation corroborates this hypothesis of prediction of antibiotic therapy response.

Using previously reported variables, the authors created, for the first time in the literature, a predictive model to determine which patients can benefit from a second paracentesis to adjust antibiotic therapy (in case of inappropriate response) and to avoid dispensable invasive procedures (in patients with favorable outcomes). Therefore, our model allowed the identification, with reasonable accuracy, of individuals in whom the following paracentesis may have benefits, with a sensitivity of 97% and a negative predictive value of 77%. Furthermore, if we applied this model in our population, 65% of the patients could have avoided the follow-up paracentesis, thus avoiding further complications in frail patients.

As a complication of cirrhosis, SBP tends to indicate a significant progression of the disease. This is the reason why the identification of risk factors for SBP has an essential role in evaluating the disease course [17]. In our cohort, DM was present in 39% of patients, with a trend more prevalent in group 2. Tergast et al. [1], in their study, determined DM as a risk factor for SBP development in patients with cirrhosis due to alterations of the immune system, namely in leukocyte function, and to the polyneuropathy induced by DM. These changes lead to dyskinesia of bowel muscles and prolonged intestinal transit time, with an increased risk for bacterial translocation from the gut [18].

An interesting finding was the higher prevalence of positive AF cultures at admission in patients who did not respond to antibiotics. This fact emphasizes the role of a fine collection of AF sent to microbiologic analysis. According to the American Association for the Study of Liver Diseases (AASLD), in cases of SBP suspicion, AF should be cultured, at the bedside, in aerobic and anaerobic blood cultures bottles, prior to initiating antibiotic therapy [9]. Some studies report a higher rate of bacterial growth when AF is collected in this manner when compared to other containers (80 vs. 50%) [15]. Therefore, a positive AF culture is an essential guide of antibiotic therapy, mainly in patients with inadequate response to empirical treatment. Moreover, we have previously reported a higher prevalence of multidrug-resistant (MDR) bacte-

rial infections in our center, namely SBP. We believe that SBP prophylaxis with quinolones is associated with the emergence of MDR infections [17]. In our study, we only obtained a positive culture in 48% of cases, and this could be related to an inappropriate collection of AF at the diagnostic paracentesis. This may be considered a potential limitation of our study and could be explained by the fact that initial paracentesis was performed in the emergency department (with some limitations in AF collection). Moreover, as a retrospective study, some information about the AF collection was unclear, namely the type of culture bottle. Some other limitations of the study should be acknowledged, such as selection bias may not be avoided entirely. Therefore, prospective and multicenter studies are needed to confirm these results.

The vast majority of paracenteses occurred without complications. However, some studies reported a 10% rate of adverse events, commonly minor complications, such as the continuous outflow of AF from the puncture site or local self-limited bleeding. Nonetheless, significant events can occur, like abdominal hematoma, bleeding into the peritoneal cavity or secondary peritonitis related to visceral perforation [9, 18]. In our study, two cases of continuous outflow of AF from the puncture site and one case of abdominal hematoma were seen.

With this study, the authors consider that clinical and analytic factors allow predicting the (un)response of antibiotic therapy. The following paracentesis should be reserved to patients with a predictable absence of response to adjust treatment. We are convinced that our results may have important implications for clinical practice and future studies.

Statement of Ethics

The study was performed according to the Declaration of Helsinki. All rules of the local ethics committee ("Comissão de Ética para a Saúde do Centro Hospitalar Universitário de São João / Faculdade de Medicina da Universidade do Porto") were followed, preserving patient identity and confidentiality.

Conflict of Interest Statement

Nothing to declare.

Funding Sources

Nothing to declare.

Author Contributions

Ana L. Santos: conception and design; analysis and interpretation of the data; drafting of the article. *Rosa Coelho*: critical revision of the article for important intellectual content. *Marco Silva*: analysis and interpretation of the data. *Rui Morais*: analysis and interpretation of the data; critical revision of the article for important intellectual content. *Hélder Cardoso*: critical revision of the article for important intellectual content. *Guilherme Macedo*: critical revision of the article for important intellectual content, final approval of the article.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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