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A COMPARATIVE RETROSPECTIVE AND PROSPECTIVE ANALYSIS OF EMERGING RESISTANCE IN EMPIRICAL ANTIBIOTIC TREATMENT AMONG LIVER CIRRHOSIS PATIENTS WITH SPONTANEOUS BACTERIAL PERITONITIS: AN INTERVENTIONAL STUDY IN A TERTIARY CARE HOSPITAL

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Keywords:

Ascitis, Antimicrobial resistance, EASL, Empirical therapy, Intervention, Paracentesis, Spontaneous bacterial peritonitis

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ABSTRACT: Background: Previous hospitalization, nosocomial infection and specific risk factors like prolonged quinolone use for Spontaneous Bacterial Peritonitis prophylaxis can be related to drug-resistant bacterial infections and high mortality in liver cirrhosis. **Aim and Objectives:** To study the prescription pattern of antibiotics used in SBP, compare the efficacy and emerging resistance of antibiotics, and classify patients with different types of ascites. **Methodology:** The study was conducted in liver cirrhosis patients with SBP retrospectively (2 years) and prospectively (6 months) by a convenient sampling technique. The study was carried out in NIMS Medicity, Thiruvananthapuram. Relevant data were collected via pre-approved data collection form and were subjected to SPSS statistics 22 and R software 4.1.1. analysis. **Results:** In our study, a total of 116 patients in the retrospective and 21 patients in the prospective study were obtained. 26 patients (22.4%) from the retrospective study and 4 patients (19%) among the prospective study had culture-positive ascitic fluid culture. E. coli was the most commonly obtained organism (69.24%). Third-generation cephalosporins showed higher resistance in the study (51.72%). **Interpretation And Conclusion:** This study's findings helped to figure out emerging antibiotic resistance in TGCs among Community-Acquired SBP. Strict adherence to the EASL guidelines for a second-time diagnostic paracentesis after 48 hours of empirical antibiotic therapy initiation (intervention of this study) could be continued as a powerful tool in identifying the accurate efficiency and response to the empirical antibiotic therapy used.

INTRODUCTION: Liver Cirrhosis is a condition characterized by an irreversible change in liver tissues and cells that progressively degenerates and causes replacement with fibrous connective tissue. It is often called permanent scarring of the liver [1].

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Ascites is the accumulation of fluid in the peritoneal cavity causing abdominal swelling [1, 2]. Spontaneous Bacterial Peritonitis is defined as sudden bacterial infection of ascitic fluid, provided there is no other intra- abdominal or surgically curable origin of infection, with an elevated ascitic fluid PMN count ≥ 250 cell/mm^3 [3, 4].

Liver Cirrhosis is said to be one of the leading causes of mortality and morbidity worldwide. It is the 11th cause of morbidity and 15th of mortality, computing 2.2% of deaths worldwide as if in 2016. Patients with cirrhosis and ascites are at increased

risk of developing SBP. The prevalence of SBP is 1.5 – 3.5% and 10% in outpatients and inpatients, respectively. The chances of recurrent SBP are more [1, 5] and [6]. In Liver Cirrhosis patients, the incidence of SBP is explained with poor long-term prognosis. European Association for the Study of the Liver Guidelines (EASL) is the foremost guideline used in treatment of SBP. Gram negative aerobic bacteria are the most common causative organism of SBP. The first-line antibiotic agents are third-generation Cephalosporins. Cefotaxime (TGC) is extensively used at a dose of 4 g/day, five-day therapy is recommended. Other penicillin derivatives such as Amoxicillin/Clavulanic acid, Piperacillin Tazobactam are recommended with or without Quinolones such as Ofloxacin, Ciprofloxacin and Norfloxacin.

But Quinolones are not recommended for treatment in patients who were already on prophylaxis. Spontaneous bacterial peritonitis usually subsides with antibiotic therapy which is evident by a reduction in ascitic PMN count following a second paracentesis (Level A1). Worsening patient condition and symptoms are indicators of failure of therapy. The therapy failure can be either due to bacterial resistance developed or secondary bacterial peritonitis [1].

However, several clinical studies indicate that recurrent use of antibiotics and other factors such as nosocomial infections, misuse of antibiotics, and improper use have all led to antimicrobial resistance to such agents by the organism. Proper knowledge about local epidemiological patterns of antibiotic resistance and proper susceptibility testing of the isolated organism will help improve the clinical outcome and is of utmost necessity as the knowledge and information existing regarding the spectrum of bacteria and pattern of resistance is scarce [1]. The study was conducted to analyze the prescription pattern of antibiotics used in SBP, compare antibiotic efficacy and emerging resistance, and classify patients with different types of ascites.

MATERIALS AND METHODS:

Study Setting: NIMS Medicity, a Tertiary Care Hospital in Neyyattinkara, Thiruvananthapuram.

Sample Size: The study was conducted on 137 patients (Retrospective: 116 and Prospective: 21)

Study Design: Prospective and Retrospective Interventional Study.

Criteria for Patient Selection

Inclusion Criteria:

- Patients under the age group of 18-88 years old.
- Liver Cirrhosis patients with ascites.
- Patients with the diagnosis of ascitic fluid PMN cell count > 250 cells/mm3.

Exclusion Criteria:

- Patients with other infections, associated pancreatic diseases, DAMA.
- Patients who were unable to communicate, had severe coagulopathy (>2.0), not willing to enrol in the study (Among prospective cases).
- Vulnerable populations- people with chronic painful health conditions like trauma, psychiatric morbidity, pregnant women, and lactating women.

Study Duration: Prospective study: The duration of the study was from March 2021 to August 2021. Retrospective mining of data: Carried out from medical records of SBP of the time period January 2018- January 2020.

Study Variables:

- **Socio-Demographic Factors:** Age, gender, social history.
- **Clinical Factors:** Hemogram parameters, ascitic fluid parameters (TC, DC), SAAG, ascitic fluid culture: positive/ sterile, sensitivity, SBP treatment guidelines, ß- lactam antibiotics, other antibiotic regimens, paracentesis, patient outcome, altered sensorium, CTP, and MELD score, resistance, history SBP, risk factors.

Intervention: A second diagnostic paracentesis was carried out to find out the efficacy of Penicillin derivatives (Piperacillin + Tazobactam) among prospective cases.

Tool Used: Self-Structured Questionnaire and EASL guidelines.

Study Procedure:

- Topic selection

- Review of literature
- Protocol presentation
- Ethical Committee approval
- Data collection retrospectively and prospectively
- Statistical analysis: SPSS Version 22, R Version 4.1.1.
- Result submission.

Ethical Consideration: Clearance was obtained from the Ethical Committee of NIMS Medicity, Neyyattinkara, Thiruvananthapuram (NIMS/IEC/2021/03/03)

Budget: The entire expense of the study was met by the student investigators.

Data Collection and Analysis: A comparative retrospective and prospective interventional study were conducted in a tertiary care teaching hospital, NIMS Medicity, Neyyattinkara, Thiruvananthapuram, in South Kerala. Retrospective data was collected between January 2018 to January 2020, and prospective data were collected in 2021 (March to August) in a predetermined structured data collection form. The Institutional Ethical Committee of NIMS Medicity, Neyyattinkara, Thiruvananthapuram, approved the protocol. The prospective study participants were selected based on the inclusion criteria.

The study objectives and subject inclusion criteria were explained to the participants. Written informed consent form was obtained from all prospective patients or their representatives in cases where patients were unable to sign due to the disease condition. Based on EASL guidelines, the diagnosis of SBP was made in patients whose PMN count from diagnostic and therapeutic paracentesis revealed a value ≥ 250 cells/μL. From each participant, general sociodemographic details, laboratory values such as Hemogram, Renal function tests, Liver function tests, Ascitic fluid analysis, and treatment regimen details were collected. The data were statistically interpreted using SPSS statistics 22 software and R software version 4.1.1.

RESULTS: The baseline characteristics obtained from retrospective and prospective samples were described with respect to the following variables:

✓ Age

✓ Gender

✓ Social history

Distribution of Age: In both retrospective and prospective cases, most individuals were 47-60 years old. In the retrospective case, 65 (56.03%) belonged to the age category of 47-60 years. In prospective cases, 13 (61.90%) were in the age category of 47-60.

TABLE 1: DISTRIBUTION OF AGE

Age Group	Retrospective		Prospective	
	Frequency (N)	Percentage(%)	Frequency (N)	Percentage(%)
18-32	1	0.86	1	4.76
33-46	9	7.76	1	4.76
47-60	65	56.03	13	61.91
61-74	34	29.31	5	23.81
75-88	7	6.03	1	4.76
Total	116	100	21	100
Mean age	57.96 ± 10.04		56.90 ± 9.46	

TABLE 2: DISTRIBUTION OF GENDER AMONG RETROSPECTIVE AND PROSPECTIVE CASES

Gender	Retrospective		Prospective	
	Frequency (N)	Percentage(%)	Frequency (N)	Percentage(%)
Male	100	86	16	76
Female	16	14	5	24
Total	116	100	21	100

The table shows the prevalence of SBP occurrence with gender both retrospectively and prospectively. In our study of 116 retrospective patients, 100 (86%) were males and only 16 (14%)

were females. Out of 21 prospective SBP patients, 16 (76%) were males and 5 (24%) were females. This indicated that gender influences the prevalence; however, we had a greater number of males than females in our study.

TABLE 3: DISTRIBUTION BASED ON THE SOCIAL HISTORY OF PATIENTS

Social History	Pattern	Retrospective		Prospective	
		Frequency (N)	Percentage (%)	Frequency (N)	Percentage (%)
Alcoholic	Moderate	12	10.35	4	19.05
	Chronic	25	21.56	5	23.81
Smoking	Moderate	1	0.86	6	28.57
	Chronic	27	23.28	0	0
Both (Moderate Smoking & Alcoholic)		13	11.20	0	0
Nil		38	32.75	6	28.57
Total		116	100	21	100

Among 116 retrospective patients, 78 patients (67.24%) had social history, and 38 (32.76%) had no social history. Whereas, in prospective cases, 15 out of 21 (71.42%) patients had social history, and 6 (28.57%) had no social history.

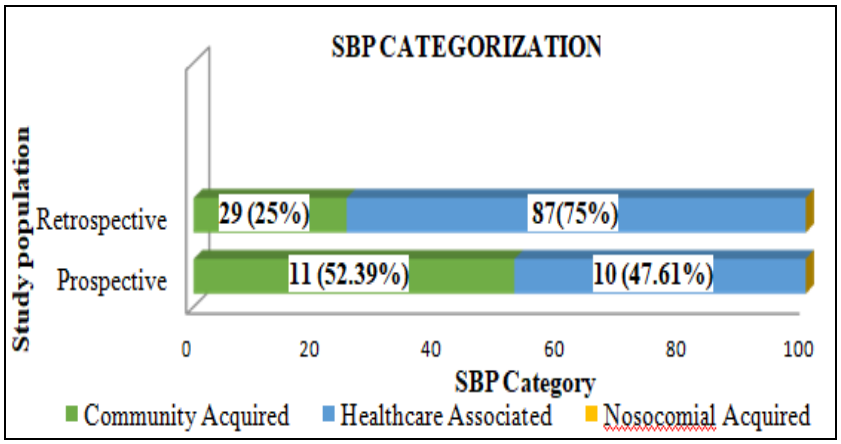

FIG. 1: CLASSIFICATION OF SBP IN RETROSPECTIVE AND PROSPECTIVE CASES BASED ON EASL GUIDELINES

We had no incidence of Nosocomial or Hospital Acquired SBP. These results are contradictory to the study conducted by Chon *et al.,* 7 their study reported 81.5% Community Acquired SBP and 18.5% of Hospital Acquired SBP.

Prescription Analysis:

TABLE 4: CATEGORIZATION OF SBP AND EMPIRICAL ANTIBIOTICS GIVEN IN RETROSPECTIVE CASES (N=116)

Empirical Therapy	Community-Acquired		Health Care Associated		P Value
	Frequency	Percentage (%)	Frequency	Percentage (%)	
TGC	21	**18.1**	64	**55.18**	
Piperacillin +Tazobactam	7	6.03	18	15.51	
Meropenem	1	0.86	5	4.31	
Subtotal (N)	29	25	87	75	0.5386
Total (n)	116 (100%)				

Third Generation Cephalosporins are the EASL-recommended empirical antibiotic therapy in Community-Acquired SBP. Piperacillin + Tazobactam has been recommended for Health Care Associated and Hospital Acquired SBP in low MDR prevalent areas. Carbapenem alone or combined with Vancomycin or Linezolid is recommended for the high prevalence of MDR species or sepsis [1].

TABLE 5: THIRD-GENERATION CEPHALOSPORINS PRESCRIBED IN RETROSPECTIVE PATIENTS (N = 85)

Empirical Antibiotics	CommunityAcquired N (%)	Health CareAssociated N (%)	P Value
Third GenerationCephalosporins	0 (0)	0 (0%)	
Piperacillin + Tazobactam	10 (47.62)	10 (47.62)	
Meropenem	1 (4.76)	0 (0)	
Subtotal	11 (52.38)	10 (47.62)	0.956
Total	21 (100)		

TABLE 6: CATEGORIZATION OF SBP AND EMPIRICAL ANTIBIOTICS GIVEN IN PROSPECTIVE CASES (N=21)

Third Generation Cephalosporins	Retrospective Study Participants	
	Frequency(N)	Percentage(%)
Cefoperazone – Sulbactam	**55**	**64.71**
Ceftriaxone	27	31.76
Ceftriaxone - Sulbactam	2	2.35
Cefuroxime	1	1.18
Total	85	100

Third Generation Cephalosporins are the EASL-recommended empirical antibiotic therapy in Community-Acquired SBP. Piperacillin + Tazobactam has been recommended for Health Care Associated and Hospital Acquired SBP in low MDR prevalent areas. Carbapenem alone or combined with Vancomycin or Linezolid is recommended for the high prevalence of MDR species or sepsis [1].

TABLE 7: INITIAL EMPIRICAL ANTIBIOTIC AND PRIMARY PROPHYLAXIS HISTORY IN PROSPECTIVE PATIENTS (N = 21)

ProphylacticPattern	Initial Emprical Antibiotic Therapy		Total N (%)
	MeropenemN (%)	Piperacillin +Tazobactam N (%)	
Irregular	0 (0)	1 (4.76)	1 (4.76)
Regular	0 (0)	9 (42.86)	9 (42.86)
Nil	1 (4.76)	10 (47.62)	11 (52.38)
Total	1 (4.76)	20 (95.24)	21 100)

TABLE 8: REGULAR PROPHYLACTIC CATEGORY AND INITIAL EMPIRICAL ANTIBIOTIC THERAPY (N = 9)

ProphylacticDrugs	Initial Empricalantibiotic Therapy		Otal N (%)
	MeropenemN (%)	Piperacillin +Tazobactam N (%)	
Ciprofloxacin	0 (0)	2 (22.22)	2 (22.22)
Norfloxacin	0 (0)	4 (44.45)	4 (44. 44)
Ofloxacin	0 (0)	3 (33.33)	3 (33.33)
Total	0 (0)	9 (100)	9 (100)

TABLE 9: DETERMINATION OF EFFICACY OF BETA-LACTAM ANTIBIOTICS

Criteria	No. of Patients (N=116)	Percentage (%)
Antibiotic Shift Done	53	45.69
No Antibiotic Shift	63	54.31
Total	116	100

TABLE 10: CHANGE IN EMPIRICAL ANTIBIOTIC THERAPY IN RETROSPECTIVE CASES (N = 53)

Antibiotic Shift	No. of Cases (N = 53)	Percentage(%)
Cefoperazone + Sulbactam toPiperacillin + Tazobactam	28	52.84
Ceftriaxone to Piperacillin + Tazobactam	20	37.74
Ceftriaxone to Meropenem	1	1.88
Piperacillin + Tazobactam to Meropenem	2	3.78
Cefuroxime to Cefoperazone + Sulbactam	1	1.88
Cefoperazone + Sulbactam to Meropenem	1	1.88
Total	53	100

In another study conducted by *Santoiemma P et al.*, [9] Empirical antibiotics were changed in 47.8% of patients.

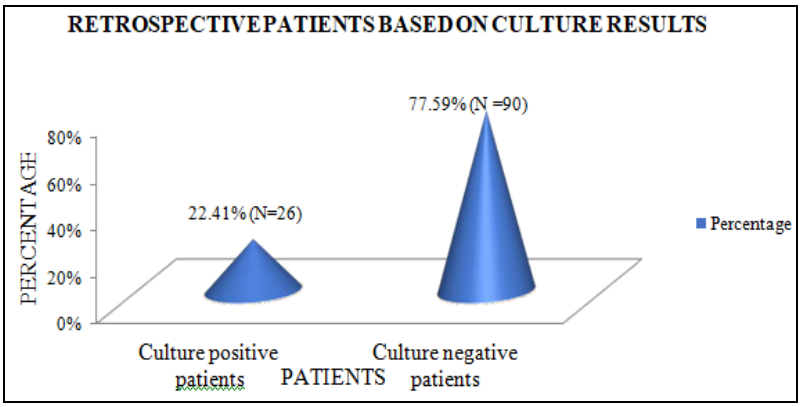

FIG. 2: DISTRIBUTION OF RETROSPECTIVE PATIENTS BASED ON CULTURE RESULTS (N = 116)

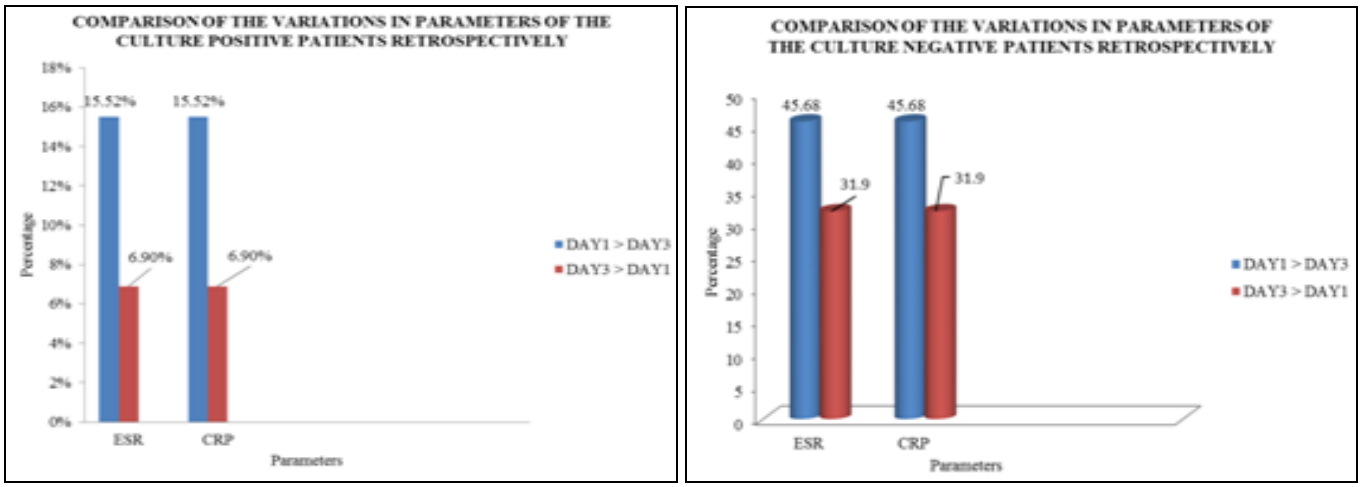

FIG. 3: COMPARISON OF THE VARIATIONS OF ESR AND CRP VALUES IN PATIENTS RETROSPECTIVELY (N = 116)

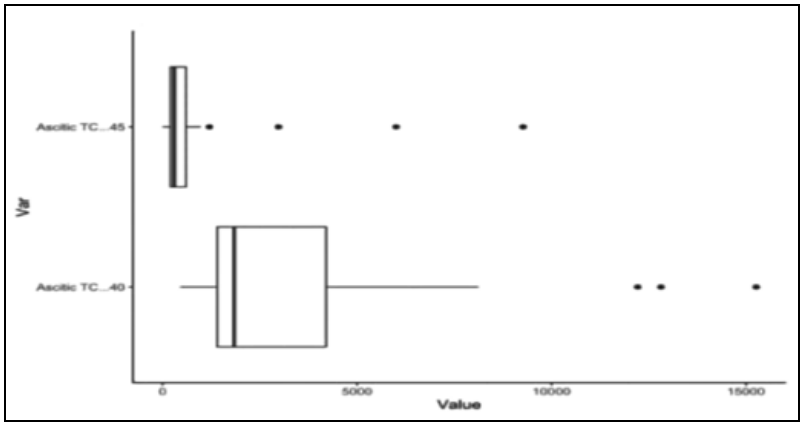

FIG. 4: MEAN ASCITIC COUNT VALUES OBTAINED FROM PARACENTESIS DAY 1 AND DAY 3 IN PROSPECTIVE CASES (N = 21)

According to the study conducted by *Muneer et al.*, [8] 25% of the SBP patients showed improved ascitic PMN count who had done the second tapping. No improvement in the PMN count indicates the need for a change in the initial antibiotic. In our study, efficacy to Piperacillin + Tazobactam was shown in 76.19% (N=16) of patients, and a shift to Meropenem was done in 23.81% (N=5).

In a study conducted by *Santoiemma P et al.*, [9] Empirical antibiotics were changed in 47.8% of patients.

TABLE 11: PATIENT RESPONSE TO EMPIRICAL THERAPY AMONG PROSPECTIVE PATIENTS (N = 21)

Patient Response ToAntibiotics	Frequency (N=21)	Percentage (%)
Efficacy to Piperacillin +Tazobactam	16	76.19
Change from Piperacillin +Tazobactam to Meropenem	5	23.81
Total	21	100

In another study conducted by *Santoiemma P et al*., [9] Empirical antibiotics were changed in 47.8% of patients.

Assessment of Need for Change in Empirical Therapy among Prospective Patients:

TABLE 12: PAIRED SAMPLE STATISTICS FOR ESR, CRP AND ASCITIC TC AMONG PROSPECTIVE CASES (N=5)

Parameter	Mean
ESR Day 1	65.20 ± 20.861
ESR Day 3	71.20 ± 23.931

Parameter	Mean
CRP Day 1	49.560 ± 20.0921
CRP Day 3	60.340 ± 17.7135

Parameter	Mean
Ascitic TC Day 1	4504.40 ± 4420.266
Ascitic TC Day 3	4908.00 ± 4360.764

TABLE 13: MEAN DIFFERENCE AND P-VALUE SIGNIFICANCE OF LABORATORY PARAMETERS USING PAIRED T-TEST (N=5)

Meld	Frequency (N)	Percentage (%)	P-Value
10-19	2	40	
20-29	2	40	0.801
30-39	1	20	
Total	5	100	

TABLE 14: MELD SCORING AMONG PROSPECTIVE PATIENTS (N = 21)

Parameters	Paired Differences	t	p-Value
	Mean Diff. ± Std. Deviation		
ESR day 1- ESR day 3	-6.000 ± 7.314	-1.834	0.141
CRP day 1 CRP day 3	-10.7800 ± 8.0884	-2.980	< 0.041
Ascitic TC day1- day3	-403.600 ± 498.119	-1.812	0.144

TABLE 15: MELD SEVERITY SCORING AMONG PROSPECTIVE PATIENTS RESISTANT TO PIPERACILLIN + TAZOBACTAM AS EMPIRICAL THERAPY (N=5)

Meld Score	Prospective (N=21)	
	Frequency (N)	Percentage (%)
10 – 19	13	62
20 – 29	6	28.5
30 – 39	2	9.5
Total	21	100

TABLE 16: CORRELATION OF SERUM AMMONIA WITH ASCITIC TC (N=5)

Parameter	Mean Ascitic TC	Calculated Value	P-Value
Mean Ascitic TC II	4112.905	0.8467	0.407
Mean Serum Ammonia	28		7

TABLE 17: CLASSIFICATION OF ASCITES

Ascites Type	Retrospective		Prospective	
	Frequency	Percentage	Frequency	Percentage
Transudative	116	100%	19	90.5%
Exudative	0	0%	2	9.5%
Total	116	100%	21	100%

TABLE 18: CLASSIFICATION OF SBP BASED ON CULTURE REPORT

Type	Retrospective		Prospective	
	Frequency	Percentage	Frequency	Percentage
NNBA	0	0	0	0
CNNA	90	77.6%	17	81%
Positive	26	22.4%	4	19%
Total	116	100%	21	100%

According to the study conducted by *Adriano E et al*, [10] 160 SBP cases were identified and was classified as culture positive (n=56) and culture-negative-CNNA (n=104). According to a study conducted by *Yakar T et.al*, [11] from the culture growth of 76 patients, bacteria isolated were *E. coli, Klebsilla Pneumonia, Pseudomonas Aeuroginosa, acinibacter, Streptococcus species (S.*

pneumonia, S. aureus, Coagulase(-) Staphylococcus) and Enterococcus. In prospective cases (N=1) was polymicrobial which contained both *E. coli* and *Enterococcus cloacae*.

TABLE 19: CLASSIFICATION OF POSITIVE CULTURE REPORT (N= 26)

Classification	Retrospective		Prospective	
	Frequency	Percentage	Frequency	Percentage
Monomicrobial	26	100%	3	75%
Polymicrobial	0	0	1	25%
Total	26	100%	4	100%

TABLE 20: CLASSIFICATION OF ORGANISM IN MONOMICROBIAL POSITIVE CULTURE (N= 26)

Organism	Retrospective		Prospective	
	Frequency	Percentage	Frequency	Percentage
E .coli	18	69.23%	2	66.68%
Klebsiella pneumoniae	3	11.54%	0	0
Staphylococcus aureus	1	3.85%	0	0
Streptococcus pneumoniae	2	7.69%	0	0
Enterococcus cloacae	2	7.69%	1	33.32%
Total	26	100%	3	100%

TABLE 21: CLASSIFICATION OF ORGANISM BASED ON CULTURE REPORT (N= 26)

Organism	Retrospective N (%)		Prospective N (%)	
	N	%	N	%
Gram Positive	3	11.5	0	0
Gram Negative	23	88.4	5	100
Total	26	100	5	100

Resistance Pattern of Organism to Antibiotics:

TABLE 22: RESISTANCE PATTERN IN VARIOUS ORGANISMS

AntibiotIcs	*Escherichia coli*	*Staphylococcus aureus*	*Enterococcus cloacae*	*Klebsiella pneumoniae*	*Streptococcus pneumoniae*
	Frequency (N) Percentage (%)	Frequency (N) Percentage (%)	Frequency (N) Percentage(%)	Frequency (N) Percentage(%)	Frequency(N) Percentage(%)
Norfloxacin	5 (12.25)	-	1 (20)	1 (12.5)	1 (14.2)
Ciprofloxacin	6 (14.64)	-	1 (20)	1 (12.5)	-
Levofloxaci n	2 (4.84)	-	1 (20)	-	-
Cefazolin	6 (14.64)	-	1 (20)	-	-
Cefepime	4 (9.76)	1 (50)	-	1 (12.5)	2 (28.6)
Cefoperazone + Sulbactam	6 (14.64)	-	1 (20)	2 (25)	2 (28.6)
Cefuroxime	2 (4.84)	-	-	-	-
Ceftriaxone	6 (14.64)	1 (50)	-	1 (12.5)	2 (28.6)
Ofloxacin	3 (7.31)	-	-	2 (25)	-
Cefotaxime	1 (2.44)	-	-	-	-
Total	41 (100)	2 (100)	5 (100)	8 (100)	7 (100)

TABLE 23: COMPARISON OF ESR AND CRP ON DAY 3 AGAINST DAY 1 IN RETROSPECTIVE PATIENTS (N = 116).

Parameter (Retrospective)	Paired Differences	t Value	p-Value (2-Tailed)
	Mean Diff. ± Std. Deviation		
ESR DAY 3 – ESR DAY 1	10.932 ± 28.449	3.645	< 0.000
CRP DAY 3 – CRP DAY 1	5.0436 ± 21.8537	2.189	< 0.031

According to EASL guideline, [1] a reduction in ascitic fluid count is and indicative of effective antibiotic therapy.

TABLE 24: COMPARISON OF ESR AND CRP ON DAY 3 AGAINST DAY 1 IN PROSPECTIVE PATIENTS (N = 21)

Parameter (Prospective)	Paired Difference	t Value	p Value (2-Tailed)
	Mean Diff. ± Std. Deviation		
ESR DAY 3 – ESR DAY 1	- 24.000 ± 21.703	- 4.56016	< 0.000
CRP DAY 3 – CRP DAY 1	- 10.4000 ± 14.6886	- 2.91916	< 0.010

According to EASL guideline, [1] a reduction in ascitic fluid count is and indicative of effective antibiotic therapy.

TABLE 25: DURATION OF PROPHYLAXIS-RETRO-SPECTIVE (N = 116)

Prophylaxis	Mean ± S.D
Ofloxacin	4.27 ± 2.183
Norfloxacin	4.06 ± 2.657
Ciprofloxacin	5.25 ± 4.717
Total	4.28 ± 2.568

TABLE 26: DURATION OF PROPHYLAXIS – PROSPECTIVE (N = 21)

Prophylaxis	Mean ± S.D
Ofloxacin	7.00 ± 4.359
Norfloxacin	7.33 ± 2.082
Ciprofloxacin	5.00 ± 1.414
Total	6.63 ± 2.825

DISCUSSION: Patients with liver Cirrhosis have a weaker immune system and are at an increased risk of fatal bacterial infections and sepsis [5]. Besides depleted liver functions, bacterial infections are also life-threatening complications of liver cirrhosis. The literature says that there is a four-fold increase in mortality rate among liver cirrhosis patients with bacterial infections. One of the causes of high mortality and morbidity is increased antimicrobial resistance [6].

Our study was a retrospective and prospective comparative study. We included a total of 116 SBP patients in the retrospective study and 21 patients prospectively. Our present study's mean age was 57.96 ± 10.04 among the retrospective patients. In prospective samples, the mean age was 56.90 ± 9.46. In a study conducted by Balaraju *et al.,* [7] the mean age of 48.4 ± 14 was included. Male patient enrolment in our study was more similar to that of Balaraju *et al.,* [7]. In our study 50 out 116 patients (43.1%) among retrospective cases and 9 out of 21 patients (42.86%) among prospective cases had a history of alcoholism. These results were consistent with a study conducted by Numan *et al.,* [20]. Also, in our study 41 out of 116 retrospective patients and 6 out of 21 (28.57%) prospective patients had a smoking history.

In the study by Numan *et al.,* 34 patients with alcoholic history 28.3% and a smoking history was seen in 41.5%. Duration of hospital among the retrospective group compared with prospective study groups was reduced from the mean value of 8.56 to 7.86 days. According to EASL guideline [1], SBP is categorized as healthcare-associated, hospital-acquired or nosocomial SBP, and Community-acquired SBP. In our study, among the retrospective SBP patients, healthcare-associated SBP was 75%, and community-acquired SBP was 25%. Whereas among prospective cases, healthcare-associated was 47.61% and community-acquired was 52.39%. We had no incidence of nosocomial or hospital-acquired SBP.

These results contradict the study conducted by Chon *et al.,* 18 their study reported 81.5% community-acquired SBP and 18.5% hospital-acquired SBP. Third Generation Cephalosporins are the EASL-recommended empirical antibiotic therapy in Community-Acquired SBP. Cefotaxime has been used extensively in patients with high ascitic fluid since it covers most causative organisms.

Piperacillin + Tazobactam has been recommended for Health Care Associated and Hospital Acquired SBP in low MDR prevalent areas. Carbapenem alone or combined with Vancomycin or Linezolid is recommended for the high prevalence of MDR species or sepsis [1]. In our retrospective study group, 21 out of 29 cases (72.41%) of Community-Acquired SBP samples were treated with Third Generation Cephalosporins in accordance with EASL guidelines. Similarly, in the case of Health Care Associated SBP, TGC was given as empirical therapy for 64 out of 87 cases (73.56%).

There was no significant difference between Community Acquired and Health Care Acquired SBP (p-value = 0.5386). This showed that among retrospective cases, the prescription pattern was not in accordance with EASL. Among prospective cases due to reduced clinical response, Piperacillin + Tazobactam was given for 20 out of 21 cases

regardless of the type of SBP. There was no significant difference between Community Acquired and Health Care Acquired SBP where p value was 0.9568.

The efficacy of Beta Lactam antibiotics was analysed in both retrospective patients (n=116) and prospective patients (n=21). The initial antibiotics were changed in 53 (45.69%) samples. These patients required different antibiotic shifts: Cefoperazone + Sulbactam to Piperacillin + Tazobactam, Ceftriaxone to Piperacillin + Tazobactam, Piperacillin + Tazobactam to Meropenem, Ceftriaxone to Meropenem and Cefuroxime to Cefoperazone + Sulbactam due to the worsening conditions after the initiation of empirical therapy. The elevated laboratory parameters such as ESR, CRP, clinical observations, and clinical manifestations determined the worsening situations. All these parameters were found to be elevated in the third day after initiation of empirical antibiotic, indicating the reduced efficacy of empirical therapy in these patients. The remaining 63 subjects (54.31%) showed improvement in their inflammatory conditions, where Third Generation Cephalosporins were given as the empirical antibiotic therapy. According to the study conducted by Elsadek *et al.,* [21] ESR, CRP, and Procalcitonin were used for the prompt diagnosis of SBP.

There were 21 study subjects for the prospective study. For analyzing the prospective studies, the diagnostic paracentesis was done twice. In the initial tapping, enormous number of PMN cells was found. The successive tapping showed a significant reduction in the ascitic PMN cell counts. The significant reduction in the ascitic PMN cell counts emphasizes the efficacy of the initially administered antibiotics. When compared to the retrospective patients, Piperacillin + Tazobactam was the administered empirical antibiotic for all the cases. According to the study conducted by Muneer *et al.,* [8] 25% of the SBP patients showed improved ascitic PMN count who had done the second tapping. No improvement in the PMN count indicates the need for change in the initial antibiotic. The need for change in antibiotics were determined in prospective patients (n=21). This was assessed only in 5 (23.81%) samples requiring an antibiotic shift from Piperacillin + Tazobactam to Meropenem due to their worsening condition even after the initial empirical Piperacillin + Tazobactam therapy. The elevated laboratory parameters such as ascitic TC, ESR, CRP, and clinical observations and symptoms determined the worsening condition. All these parameters were found to be elevated on the third day after initiation of empirical antibiotic, indicating the reduced efficacy of empirical therapy. The remaining 16 study subjects (76.19%) were noted to have an improvement in their disease condition. They did not require any change in antibiotic, which indicates that most cases were effective with the empirical therapy using Piperacillin + Tazobactam. We analyzed the correlation between MELD severity scoring and drug resistance, and the p-value was highly insignificant. Serum Ammonia was correlated with Ascitic TC and was found to have an insignificant correlation. This can be due to the very small sample size as a clear clinical correlation exists. Even though the sample size was very few (N=5) CRP value in correlation with disease severity provided a highly significant p-value (p=0.04).

In our study, we classified ascites into two types. The majority of them were transudative ascites in both retrospective and prospective samples. The exudative type was only found in prospective samples (N=2), and they could be correlated in patients with a medical history of Hepatocellular Carcinoma.

Another classification was made on SBP based on the presence and absence of organisms in which 77.6 % (N=90) of them were culture negative, and 22.4% (N=26) were culture positive.

In prospective patients, 81% (N=17) were classified as CNNA, and 19% (N=4) were culture-positive. In both prospective and retrospective, NNBA type of classification was absent.

According to the study by Ardino E et al., 10 160 SBP cases were identified and classified as culture-positive (N=56) and culture-negative-CNNA (N=104). In our study, among the culture-positive, 100% (n=116) of the organism was monomicrobial in retrospective patients. But in prospective samples, the polymicrobial organism was also

found at 4.8% (N=1) and the remaining were monomicrobial (N=20). This indicates that the exudative type of ascites is rare than transudative and also majority of the ascitic fluid contain monomicrobial organism.

According to our study, in retrospective monomicrobial positive culture E. coli was found to be most prevalent organism 69.23% (N=18) followed by *Klebsiella pneumoniae* 11.54% (N=3), Streptococcus pneumonia 7.69% (N=2), *Enterococcus cloacae* 7.69% (N=2), *Staphylococcus aureus* 3.85% (N=1). According to a study conducted by Yakar T *et.al.,* [11 from the growth culture of 76 patients the bacteria isolated were *E. coli, Klebsiella pneumonia, Pseudomonas aeruginosa, Acinibacter, Streptococcus species (S. pneumonia, S. aureus, Coagulase (-) Staphylococcus) and Enterococcus*. In the polymicrobial organism present in prospective samples, E. coli and Enterococcus were found together.

Enterococcus cloacae shows resistance to Third Generation Cephalosporins and Fluoroquinolones, with N=1 and 20% each. *Klebsiella pneumoniae* shows more resistance to Ofloxacin and Cefoperazone-Sulbactam (25%) followed by Ciprofloxacin, Ceftriaxone, Cefepime and Norfloxacin (12.5%). Streptococcus pneumonia shows more resistance to Ceftriaxone, Cefoperazone-Sulbactam and Cefepime (28.5%) followed by Norfloxacin (14.2%).

Elevated ESR and CRP indicated decreased efficacy of antibiotic even after intake antibiotic. In culture-positive SBP patients, antibiotic resistance can be detected by culture sensitivity. Whereas 48 hours post haemogram parameters like ESR, CRP can be used for culture-negative or sterile culture forms of SBP. The p-value of the test is found to be significant (p-value 0.000)

In our study 90 patients (77.6%) were negative on ascitic fluid culture, whereas 26 patients (22.4%) had non-sterile or culture-positive ascitic fluid. So, according to EASL guidelines, CRP and ESR are relevant haemogram parameters in measuring the severity in the case of sterile SBP. In our study, prospective patients had undergone a second diagnostic tapping, which enabled them to detect the efficacy of antibiotics apart from ESR, CRP values. A diagnostic paracentesis 48 hours post-antibiotic intake is recommended by EASL guidelines. An increase in the second-time ascitic fluid total count elevated ESR, and elevated CRP is indicatives of decreased response and increased resistance to adopted antibiotic therapy. Ascitic fluid culture reports in the case of NNBA and culture-positive SBP can prove antibiotic resistance. In contrast, resistance in CNNA and sterile SBP was possible only by ESR, CRP, or second diagnostic tapping.

In our study, *E. coli* shows more resistance towards Ciprofloxacin, Cefazolin, Cefoperazone + Sulbactam, and Ceftriaxone (14.63%) followed by Norfloxacin (12.1%), Cefepime (9.75%), Ofloxacin (7.31%), Levofloxacin (4.8%) and Cefotaxime (2.43%).

According to a study conducted by Kriplani P.D. *et al.,* [12] the ascitic fluid culture and sensitivity was done, and the most common organism was found as *E. coli*. The resistance patterns of *E. coli* were obtained in which Ciprofloxacin (38.6%) was shown to have higher resistance to E. coli than Imipenem and Meropenem (0%).

In another study conducted by Santoiemma P *et al.*, [9] Resistance to *E. coli* was shown in n=28 and in *Klebsiella pneumoniae* was n=18.21.3% of bacteria were resistant to any one of the first line antibiotics used for SBP patients. Empirical antibiotics were changed in 47.8% of patients. In the case of Staphylococcus aureus, the resistance was shown equally by Ceftriaxone and Cefepime (50%).

CONCLUSION: In retrospective patients, Health Care associated SBP was more prevalent, and Community Acquired SBP was more prevalent in a prospective study. There was no incidence of Nosocomial infections in our study. An emerging antibiotic resistance was noted among Third Generation Cephalosporins in Community-Acquired SBP. This information indicates an urgent need to change the therapy from TGC to other antibiotics such as Piperacillin + Tazobactam, usually preferred for Hospital Acquired SBP according to EASL guidelines. In severely ill patients, urgent change to other higher antibiotics is highly essential to prevent mortality. Strict

adherence to the EASL guidelines for a second time therapeutic and diagnostic paracentesis after 48 hours of empirical antibiotic therapy initiation was concluded as an effective intervention in our study setting.

Limitations: Our study was unable to meet and attain the required sample size due to pandemic restrictions. Also, 2-year data mining was carried out for the retrospective study, whereas due to COVID-19 constraints, our prospective study was decreased to a duration of 6 months. Among the retrospective patients, diagnostic and therapeutic paracentesis after 48 hours of empirical therapy was not a practiced method, so we could not obtain culture reports and sensitivity reports among them, so the comparison between retrospective and prospective data was differently carried out. Some registers containing the retrospective data were inaccessible, so we could not meet the required sample size.

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