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Study on Risk of Bacterial Infections in Chronic Liver Disease Patients Using PPI's

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M. Sureshwara Reddy[1], Sreeram Vandavasi Guru[1*], C. Harshitha[2], B. Meghana[2], D. Vinitha Sasi[2], R. Ganga Tanuja[2]

[1]Associate Professor, General Medicine, Govt. General Hospital, RIMS, Kadapa. India.

[1]Assistant Professor, P. Rami Reddy Memorial College of Pharmacy, Kadapa. India.*

[2]Pharm –D Intern, Govt. General Hospital, RIMS, PRRMCP, Kadapa. India.

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ABSTRACT

BACKGROUND & AIMS: Patients with liver cirrhosis are at high risk of developing bacterial infections like sepsis and sepsis-related deaths. PPI's are prescribed in chronic liver disease patients without any specific indication for the long term leads to the increased risk of bacterial infections. The study aims to assess the risk of bacterial infections in chronic liver disease patients using a proton pump inhibitor. **METHODOLOGY:** In this prospective interventional cohort study, we collected data from 60 patients hospitalized with chronic liver disease and enrolled them for the study based on inclusion and exclusion criteria into two groups test (PPI's) and control (Without PPI'S). Patients were followed for 6 months after hospital discharge and data was analyzed for type of infections associated and specific treatment was provided by using student t-Test and graph pad prism **RESULTS:** Six months after hospital discharge and follow-ups; in test group 9 (30%) subjects developed SBP, 5(16.66%) subjects developed pneumonia, 4(13.3%) subjects developed UTI, 4(13.33%) subjects developed SSTI's and co-infections were developed in 4(13.33%) subjects. In control group, 2(6.6%) subjects developed SBP, 3(10%) subjects developed pneumonia, 1(3.3%) subjects developed UTI, and co-infections were developed in 1(3.3%) subjects. **CONCLUSION:** This study explains that there is an over-prescription of PPI's without a justified clinical indication. The long-term usage of PPI's increases the risk of bacterial infections, in chronic liver disease patients. Therefore, the use of PPI's in patients with chronic liver disease should be carefully assessed for proper indication and, if used, should be limited to the lowest time course.

INTRODUCTION

Chronic liver disease is the final stage of the disease where the liver is shrunk and is separated by broad fibrotic bands related to extensive necrosis and regenerative nodules of liver cells[1]. The bacterial infection is common and accounts for several deaths[2].

Gastric acidity is the most important factor and a host defense barrier. Hence, an increase in gastric pH has been associated with an increase in bacterial infections[2]. The other factors include portal hypertension, immunologic impairment, quantitative and qualitative changes in gut microbiota, intestinal dysmotility, and small intestinal bacterial overgrowth.

Patients with chronic liver disease are immune suppressed and are more susceptible to spontaneous and hospital-acquired infections. There is evidence that about one-third of cirrhotic patients present with infection at hospital admission or develop infection during hospitalization[3].

Bacterial infections account for about 30%-50% of death in cirrhotic patients. Infections present in 32%-34% of hospitalized patients with cirrhosis, which is 4-5 folds higher than hospitalized patients, and is especially higher in those with gastrointestinal bleeds (45%-60)[4].

The major causative organisms are gram-negative bacteria, like E. coli, Klebsiella spp., Enterobacter spp., and gram-positive bacteria especially Enterococci, Staphylococcus aureus, Enterococcus faecalis, and Streptococcus pneumonia[4]. Protocol for early diagnosis of infections in liver cirrhosis patients includes CBP, CRP, Urine analysis, Chest radiograph, US abdomen, blood, and urine culture, ascitic fluid analysis, absolute neutrophil count (> 250 cells/cu mm), ascetic fluid protein content <1g/dl[5,7,8].

Table No. 1: Type of infections and suggested empirical antibiotics

S.NO	TYPE OF INFECTIONS	SUGGESTED EMPIRICAL ANTIBIOTICS
1	Spontaneous Bacterial Peritonitis	Cefotaxime ceftriaxone BL-BI
2	Pneumonia	Ceftriaxone BL-BI + Macrolide levofloxacin, meropenem cetazimide + ciprofloxacin
3	Urinary tract infections	cotrimoxazole Nitrofurantoin
4	Skin & Soft tissue infections	Meropenem cetazidime
5	Meningitis	cefotaxime ceftriaxone + vancomycin Ampicillin Meropenem + vancomycin[11].

MATERIALS AND METHODS:

This prospective interventional study was conducted for a period of 6 months [June 2019 to November 2019] in south Indian Tertiary Care Teaching hospital, GGH, RIMS, Kadapa. A total of 60 patients were recruited as per inclusion criteria upon taking ICF.

Patients were recruited based on inclusion and Exclusion criteria and were categorized into two groups; Test (proton pump inhibitors) and Control (without PPI's). Later, we identified the risk of bacterial infections during the treatment course in both groups of patients by using- clinical manifestations, blood analysis, paracentesis, complete urine examination, Radiological investigations (USG abdomen, X-Ray). Following, patients were categorized based on system-wise infections and were treated with suitable antibiotics and followed-up throughout the treatment course.

RESULTS:

A total of 60 subjects were recruited for our study as per eligibility criteria after obtaining an informed consent form (ICF). We have screened 90 Chronic Liver Disease patients to recruit 60 study subjects (Patients) in the general medicine department. The demographic parameters of the study patients were collected in a patient data collection form.

We Categorized 60 subjects into "TEST" group [30 subjects] and the "CONTROL" group [30 subjects] based on medication received.

Age-wise distribution: Out of 60 subjects majority i.e.., 16 subjects were in between the age group of 50-59 years, 14 were in between 30-39 years, 14 were in between 40-49 years, and 13 were above 60 years of age, 3 were in between 20-29 years.

The subjects were assessed for bacterial infections during the treatment course by performing blood analysis, paracentesis followed by ascetic fluid analysis for protein levels, ascetic fluid culture sensitivity, blood & urine culture, complete urine examination, radiological investigations – USG abdomen, chest X-ray.

Distribution of subjects based on infections developed in TEST: Out of 30 Subjects using PPI's (TEST), 9 subjects developed Spontaneous Bacterial Peritonitis, 5 subjects developed Pneumonia, 4 subjects developed Urinary Tract Infections, 4 subjects developed Skin & Soft tissue infections, 2 subjects found to be developed both spontaneous bacterial peritonitis and urinary tract infections, 1 subject developed spontaneous bacterial peritonitis along with skin &soft tissue infections and 1 subject developed pneumonia along with SSTI.

Distribution of subjects based on infections developed in CONTROL: Out of 30 Subjects without using PPI's [CONTROL], 2 subjects developed Spontaneous bacterial peritonitis, 3 subjects developed Pneumonia, 1 subject developed urinary tract infection, and 1 subject developed UTI along with Pneumonia.

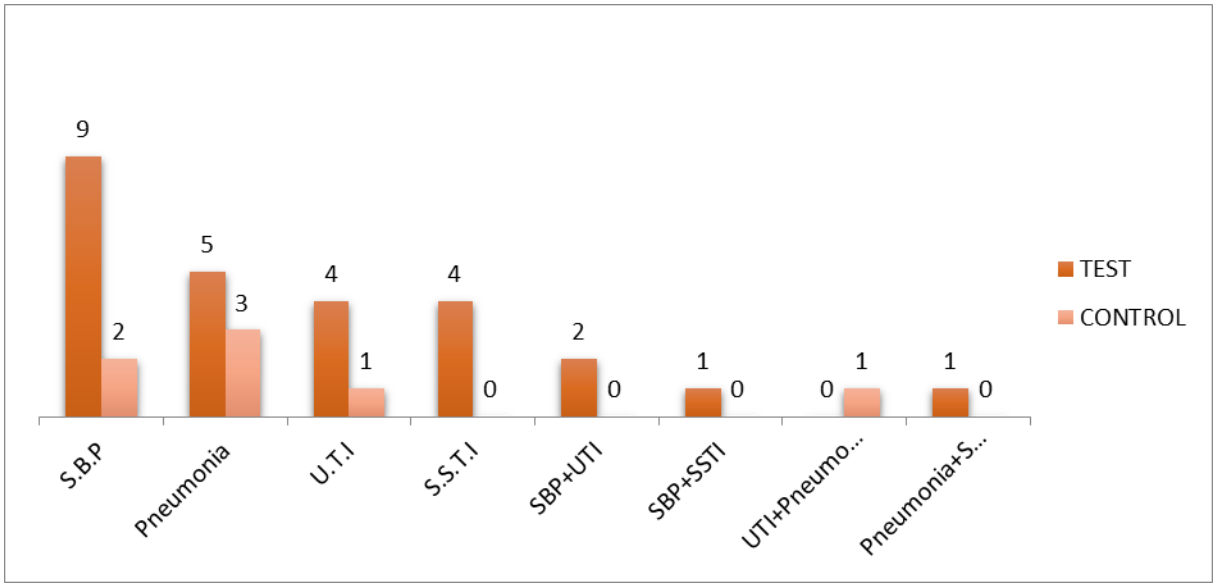

Figure No. 1: Distribution of subjects based on the bacterial infections in test & control

Percentage of bacterial infections in test & control group subjects

Among test subjects, bacterial infections were observed in 26[87%] subjects and bacterial infections were not observed in subjects 4[13%].

Among control subjects, bacterial infections were observed in 7[23%] subjects and bacterial infections were not observed in subjects 23[77%].

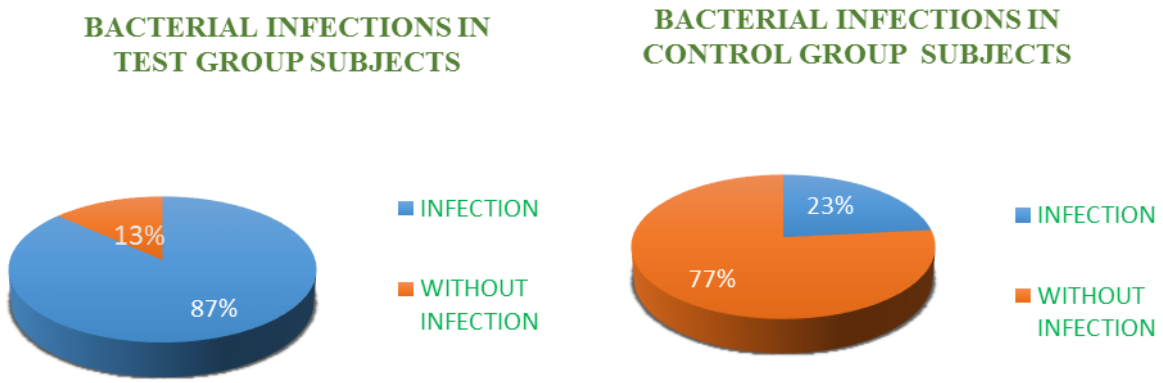

Figure No. 2: Percentage of bacterial infections in test & control group subjects

Antibiotics are given based on Bacterial infections:

We assessed for bacterial infections in all subjects during the treatment course in both groups of patients by observing clinical manifestations, to confirm the type of infection (type of

bacteria, choice of antibiotic), further we performed a culture sensitivity test, blood & urine culture, complete urine examination, radiological investigations – chest X-ray and other tests regarding the condition of infection.

SBP 11(33%) was the major infection developed in subjects and was treated with ceftriaxone.

Pneumonia was developed in subjects 8[24%] and was treated with antibiotic ceftriaxone/Azithromycin.

UTI was developed in subjects 5[15%] and was treated with ceftriaxone/Azithromycin/ofloxacin.

SSTI was developed in subjects 4[12%] and was treated with ceftriaxone/piptaz.

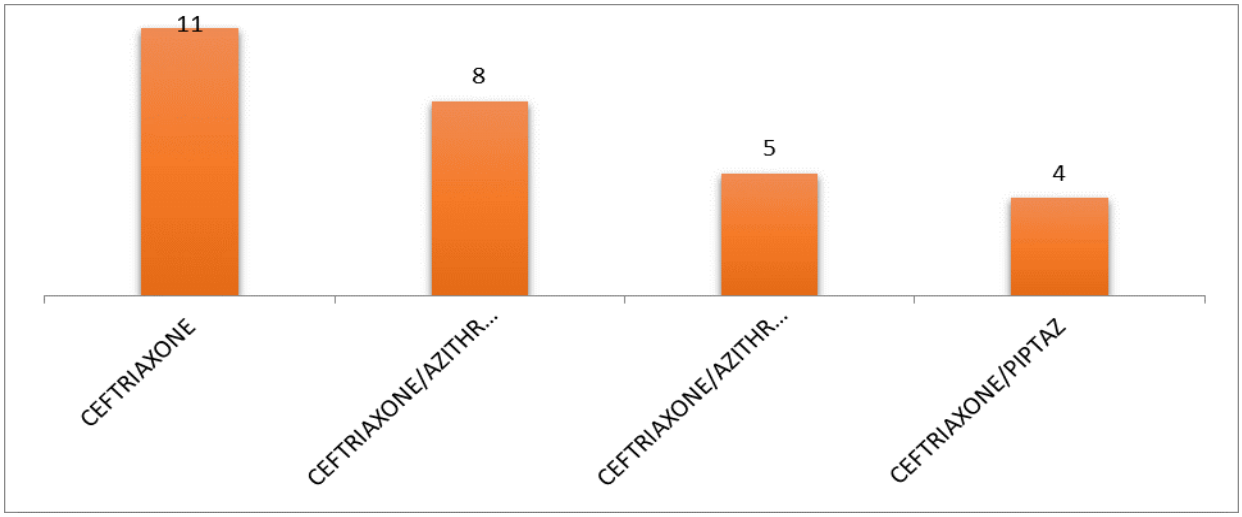

Figure No.3 Antibiotic given based on Bacterial infections

Few subjects developed more than one infection like, SBP & UTI was observed in subjects 2 [6.6%] and was treated with ceftriaxone/ciprofloxacin.

SBP & SSTI was Observed in subject 1[3%] and was treated with Ceftriaxone.

UTI & Pneumonia was observed in subjects 1[3%] and was treated with ceftriaxone/Azithromycin.

Pneumonia & SSTI was Observed in subjects 1[3%] and was treated with ceftriaxone/Azithromycin.

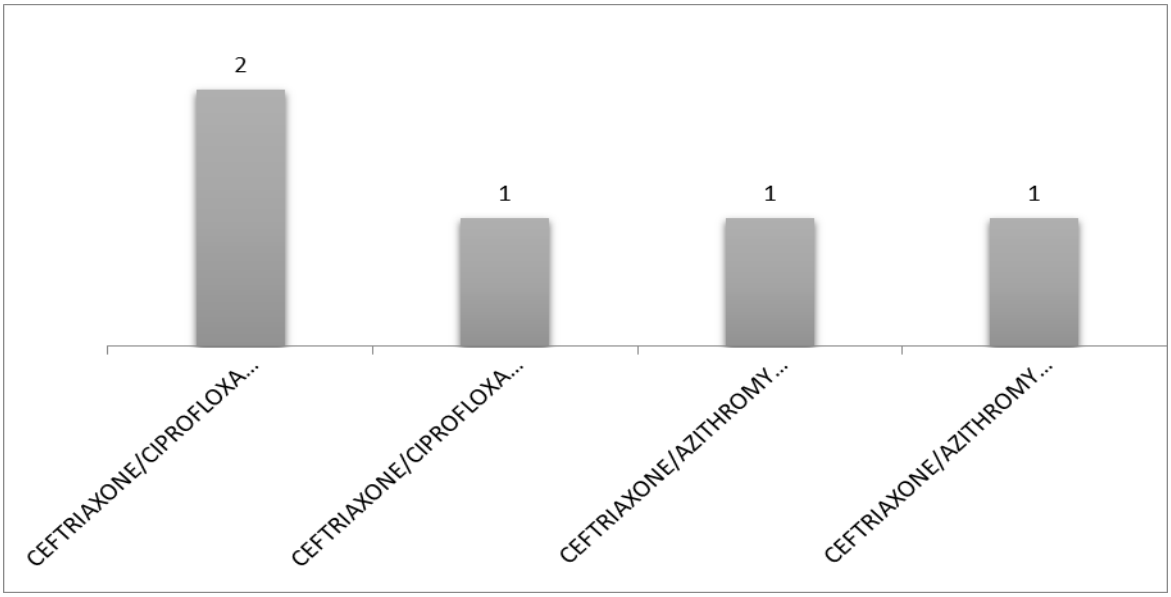

Figure No.4 Antibiotic given based on bacterial infection

Table No.2: Various types of infections and bacteria involved and choice of antibiotic given:

S.NO	TYPE OF INFECTION	NO.OF subjects in a test group	No of the subjects in control group	BACTERIA INVOLVED	ANTIBIOTIC GIVEN
1	SBP	9	2	*Enterobacteriaeceae and S.viridians*	Ceftriaxone
2	UTI	4	1	*E.coli*	Ciprofloxacin
3	PNEUMONIA	5	3	*S.Pneumonia*	Ceftriaxone & Ceftriaxone Azithromycin
4	SSTI	4	0	*Enterobacteriaceae*	Ceftriaxone
5	UTI+SBP	2	0	*E.coli and Enterobacteriaceae*	Ciprofloxacin Ceftriaxone
6	PNEUMONIA+UTI	0	1	*S.Pneumonia and E.coli*	Ceftriaxone
7	SBP+SSTI	1	0	*S.aureus and Enterobacteriaceae*	Ceftriaxone
8	PNEUMONIA+ SSTI	1	0	*S.Pneumonia and Enterobacteriaeceae*	Ceftriaxone & ciprofloxacin

DISCUSSION:

Liver cirrhosis is the end-stage of liver disease, in which the liver is gradually shrunk and is separated by broad fibrotic bands related to extensive necrosis and regenerative nodules of liver cells. Liver cirrhosis can occur at any age as end-stage organ disease is now the 12th leading cause of death worldwide causing roughly 31,000 deaths in 2017.

Patients with cirrhosis have altered and impaired immunity, which favors bacterial translocation. The immuno-compromised state predisposes cirrhotic patients to an increased risk of bacterial infection. Bacterial infections are one of the most frequent complications in cirrhosis and result in high mortality rates.

Among test subjects, bacterial infections were observed in 26[87%] subjects and bacterial infections were not observed in 4[13%] subjects. Among control subjects, the bacterial infections were observed in 7[23%] subjects and bacterial infections were not observed in 23[77%], subjects which were supported by J.S.Bajaj, et al.

We assessed for bacterial infections in all subjects during the treatment course in both groups of patients by observing clinical manifestations, to confirm the type of infection (a type of bacteria, choice of antibiotic), further we performed a culture sensitivity test, blood & urine culture, complete urine examination, radiological investigations – chest X-ray and other tests regarding the condition of infection, the same was explained in Strauss E. Ann Hepatol, *et al*.

We assessed for bacterial infections in Test subjects during the treatment course. Among them, the bacterial infections are found in 26[87%] subjects, whereas, 4 patients without bacterial infections found in subjects were 4[13%]. We assessed for bacterial infections in Control subjects during the treatment course. Among them, the following percentage of bacterial infections found in subjects was 7[23%], whereas, without bacterial infections found in subjects were 23[77%], which was explained by Samuel Raimundo Fernandes, et al.

Out of 30 Subjects using PPI's (TEST), 9 subjects developed Spontaneous Bacterial Peritonitis, 5 subjects developed Pneumonia, 4 subjects developed Urinary Tract Infections, 4 subjects developed Skin & Soft tissue infections, 2 subjects found to be developed both spontaneous bacterial peritonitis and urinary tract infections, 1 subject developed spontaneous bacterial peritonitis along with skin &soft tissue infections and 1 subject developed pneumonia along with SSTI. Out of 30 Subjects without using PPI's

[CONTROL], 2 subjects developed Spontaneous bacterial peritonitis, 3 subjects developed Pneumonia, 1 subject developed urinary tract infection, and one subject developed UTI along with pneumonia, which was supported by Jia Zhu, *et al; and* Jacqueline G. O'Leary, *et* al.

CONCLUSION:

The incidence of bacterial infections was greater in subjects with long-term use of proton pump inhibitor when compared with the subjects not receiving PPI's resulting in increased Morbidity and Mortality. So, the use of PPIs in patients with chronic liver disease should be carefully assessed for proper indication and, if used, should be limited to the lowest time course.

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