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Original Article

Clinical Findings, Bacterial Agents, and Antibiotic Resistance in Children with Spontaneous Peritonitis in Southern Iran: An Academic Tertiary Referral Center's Experience

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What's Known

- Early antibiotic treatment of Spontaneous bacterial peritonitis (SBP) is crucial. Current guidelines for the treatment of SBP recommend third-generation cephalosporins as first-line therapy. However, these guidelines did not take into account new research on regional differences in infection patterns or changes in antibiotic resistance.

What's New

- Although guidelines recommend third-generation cephalosporins as the primary antibiotic for the empirical treatment of SBP, the present study showed high bacterial resistance. Ultimately, empirical therapy should be tailored to each region's bacterial resistance features. Consequently, antibiotics such as ceftazidime, gentamicin, and cotrimoxazole are recommended for the empirical treatment of SBP.

Abstract

Background: Spontaneous bacterial peritonitis (SBP) is a fatal complication of ascites fluid infection. The causes of SBP in children differ from those in adults, and these bacteria are frequently resistant to antibiotics. Therefore, this study investigated the clinical findings, bacterial etiology, and antimicrobial resistance in children with SBP.

Methods: This study was conducted on all new pediatric ascites patients, who were admitted to the Department of Pediatric Gastroenterology, Namazi Hospital, affiliated with Shiraz University of Medical Sciences (Shiraz, Iran) from 2021 to 2022. Required data such as demographic information, and clinical information such as complete blood count (CBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), Gram staining, blood culture by Automated Blood Culture System (BACTEC), and antibiogram of ascites fluids by disc diffusion method were all collected. Finally, the data were statistically analyzed using SPSS Software (version 26). Besides, the *t* test, Fisher's exact, Mann-Whitney, and Chi square tests were used for data analysis. In all tests, $P \leq 0.05$ was considered statistically significant.

Results: The present study examined 62 children with ascites of which 18 (29%) had SBP. The median (IQR) age was 2.5 (8.1) years. Thirty-four (54.8%) of the participants were girls. Abdominal pain was the most common clinical manifestation in patients (54%), and there was a significant association between abdominal pain and SBP (P=0.02). In 12 positive ascites fluid cultures, coagulase-negative staphylococci had the highest frequency (25%), followed by *Escherichia coli* (16.7%). Third-generation cephalosporins had a 25% sensitivity in the total positive cultures. This sensitivity was 33.3% for Gram-negative cultures and 16.6% for Gram-positive cultures.

Conclusion: Although third-generation cephalosporins are recommended as the primary antibiotic for the empirical treatment of SBP, the present study found high bacterial resistance. Finally, empirical therapy should be tailored to each region's bacterial resistance features.

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Keywords ● Peritonitis ● Ascites ● Liver cirrhosis ● Drug resistance

Introduction

Spontaneous bacterial peritonitis (SBP) affects almost entirely cirrhotic patients. It has been described as an ascitic fluid infection without any intra-abdominal source, which can be surgically treated.[1] The prevalence of SBP is estimated to be between 10-30%, which accounts for 4% of cirrhosis-related emergency room visits.[2] Without early therapeutic intervention, SBP mortality ranges from 20% to 40%.[3] SBP patients usually have symptoms such as fever, abdominal pain, renal dysfunction, hypertension, and encephalopathy.[4] Although fever, abdominal pain, nausea, and vomiting are the prominent symptoms of SBP, not all affected children present these symptoms.[5] In fact, only a small number of individuals exhibit typical symptoms, and the rest exhibit encephalopathy, ascites, and renal dysfunction.

The diagnosis of SBP is established by a positive ascitic fluid bacterial culture and an increased absolute polymorphonuclear leukocyte (PMN) count (≥250 cells/mm^3). An Increase in ascitic fluid PMN is sufficient to diagnose SBP and initiate empiric antibiotic therapy.[6, 7] Historically, Gram-negative bacteria have been the leading cause of SBP, with *Escherichia coli* and *Klebsiella* spp. being the most frequently isolated species. However, significant changes in the pattern of infection have occurred in cirrhotic patients.[8] Early antibiotic treatment of SBP is crucial. Third-generation cephalosporins are currently recommended as first-line therapy for SBP. However, these guidelines do not take into account the new research on regional differences in infection patterns or changes in antibiotic resistance.

Due to the widespread use of third-generation cephalosporins as first-line therapy for various bacterial infections, the landscape of microbiological resistance is constantly changing, which makes SBP management much more challenging. Therefore, the empirical choice of antibiotic treatment should be guided by data on the expected local microbiology and their regional resistance pattern.[9-11] In this way, this study aimed to determine the clinical findings, bacterial etiological variables, and antimicrobial resistance in children with SBP hospitalized in Namazi Tertiary Teaching Hospital in Shiraz, Iran.

Patients and Methods

This cross-sectional study was conducted in the Department of Pediatric Gastroenterology, Namazi Hospital, affiliated with Shiraz University of Medical Sciences (Shiraz, Iran), from 2021 to 2022. All patients with new ascites and cirrhotic patients with symptoms such as abdominal pain, fever, change in consciousness, decreased blood pressure, increased ascites, and peripheral leukocytosis were included. Patients who did not consent to paracentesis or had secondary peritonitis were excluded from the study. The sample size was obtained based on the census. The protocol of this study was reviewed and approved by the Medical Ethics Committee of Shiraz University of Medical Sciences (code: IR.SUMS.MED.REC.1401.415).

The patients' information was collected using a comprehensive checklist, including demographic data, clinical findings, and laboratory test results; such as serum and ascites total protein, albumin, glucose, complete blood count (CBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), ascites fluid culture, blood culture, lactate dehydrogenase (LDH), underlying disease, prior antibiotic consumption, prior diuretic usage, variceal bleeding history, prior SBP, Model for end-stage liver disease (MELD) Na score, Pediatric end-stage liver disease (PELD) score; as well as fever, abdominal pain, and encephalopathy.

In these patients, paracentesis is the standard method of collecting peritoneal fluid,[12] which was performed after explaining its necessity and potential complications to their parents or guardians. Then, written informed consent was obtained from them. For this purpose, 10 mL of ascites fluid was injected into a blood culture vial of Automated blood culture system (BACTEC). The isolated organisms were determined using standard microbiological methods, and disc diffusion antibiograms were performed in accordance with the Clinical and Laboratory Standards Institute (CLSI). SBP was confirmed by Gram staining, positive culture, or ≥250 polymorphonuclear cells in the peritoneal fluid. After paracentesis, all patients received intravenous cefotaxime (150 mg/Kg/day). After 48 hours of antibiotic treatment, the patients were clinically re-evaluated to see whether the fever had subsided, and other symptoms had improved.

Statistical Analysis

Data were analyzed using SPSS version 26 (SPSS Inc., Chicago, IL, United States). Descriptive statistics were presented as mean±SD, or frequency and percentages. Moreover, the *t* test, Fisher's exact, Mann-Whitney, and Chi square tests were used to make the comparisons and evaluate the correlations between variables. In all tests, P≤0.05 was

considered statistically significant.

Results

The present study examined 62 children with ascites, of which 18 (29%) had SBP. The median (IQR) age of the participants was 2.5 (8.1) years. 34 (54.8%) patients were girls, and 28 (45.1%) were boys. Both groups of patients had a history of underlying diseases. Biliary atresia and Wilson's disease were the main underlying disorders.

The mean score of MELD in the groups with and without SBP was 17±1.41 and 22.75±9.08, respectively. In these groups, the mean of PELD score was 26.08±10.53 and 24.06±12.33, respectively. A significant number of patients in both groups had a PELD or MELD score above 12. However, there was no significant relationship between the two scores and the frequency of SBP. The most common clinical manifestation in both groups was abdominal pain. During the clinical examination, 34 (54%) of all the patients, had abdominal pain. There was a significant relationship between abdominal pain and SBP (P=0.02). Demographic and clinical characteristics of patients are presented in table 1.

In terms of blood markers, the median (IQR) WBC in the group with SBP was 7600 (9300), and in the group without SBP was 7850 (6675) (P=0.76). The average number of polymorphonuclear cells in the group with and without SBP was 70.83±13.20 and 61.97±15.08, respectively, indicating a significant association between higher levels of polymorphonuclear cells and SBP (P=0.04). In the SBP group, the median (IQR) of ESR and CRP were 7 (21) and 17 (56.7), respectively. In the non-SBP group, the median (IQR) of ESR and CRP were 20 (47) and 14 (42.5), respectively (P=0.10, P=0.83, respectively). Two of the patients with SBP had a positive bacterial smear. Blood cultures were positive in one of the patients with SBP and four patients without SBP, most of which were related to Gram-positive bacteria.

Regarding ascites fluid assessments, the median (IQR) of total cells in the ascites fluid in the group with SBP was 1120 (3530), and 340 (1220) in the group without peritonitis, which indicated a significant association (P=0.01). The median of white blood cells (WBC) in ascites fluid was almost four times higher in the peritonitis group than in the group without peritonitis, which was statistically significant (P=0.001). The number of neutrophils (PMN count) was significantly higher in the group with SBP. Therefore, no patient in the group without SBP had a neutrophil count greater than 250 (P=0.0001). The median (IQR) ascites fluid glucose in the group with SBP was 96 (60.7), and in the group without SBP was 101 (33), indicating a significant association between lower glucose and SBP (P=0.02).

Table 1: Demographic and clinical characteristics of patients with ascites

Variables		Total (%)	Peritonitis (%)		P value
			Positive	Negative	
Age (year) median (IQR)		2.5 (8.1)	3.5 (8.25)	2.25 (7.58)	0.34 ††
Sex	Female	34 (54.8)	10 (29.4)	24 (70.6)	0.94 **
	Male	28 (45.2)	8 (28.6)	20 (71.4)	
Underlying disease	Positive	59 (95.2)	18 (30.5)	41 (69.5)	0.55*
	Negative	3 (4.8)	0 (0)	3 (100)	
Prior antibiotic	Positive	20 (32.3)	5 (25)	15 (75)	0.62**
	Negative	42 (67.7)	13 (31)	29 (69)	
Prior diuretic	Positive	22 (35.5)	7 (31.8)	15 (68.2)	0.72**
	Negative	40 (64.5)	11 (27.5)	29(72.5)	
Variceal bleeding	Positive	10 (14.1)	3 (30)	7 (70)	0.94**
	Negative	52 (83.9)	15 (28.8)	37 (71.2)	
Prior SBP	Positive	2 (3.2)	0 (0)	2 (100)	>0.99*
	Negative	60 (96.8)	18 (30)	42 (70)	
MELD/Na (mean±SD)		21.6±8.38	17±1.41	22.75±9.08	0.29††
PELD (mean±SD)		24.7±11.73	26.08±10.53	24.06±12.33	0.57††
Fever	Positive	26 (41.9)	6 (23.1)	20 (76.9)	0.38**
	Negative	36 (58.1)	12 (33.3)	24 (66.7)	
Abdominal pain	Positive	34 (54.8)	14 (41.2)	20 (58.8)	0.02**
	Negative	28 (45.2)	4 (14.3)	24 (85.7)	
Encephalopathy	Positive	10 (16.1)	3 (30)	7 (70)	0.94**
	Negative	52 (83.9)	15 (28.8)	37 (71.2)	

*Fisher's Exact Test; **Chi square Test; †Mann Whitney Test; ††Independent *t* Test; PELD: Pediatric End-Stage Liver Disease; MELD: Model for End-stage Liver Disease; SBP: Spontaneous Bacterial Peritonitis. Data were expressed as n (%) or mean±SD or median (IQR). P<0.05 was considered statistically significant.

Table 2: Laboratory findings of 62 children with ascites and comparison among positive versus negative peritonitis patients

Variable			Total	Peritonitis		P value
				Positive	Negative	
Ascites	Gram stain	Positive	3 (4.8%)	2 (66.7%)	1 (33.3%)	0.16*
		Negative	59 (95.2%)	16 (27.1%)	43 (72.9%)	
	Culture	Positive	12 (19.4%)	12 (100%)	0 (0%)	<0.0001**
		Negative	50 (80.6%)	6 (12%)	44 (88%)	
	Total cell		410 (1790)	1120 (3530)	340 (1220)	0.01†
	WBC		145 (367)	440 (2070)	100 (260)	0.001†
	PMN percent		30 (65)	70 (82)	30 (49)	0.014†
	PMN number		16 (133)	266 (1312)	12 (55)	0.001†
	Total protein		1 (1)	0.9 (1.35)	1 (1.08)	0.51†
	Albumin		0.3 (0.4)	0.35 (0.4)	0.3 (0.57)	0/40†
	Glucose		100 (30)	96 (60.7)	101 (33)	0.02†
Blood	B/C	Positive	5 (8.1%)	1 (20%)	4 (80%)	0.63*
		Negative	57 (91.9%)	17 (29.8%)	40 (70.2%)	
	WBC		7822 (7000)	7600 (9300)	7850 (6675)	0.76†
	Platelet		120000 (161000)	114000 (121500)	145000 (160000)	0.62†
	Segment		64.4±15	70.8±13.2	61.9±15	0.04††
	CRP		14.5 (43.5)	17 (56.7)	14 (42.5)	0.83†
	ESR		18 (36)	7 (21)	20 (47)	0.10†
	LDH		86.5 (60.25)	93.5 (27.75)	75 (70)	0.22†

*Fisher's exact test; †Mann Whitney Test; ††Independent *t* Test; Data were expressed as n (%) or mean±SD, or median (IQR). P<0.05 was considered statistically significant.

Furthermore, as indicated in table 2, there was no significant difference between the two groups in terms of protein and albumin (P=0.51, P=0.40, respectively).

Out of 18 ascites fluid samples from patients with peritonitis, 12 ascites fluid samples were positive, and the frequency of Gram-positive bacteria was higher than Gram-negative bacteria. Meanwhile, the highest frequency was related to Gram-positive coagulase-negative staphylococci (25%), followed by *E. coli* with a frequency of 16.7% (table 3). The most prevalent pathogen causing peritonitis, coagulase-negative staphylococci, were shown to be 100% sensitive to gentamicin, doxycycline, cotrimoxazole, oxacillin, vancomycin, and linezolid. However, about 33-66% were sensitive to ciprofloxacin, erythromycin, cefepime, cefoxitin, cephalexin, clindamycin, and levofloxacin. This bacterium was not sensitive to penicillin.

Gram-negative bacteria had 100% sensitivity to colistin, polymyxin B, chloramphenicol, and levofloxacin. Between 50% to 75% were sensitive to imipenem, meropenem, amikacin, gentamicin, tobramycin, ciprofloxacin, aztreonam, and ceftazidime. About 20-50% were sensitive to piperacillin, tetracycline, ceftriaxone, cefepime, cefotaxime, cotrimoxazole, and co-amoxiclav. Finally, the bacterial strains were entirely resistant to tigecycline, cefuroxime, cefazolin, cefixime, ampicillin-sulbactam, and ampicillin. Additionally, 50% of the pathogens were extended-spectrum beta-lactamase producers. Only three of the 12 strains, isolated from the peritoneum of the studied patients, were sensitive to third-generation cephalosporins, including two Gram-negative strains and one Gram-positive strain. All samples were 25% sensitive to third-generation

Table 3: Ascites fluid culture findings

Microorganism		Frequency n (%)
Gram-positive bacteria	*Staphylococcus* coagulase negative	3 (25%)
	Enterococcus spp. + *candida*	1 (8.33%)
	Methicillin-sensitive *Staphylococcus aureus*	1 (8.33%)
	Streptococcus spp.	1 (8.33%)
	Corynebacterium diphtheriae	1 (8.33%)
Gram-negative bacteria	*Escherichia coli+Klebsiella*	1 (8.33%)
	Klebsiella	1 (8.33%)
	Enterobacter spp.	1 (8.33%)
	Escherichia coli	2 (16.69%)

cephalosporins. The Gram-negative strains were 33.3% sensitive, and the Gram-positive strains were 16.6% sensitive.

Discussion

Bacterial peritonitis is a severe infection in individuals with ascites and is considered the largest abscess in humans. Bacterial peritonitis is more frequent in those with advanced liver cirrhosis who have ascites with symptoms such as fever, abdominal pain, hepatic encephalopathy, diarrhea, shock, and hypotension.[13, 14] In the present study, abdominal pain was the most prevalent clinical manifestation, which was significantly more common in children with bacterial peritonitis. There was no correlation between the occurrence of SBP and age, sex, underlying disease, fever, encephalopathy, or history of antibiotic and diuretic usage. About one-third of the ascites patients had SBP, which was consistent with previous studies.[3, 15] Additionally, in terms of age and sex distribution, the present study was similar to our previous studies.[16, 17] Antibiotic resistance is a rising problem among SBP patients. Ceftriaxone, a commonly used antibiotic, is becoming less effective against SBP, as bacteria such as *Staphylococcus epidermidis* and Gram-negative Extended-spectrum beta-lactamases (ESBLs) develop resistance. This resistance has resulted from antibiotic overuse and abuse and could complicate infection treatment and might result in prolonged hospital stays, increased healthcare expenses, and even death. It is vital to use antibiotics cautiously and to study innovative therapies to fight antibiotic-resistant bacteria.[18, 19]

Aerobic Gram-negative bacteria (especially *E. coli*) enter the ascitic fluid from the intestinal lumen and are the most important cause of bacterial peritonitis, while Gram-positive bacteria must also be considered.[16, 20] In the present study, both Gram-positive and Gram-negative bacteria were found in equal numbers. However, the most prevalent strain, coagulase-negative staphylococci (25%), was among Gram-positive bacteria. With a frequency of 16.7%, *E. coli* was the next. Only three of the 12 strains isolated from the peritoneum of the studied patients were sensitive to third-generation cephalosporins, two of which were Gram-positive. The overall sensitivity to third-generation cephalosporins was 25%, specifically 33.3% for Gram-negatives and 16.6% for Gram-positives. According to current guidelines, third-generation cephalosporins represent the first line of treatment.

Almeida and colleagues investigated the effect of microbiological changes on SBP in three different time periods in 2018. In the first period (1997-1998), there were 33 positive culture cases. The most common of which were *E. coli* in 13 cases (36.11%), coagulase-negative *Staphylococcus* in 6 (16.66%), *K. pneumoniae* in 5 (13.88%), *S. aureus* in 4 (11.11%), and *Staphylococcus faecalis* in 3 (8.33%) cases. In the second period (2002-2003), there were 43 positive culture cases. The most common of which were coagulase-negative *Staphylococcus* in 16 (35.55%), *S. aureus* in 8 (17.77%), *E. coli* in 7 (15.55%), and *K. pneumoniae* in 3 (6.66%) cases. In the third period (2014-2015), there were 58 cases (seven with two bacteria). The most frequent of which were *E. coli* in 15 (23.1%), *Streptococcus viridans* in 12 (18.5%), and *K. pneumoniae* in 10 (15.4%) cases. None of the patients received prophylactic antibiotic prophylaxis. Considering all staphylococci, the frequency increased by 50% in the second period and decreased in the third period. Similarly, the prevalence of resistant *E. coli* increased to 14%. Ultimately, they concluded that there was a change in the bacterial population that caused SBP, with a high frequency of Gram-positive organisms as well as increased resistance to empirically recommended antibiotics.[21]

In a cross-sectional study, Ghobri and colleagues reported that 33.3% of children with chronic liver disease and ascites had an ascitic fluid infection. Gram-positive bacteria were identified in six cases, while Gram-negative bacteria were identified in five cases. Fever and abdominal pain were significantly related to infectious ascites. Similarly, abdominal pain was significantly more frequent in the group with bacterial peritonitis in our study.[3]

Wang and colleagues investigated 160 patients retrospectively in 2017 and indicated that the most common organism causing culture-positive SBP was *E. coli*, which accounted for 37.5% of positive cultures. *Streptococcus* (23.2%), *Enterococcus* (10.7%), *Klebsiella* (8.9%), and *Staphylococcus* (8.9%) species were among the least common organisms. Only 57% of organisms were sensitive to third-generation cephalosporins, and there was significant resistance in the bacterial population. These findings were consistent with those of the present study.[22]

Angeloni and colleagues, in a study of 32 patients, showed that treatment with cefotaxime was successful in 59% of cases, while 41% of patients required modification of the initial antibiotic. Such high resistance rates indicated the need for alternative first-line antibiotics.[23]

In 2006, Haghighat and colleagues found *Streptococcus pneumoniae* as the most common

cause of SBP in children after studying 12 patients with liver disease and ascites. Moreover, a third-generation cephalosporin, such as ceftriaxone or cefotaxime, was recommended for empirical treatment in this population.[16] This was inconsistent with the findings of the present study. As both studies were carried out in the same setting, this discrepancy suggested that the bacterial population causing SBP has changed over time, with a high frequency of Gram-positive organisms and an increase in resistance to previously recommended empirical antibiotics.[16]

In a retrospective study of 288 patients with SBP, Li and colleagues showed that Gram-negative bacteria, Gram-positive bacteria, and fungi accounted for 58.2%, 27.8%, and 2.9% of the positive cultures, respectively. The main pathogenic bacteria were *E. coli*, *K. pneumoniae*, *Enterococcus*, and *S. aureus*. Notably, in hospital infections, *E. coli* and *K. pneumonia* developed beta-lactamase, which had a wider spectrum than in non-hospital infections. The combination of piperacillin/tazobactam was a more effective treatment for non-hospital infections than hospital infections caused by *E. coli.*[24]

The small sample size, the short study period, and its descriptive design were some of the limitations of this study. Therefore, it is recommended to conduct more studies using clinical trials or cohort designs with larger sample sizes.

Conclusion

With the change in the bacterial population causing SBP, the frequency of Gram-positive organisms and the resistance to empirically recommended antibiotics have increased. This study indicated the need to include antibiotics that cover Gram-positive bacteria in the empirical treatment protocols for SBP. Based on the antibiogram patterns of the isolated bacteria in this study, a combination of ceftazidime, gentamicin, and cotrimoxazole could be a first-line therapy for SBP in the studied center.

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Authors' Contribution

S.S: Study design, data gathering, drafting and reviewing the manuscript; N.H: Study design, and reviewing the manuscript; Gh.P: Study design, and reviewing the manuscript; M.D: Data gathering, drafting; H.R: Data gathering, drafting; M.H: Study design, reviewing the manuscript; MH.I: Study design, reviewing the manuscript; SM.D: Study design, reviewing the manuscript; M.A: Study design, reviewing the manuscript; N.Ach: Data gathering, drafting t; I.Sh: Study design, reviewing the manuscript; A.A: Data gathering, drafting; All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of Interest

Mohammad Hadi Imanieh and Gholamreza Pouladfar, as the Editorial Board Members, were not involved in any stage of handling this manuscript. A team of independent experts was formed by the Editorial Board to review the article without their knowledge.

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