Original Article ISSN (O):2395-2822; ISSN (P):2395-2814

Comparison of Efficacy of Rifaximin and Norfloxacin in Prevention of Spontaneous Bacterial Peritonitis.

Sushil Narang[1], Nilesh Pandav[2], Kaushal Vyas[3], Sunny Bherwani[4], Meemansa Buch[5]

[1]Assistant Proffessor Department of gastroenterology, Sheth VS Hospital and Smt NHL Medical College, Ahmedabad.
[2]Senior Resident Department of gastroenterology, Sheth VS Hospital and Smt NHL Medical College, Ahmedabad.
[3]Proffessor Department of gastroenterology, Sheth VS Hospital and Smt NHL Medical College, Ahmedabad.
[4]Resident Department of gastroenterology, Sheth VS Hospital and Smt NHL Medical College, Ahmedabad.
[5]Resident, Department of Medicine, Sheth VS Hospital and Smt NHL Medical College, Ahmedabad.

Received: January 2018
Accepted: January 2018

ABSTRACT

Background: Norfloxacin is the most commonly used agent for the prophylaxis against spontaneous bacterial peritonitis (SBP) in patients with liver cirrhosis. Rifaximin, another broad spectrum antibiotic, is used for the treatment of traveler's diarrhea and hepatic encephalopathy. Objective: We aimed to test the efficacy of rifaximin versus norfloxacin for prevention of SBP in patients with hepatitis C virus (HCV)-related liver cirrhosis. **Methods:** 100 patients with HCV-related liver cirrhosis and ascites were included in study and divided into two groups of matching age, sex and Child–Pugh class. Group I patients were given norfloxacin 400 mg/day and group II patients were given total dose of rifaximin 1200 mg/day in three divided doses. The follow up time was one year. **Results:** Patients on rifaximin developed fewer episodes of SBP than those on norfloxacin (8% vs 16% respectively) although it was statistically insignificant (p=0.265). Also, the duration before developing a new attack of SBP was longer in patients treated with rifaximin as compared to those taking norfloxacin (9.0 vs. 5.5 months, respectively). Additionally, rifaximin significantly reduced the rate of new compared to past episodes of SBP by 24% (p while the rate reduction with norfloxacin was only by 18% and not statistically significant (p= 0.45). Overall survival was equal in both groups. **Conclusion:** Rifaximin is – at least – as good as norfloxacin. It seems to be an appropriate alternative for long-term primary and secondary prophylaxis of SBP in cirrhotic patients with ascites.

Keywords: Rifaximin, Norfloxacin, Spontaneous Bacterial Peritonitis.

INTRODUCTION

Spontaneous bacterial peritonitis (SBP) is a common bacterial infection in patients with cirrhosis and ascites, occurring in up to 30% of patients with cirrhosis, and having an estimated mortality rate of 22%. Nearly half of the episodes of spontaneous bacterial peritonitis (SBP) are already present at the time of hospital admission, while the other half occur during period of hospitalization. Ascitic fluid cytology analysis usually demonstrates an increased number of neutrophils, which must reach a count of at least 250/ mm3 for confirming the diagnosis of SBP. The most common pathogens include Gram-negative bacteria (usually Escherichia coli) and Gram-positive cocci (mainly streptococcus species and enterococci) that are cultured in SBP but the positive culture rate is only 40% Ascites culture,[1-3] however, might be negative in up to 60% of patients who have increased ascites neutrophil count, a category also known as ‘‘culture-negative SBP”. A third category of patients might have ‘‘bacterascites”, in which cultures are positive but ascitic neutrophil count is less than 250/mm.[3] In both categories the clinical presentation is almost similar to classic SBP, and patients should be treated in a same manner as per classic ascites.[4]

Small intestinal dysmotility and bacterial overgrowth, which are commonly seen in patients with liver cirrhosis, are the main contributing factors that invite enteric bacteria ‘‘translocation” from the intestinal lumen to mesenteric lymph nodes and other extra intestinal sites, resulting in SBP.[5]

Initially the mortality from SBP exceeded 90%, but it has been reduced to approximately 20% with early diagnosis and treatment. Treatment of SBP includes empirical antibiotic therapy, which must be given immediately after its diagnosis, without awaiting the results of ascitic fluid culture.[6,7] Cefotaxime, a third-generation cephalosporin, is the drug of choice because it covers most causative organisms and has high ascitic fluid concentration.[7,8] Ciprofloxacin, given either for 7 days intravenously or for 2 days intravenously followed by 5 days orally, results in a

Name & Address of Corresponding Author
Dr. Sushil Narang
Assistant Proffessor,
Department of gastroenterology,
Sheth VS Hospital and Smt NHL Medical College, Ahmedabad.

similar SBP resolution rate and achieves hospital survival comparable with cefotaxime.[10]

Cirrhotic patients with low ascitic fluid protein concentration <1.5G/dl and/or high serum bilirubin levels are at a high risk of developing a first episode of SBP.[11] Recurrence rate of SBP is about 70% in the patients who have survived an episode of SBP.[12] Studies have evaluated long-term prophylaxis in patients with or without prior history of SBP. The ideal prophylactic agent should be affordable, safe, and effective at reducing the amounts of pathogenic microorganisms from the gut while preserving the protective flora.Norfloxacin is the most commonly used approach for the prophylaxis of SBP in patients with ascites, at a dose of 400 mg/day orally.[13-15]

One study has shown that a good number of infections following acute gastrointestinal hemorrhage were caused by Gram-positive bacteria, which was likely due to invasive procedure done in these patients. In addition, 30% of the isolated Gram-negative bacteria were resistant to quinolones and 30% were resistant to trimethoprim–sulfamethoxazole.[16] SBP was reduced at the expense of more resistance of gut flora to norfloxacin in that group. Rifaximin is another broad spectrum antibiotic with only trivial absorption from the gut.[17] It acts by inhibiting bacterial RNA synthesis. Rifaximin has demonstrated broad spectrum antibacterial activity against Gram-positive and Gram-negative organisms, both aerobes and anaerobes, with considerable low risk of developing resistance.[18-20]

AIM

The main aim of this study was to test the efficacy of rifaximin in comparison with norfloxacin for the prevention of spontaneous bacterial peritonitis in patients with HCV related liver cirrhosis and ascites.

MATERIALS AND METHODS

A total of 100 patients with decompensated HCV related liver cirrhosis (Child–Pugh classes B and C) who were admitted to the Gastroenterology department, VS Hospital during the period from June 2016 till may 2017 were included in the study. Patients were selected for long-term antibiotic prophylaxis according to the recommendations (Evidence class I, level A) of the AASLD for participating in this study.

Exclusion criteria

Were etiologies of liver cirrhosis other than HCV, recent abdominal surgery (within past 6 months), abdominal malignancy (including hepatocellular carcinoma), portal vein thrombosis, splenectomy and hypersensitivity to norfloxacin or rifaximin.

Patients were divided into two groups of matching age, sex and Child–Pugh class.

Group I (50 patients) were given norfloxacin 400 mg/day as a single dose, and

Group II (50 patients) were given rifaximin 1200 mg/day in three divided doses.

Patients were then reviewed regularly for a year. Other study endpoints were developing SBP (or any other infection requiring systemic antibiotic treatment), emergence of hepatocellular carcinoma, compliance failure, death, or liver transplantation.

Patients lost to follow-up or who discontinued prophylaxis without permission for more than seven days were designated as ‘‘compliance failure”.

Qualitative data was described using number and percent. Quantitative data was described using mean and standard deviation for normally distributed data while abnormally distributed data were expressed using median, minimum and maximum. Comparison between different groups regarding categorical variables was tested using Chi-square test. For normally distributed data, comparison between the two studied groups was done using independent t-test while for abnormally distributed data, comparison was done using Mann Whitney test.

RESULTS

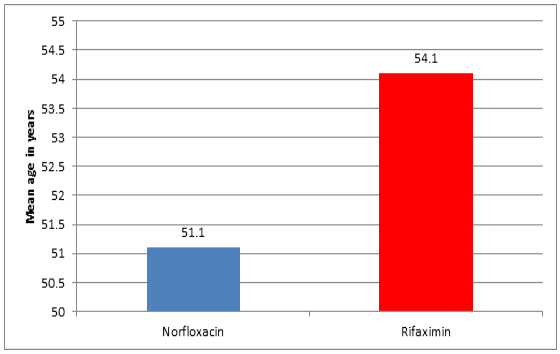
The baseline characteristics of the study population are summarized in [Table 1]. A total of 100 patients with HCV-related liver cirrhosis were included in the study. They were divided into two groups (Norfloxacin versus Rifaximin group; 50 patients each) of matching age, sex and Child–Pugh class.26% of patients in both groups were Child class B, while 74% were Child class C.

Patients who received rifaximin prophylaxis developed fewer episodes of SBP than those on norfloxacin (8% vs 16% respectively), with statistically nonsignificant difference. Also, the duration before developing a new attack of SBP was longer in patients treated with rifaximin as compared to those taking norfloxacin (9.0 vs. 5.5 months, respectively). = 0.05), Additionally, rifaximin significantly reduced the rate of new compared to past episodes of SBP by 24% (p while the rate reduction with norfloxacin was only by 18% and not statistically significant (p= 0.45), as demonstrated in [Table 2]. Culture of ascitic fluid from patients who developed new SBP were mostly negative. The only positive culture was detected in one patient from the norfloxacin group, and it was positive for E. coli. Patients who developed SBP were significantly more likely to have a past history of previous SBP (p =0.029), and had significantly worse overall survival (p <0.001) compared to patients who did not develop SBP during the study duration. Significantly higher baseline values for serum bilirubin (3.2; vs. 2.9 mg/dl; p= 0.005), prothrombin time (16.9 vs. 16.12 s, p= 0.034) and Child–Pugh score (11.67 vs. 11.56, p =0.017) were also found among patients who developed SBP compared with those who did not,

whereas ascitic fluid total protein and renal function tests were comparable in both. Although 53.33% of SBP patients were on norfloxacin vs. 46.67% on rifaximin, the difference, however, did not prove to be statistically significant (p= 0.567), as shown in [Table 3]. The rate of adherence to therapy (compliance) was higher with norfloxacin (86%) compared to rifaximin (78%), with statistically nonsignificant difference. Patient's survival was equal for norfloxacin and rifaximin patients (66.0%, both), as demonstrated in [Table 4]. The death rate was comparable in both groups (12.0% for norfloxacin vs. 6.0% for rifaximin; [Table 1], and the leading causes of death were hepatorenal syndrome, massive variceal bleeding and hepatic encephalopathy.

Table 1: Comparison between the Two Groups According To Baseline Characteristics.

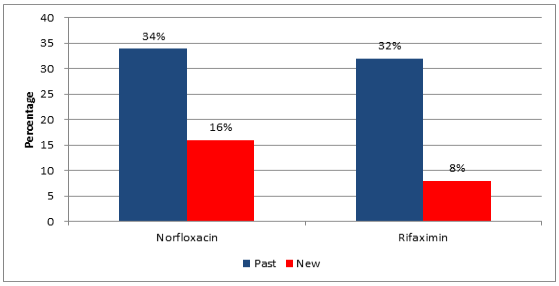
		Norfloxacin (n=50)	Rifaximin (n=50)	P value
Age (years)		51.1+3.28	54.1+3.41	0.05
Sex	Male	38 (76%)	38 (76%)	1.00
	Female	12 (24%)	12 (24%)	
Prophylaxis type	Primary (High Risk)	36 (72%)	38 (76%)	0.64
	Secondary (Previous SBP)	14 (28%)	12 (24%)	
Child-Pugh Class	B	13 (26%)	13 (26%)	1.00
	C	37 (74%)	37 (74%)	
Child score		11.67+1.98	11.56+2.04	0.017
Ascites	Mild	13 (26%)	11 (22%)	0.751
	Moderate/Severe	37 (74%)	39 (78%)	
Serum bilirubin (mg/dl)		2.78+1.02	2.43+1.0	0.002
Serum albumin (g/dl)		2.77+0.87	2.65+0.89	0.875
Prothrombin time (s)		16.9+1.54	16.12+1.01	0.034
Blood urea nitrogen (mg/dl)		24(17-54)	26 (16-63)	0.378
Serum creatinine (mg/dl)		1.12 (0.70-3.10)	1.03(0.70-3.10)	0.784
Serum sodium (mEq/L)		128.65+5.3	131.12+4.89	0.676
Ascitic fluid protein (g/dl)		0.87+0.34	0.92+0.24	0.991



Graph 1: Age Wise Distribution In Both Groups

Table 2. Comparison between the two groups according to follow up events

		Norfloxacin (n=50)	Rifaximin (n=50)	P value
Hepatic encephalopathy	Past	10 (20%)	12 (24%)	0.89
	New	7 (14%)	4 (8%)	0.56
	p2	0.68	0.25	
Variceal bleeding	Past	11 (22%)	11 (22%)	1.00
	New	9 (18%)	9 (18%)	1.00
	p2	0.84	0.84	
SBP	Past	17 (34%)	16 (32%)	0.92
	New	8 (16%)	4 (8%)	0.23
	p2	0.45	0.05	
Months till SBP		5.5 (3.0-10.0)	9.0 (9.0-10.0)	0.231
Ascites culture	Positive	2/9 (22.22%)	1/4 (25.0%)	0.74
	Negative	6/8 (75.0%)	3/3 (100%)	0.68
Hepatorenal syndrome		3 (6%)	2 (4%)	0.98
Hepatocellular carcinoma		6 (12%)	7 (14%)	0.78
Death		6 (12%)	3 (6%)	0.34



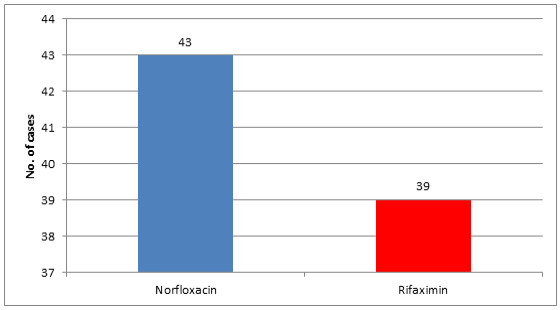
Graph 2: Frequency Of Past And New Episodes Of Spontaneous Bacterial Peritonitis

Table 3. Factors associated with SBP.

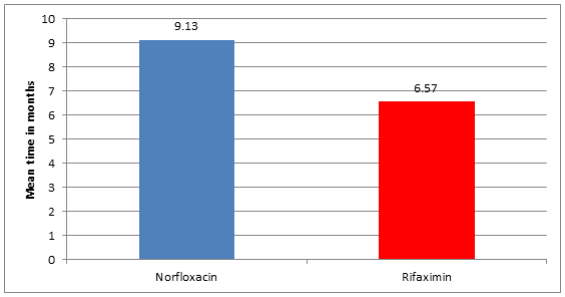
		SBP (n=15)	No SBP (n=85)	P value
Age (years)		52.75+6.02	50.99+8.43	0.76
Sex	Male	13 (86.66%)	69(81.17%)	0.679
Past SBP		12 (80.00%)	25(29.41%)	0.031*
Child-Pugh Class	B	3 (20.0%)	41 (48.23%)	0.07
	C	11 (44.0%)	41 (48.23%)	0.012*
Child score		11.98+0.99	9.03+2.02	0.021*
Serum bilirubin (mg/dl)		3.31+1.65	2.87+1.03	0.005*
Serum albumin (g/dl)		2.54+1.48	2.75+0.87	0.45
Prothrombin time (s)		17.2+1.78	*15.0+1.34*	0.03*
Blood urea nitrogen (mg/dl)		24 (17-56)	22 (15-51)	0.56
Serum creatinine (mg/dl)		1.02	1.08	0.987
Serum sodium (mEq/L)		128.32+6.9	130.12+6.02	0.862
Ascitic fluid protein (g/dl)		0.91+0.32	1.21+0.67	0.071
Antimicrobial	Norfloxacin	8 (53.33%)	42 (49.41%)	0.567
	Rifaximin	7 (46.67%	43 (50.59%)	
Overall survival (months)		6.98 + 2.22	11.12 + 2.11	0.001*

Table 4. Comparison according to compliance and overall survival

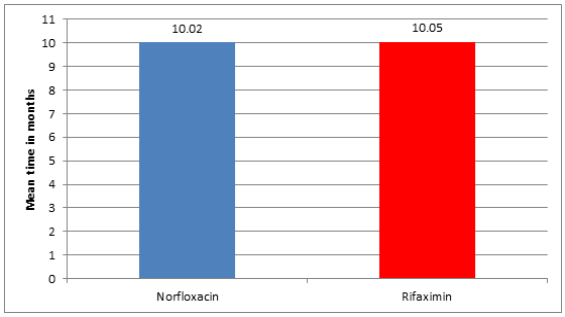
	Norfloxacin (n=50)	Rifaximin (n=50)	P value
Compliance	43 (86%)	39 (78%)	
Months till compliance failure	9.13 + 0.92	6.57 + 0.99	0.02*
Overall survival	33 (66%)	33 (66%	1.00
Months till study endpoint	10.02 + 1.89	10.05 + 2.32	0.89



Graph 3: no. Of cases according to compliance.



Graph 4: Mothstillcompliancefailure



Graph 5: Months till study endpoint

DISCUSSION & CONCLUSION

In many clinical trials it has been proven that the antibiotic rifaximin has a very good safety profile, due to its less absorption from the gut, and its lack of systemic side effects and activity.[21,22] Few adverse reactions reported were gastrointestinal like flatulence and nausea.

Norfloxacin is more likely to induce systemic side effects as it is readily absorbed from the gut; rare, but serious side effects include tendonopathy, exacerbation of myasthenia gravis and life threatening arrhythmias.[23] The European Association for the Study of the Liver (EASL) has identified three patient populations at high-risk for developing SBP:; those with low total protein content in ascitic fluid and no prior history of SBP;patients with acute gastrointestinal hemorrhage and those with a previous historyof SBP.[24]

In comparison, our patients who developed SBP during the study duration were significantly more likely to have had a history of previous SBP, higher baseline values for serum bilirubin, prothrombin time and Child–Pugh score. As expected, they also had significantly worse overall survival compared to patients who did not develop SBP. Despite the fact that 53.33% of patients who developed SBP in our study were on norfloxacin versus 46.67% on rifaximin, the difference, however, did not prove to be statistically significant.

Nevertheless, rifaximin significantly reduced the rate of new compared to past episodes of SBP by 24% (p = 0.05), while the rate reduction with norfloxacin was only by 18% and not statistically significant (p= 0.45), as demonstrated in [Table 2].

Only one recent study by Lutz et al. prospectively evaluated 152 ascitic patients and compared the risk of doveloping SBP. They compared between rifaximin and ciprofloxacin.[25] It was a four-week follow-up study, in which they reported a significantly lower rate of SBP in patients treated with systemic antibiotic prophylaxis (n =17), while SBP rates in patients with no prophylactic treatment (n= 108) and in patients taking rifaximin (n= 27) were comparable.

On the other hand, few studies have investigated rifaximin versus placebo for SBP prophylaxis in cirrhotics. A cohort study by Hanouneh et al. found a transplant-free survival benefit with the use of rifaximin in cirrhotic patients with ascites and who had no prior history of SBP than those who didn't receive antibiotic prophylaxis.[26]

Another prospective case-control study by Danulescu et al. suggested that rifaximin can significantly decrease the increased neutrophil count in ascitic fluid of cirrhotic patients with refractory ascites compared to placebo, with a net improvement of the general condition.[27]

Vlachogiannakos et al. also showed that patients who received rifaximin had a significantly lower risk of developing variceal bleeding, hepatic encephalopathy (HE), SBP and hepatorenal syndrome than matched control subjects who did not receive antibiotic prophylaxis.[28] In comparison, our results demonstrated that patients on rifaximin developed fewer episodes of Hepatic encephalopathy than patients on norfloxacin (4.7% and 9.3%, respectively). Patient succeeded to adhere to therapy slightly better with norfloxacin than rifaximin, and for a significantly longer time. Most patients reported a difficulty to adhere to the three times per day-regimen of rifaximin.

The most important limitation of our study is that it was not a randomized, placebo controlled trial, but rather a prospective longitudinal observational study

with a relatively limited sample size. In this type of study, a selection and observer bias cannot be ruled out completely. In conclusion, rifaximin has proved itself to be – at least – as good as norfloxacin, and seems to be an appropriate antibiotic alternative for long-term primary and secondary prophylaxis of SBP in cirrhotic patients with ascites with outcomes comparable to norfloxacin. Financial burden on the patient, however, remains an issue. Larger randomized controlled trials are needed to confirm our results, and it should take into consideration possible modifications of rifaximin dose regimen to improve patient's compliance to therapy.

REFERENCES

1. Caly WR, Strauss E. A prospective study of bacterial infections in patients with cirrhosis. J Hepatol 1993;18:353–8.
2. Ferna´ndez J, Navasa M, Go´mez J, Colmenero J, Vila J, Arroyo V, et al. Bacterial infections in cirrhosis: epidemiological changes with invasive procedures and norfloxacin prophylaxis. Hepatology 2002;35:140–8.
3. Wong F, Bernardi M, Balk R, Christman B, Moreau R, GarciaTsao G, et al. Sepsis in cirrhosis: report on the 7th meeting of the International Ascites Club. Gut 2005;54:718–25.
4. Rimola A, Garcia-Tsao G, Navasa M, Piddock L, Planas R, Bernard B, et al. Diagnosis, treatment and prophylaxis of spontaneous bacterial peritonitis: a consensus document. International Ascites Club. J Hepatol 2000;32:142–53.
5. Chang CS, Chen GH, Lien HC, Yeh HZ. Small intestine dysmotility and bacterial overgrowth in cirrhotic patients with spontaneous bacterial peritonitis.Hepatology 1998;28:1187–90.
6. Felisart J, Rimola A, Arroyo V, Pe´rez-Ayuso RM, Quintero E, Gine`s P, et al. Cefotaxime is more effective than is ampicillin– tobramycin in cirrhotics with severe infections. Hepatology 1985;5:457–62. 9. Rimola A, Salmero´n JM, Clemente G, Rodrigo L, Obrador A, Miranda ML, et al. Two different dosages of cefotaxime in the treatment of spontaneous bacterial peritonitis in cirrhosis: results of a prospective, randomized, multicenter study. Hepatology 1995;21:674–9
7. Andreu M, Sola´ R, Sitges-Serra A, Alia C, Gallen M, Vila MC, et al. Risk factors for spontaneous bacterial peritonitis. Gastroenterology 1993;104:1133–8.
8. Llach J, Rimola A, Navasa M, Gine`s P, Salmero´n JM, Gine`s A, et al. Incidence and predictive factors of first episode of spontaneous bacterial peritonitis in cirrhosis with ascites: relevance of ascitic fluid protein concentration. Hepatology 1992;16:724–7.
9. Guarner C, Sola` R, Soriano G, Andreu M, Novella MT, Vila C, et al. Risk of a first community-acquired spontaneous bacterial peritonitis in cirrhotics with low ascitic fluid protein levels. Gastroenterology 1999;117:414–9. .
10. Soriano G, Guarner C, Teixido´ M, Such J, Barrios J, Enrı´quez J, et al. Selective intestinal decontamination prevents spontaneous bacterial peritonitis. Gastroenterology 1991;100:477–
11. Ferna´ndez J, Navasa M, Planas R, Montoliu S, Monfort D, Soriano G, et al. Primary prophylaxis of spontaneous bacterial peritonitis delays hepatorenal syndrome and improves survival in cirrhosis. Gastroenterology 2007;133:818–24.
12. Terg R, Fassio E, Guevara M, Cartier M, Longo C, Lucero R, et al. Ciprofloxacin in primary prophylaxis of spontaneous bacterial peritonitis: a randomized, placebo-controlled study. J Hepatol 2008;48:774–9.
13. Dupeyron C, Mangeney N, Sedrati L, Campillo B, Fouet P, Leluan G. Rapid emergence of quinolone resistance in cirrhotic patients treated with norfloxacin to prevent spontaneous bacterial peritonitis. Antimicrob Agents Chemother 1994;38:340–4.
14. Aparicio JR, Such J, Pascual S, Arroyo A, Plazas J, Girona E, et al. Development of quinolone-resistant strains of Escherichia coli in stools of patients with cirrhosis undergoing norfloxacin prophylaxis: clinical consequences. J Hepatol 1999;31: 277–83.
15. Berti T, Benoni G, Miglioli PA. Intestinal antibacterial activity of a new rifamycin derivative: compound L-105. Chemioterapia 1982;1(4):106A–11A.
16. Miglioli PA, Allerberger F, Calabro GB, Gaion RM. Effects of daily oral administration of rifaximin and neomycin on fecal aerobic flora in rats. Pharmacol Res 2001;44:373–5.
17. DuPont HL, Jiang ZD. Influence of rifaximin treatment on the susceptibility of intestinal Gram-negative flora and enterococci. ClinMicrobiol Infect 2004;10:1009–11.
18. Ferna´ ndez J, Navasa M, Planas R, Montoliu S, Monfort D, Soriano G, et al. Primary prophylaxis of spontaneous bacterial peritonitis delays hepatorenal syndrome and improves survival in cirrhosis. Gastroenterology 2007;133:818–24.
19. Terg R, Fassio E, Guevara M, Cartier M, Longo C, Lucero R, et al. Ciprofloxacin in primary prophylaxis of spontaneous bacterial peritonitis: a randomized, placebo-controlled study. J Hepatol 2008;48:774–9.
20. Sarro A De, Sarro G De. Adverse reactions to fluoroquinolones.An overview on mechanistic aspects.Curr Med Chem 2001;8(4):371–84.
21. Gine` s P, Angeli P, Lenz K, Møller S, Moore K, Moreau R, et al. EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. J Hepatol 2010;53:397–417.
22. Lutz P, Parcina M, Bekeredjian-Ding I, Nischalke HD, Nattermann J, Sauerbruch T, et al. Impact of rifaximin on the frequency and characteristics of spontaneous bacterial peritonitis in patients with liver cirrhosis and ascites. PLoS ONE 2014;9(4):e93909.
23. Novella M, Sola` R, Soriano G, Andreu M, Gana J, Ortiz J, et al. Continuous versus inpatient prophylaxis of the first episode of spontaneous bacterial peritonitis with norfloxacin. Hepatology 1997;25:532–6.
24. Danulescu RM, Ciobica A, Stanciu C, Trifan A. The role of rifaximine in the prevention of the spontaneous bacterial peritonitis. Rev Med ChirSoc Med Nat Iasi 2013;117(2):315–20.
25. Vlachogiannakos J, Saveriadis AS, Viazis N, Foudoulis K, Manolakopoulos S, Raptis S, et al. Intestinal decontamination\ improves liver haemodynamics in patients with alcohol-relateddecompensated cirrhosis. Aliment PharmacolTher 2009;29:992–9.

How to cite this article: Narang S, Pandav N, Vyas K, Bherwani S, Buch M. Comparison of Efficacy of Rifaximin and Norfloxacin in Prevention of Spontaneous Bacterial Peritonitis. Ann. Int. Med. Den. Res. 2018; 4(2):ME35-ME39.

Source of Support: Nil, **Conflict of Interest:** None declared