

Role of Rifaximin for the Treatment of Hepatic Encephalopathy in Chronic Liver Disease

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Abstract

Background: Hepatic encephalopathy (HE) is a common problem in patients with chronic liver disease (CLD) and is characterized by diminished mentation and neuromuscular abnormalities. Rifaximin has been reported to be effective for the treatment of hepatic encephalopathy (HE) in Europe and other countries. It is unknown whether rifaximin is effective for the treatment of hepatic encephalopathy in Bangladeshi patients.

Methods: A prospective, randomized, single blind, placebo controlled study was conducted to evaluate the efficacy of rifaximin among patients with cirrhosis of liver with hepatic encephalopathy. A total sixty patients of HE fulfilling inclusion criteria were randomly enrolled among those admitted under Gastrointestinal, Hepatobiliary and Pancreatic Disorders (GHPD) department of BIRDEM General Hospital during August 2012 to April 2013. Patients were divided into two groups: group A (receiving Tab. rifaximin with lactulose), the total number of patients were 31(51.7%) and group B (receiving placebo with lactulose), it was 29(48.3%). Enrolled patients were followed up for 10 days or up to discharge from the hospital or death. At enrollment and at the end of treatment, gradation of HE and estimation of portosystemic encephalopathy (PSE) index was done.

Results: In this study between two groups, mean age difference ($p=0.404$), gender difference ($p=0.668$) and CLD duration difference ($p=0.555$) were not statistically significant between two groups. At enrollment, prognostic scores e.g. Child-Turcotte-Pugh (CTP) score ($p=0.489$) and PSE index ($p=0.934$) were not significantly different between two groups. At the end of treatment, group A patients showed significantly lower HE grade ($P=0.045$) and PSE index ($P<0.05$) than group B. CTP score ($p=0.552$) was also lower in rifaximin treated group than placebo group but no significant difference was observed. The mean duration of hospital stay was significantly lower in group A than group B ($p<0.05$).

Conclusions: Hepatic encephalopathy patients treated with rifaximin plus lactulose have better outcome and less hospital stay than those treated with placebo plus lactulose.

Key words: Chronic liver disease, Hepatic encephalopathy, Rifaximin

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Introduction

Hepatic encephalopathy (HE) is a reversible neuropsychiatric syndrome associated with chronic and acute liver dysfunction. It is characterized by cognitive and motor deficits of varying severity. Early symptoms include reversal of sleep pattern, apathy, hypersomnia, irritability and personal neglect. In later stages, delirium and coma can arise with neurologic signs including hyperreflexia, rigidity, myoclonus, and asterixis.¹ The pathophysiology of HE is complex and it manifests with progressive deterioration of the superior neurological functions. HE occurs in the presence of insufficient hepatic clearance of toxins absorbed from the intestine resulting in neurochemical abnormalities across the blood brain barrier.² Elevated serum ammonia level is the best described cause of HE and is detected in 60%-80% of affected patients.^{3, 4}

Current treatment strategies are aimed at reducing the serum level of ammonia.⁵ This is done by introducing agents that reduce or inhibit production of intestinal ammonia or minimize its absorption from the gastrointestinal tract as well as correcting precipitating factors such as gastrointestinal hemorrhage, electrolyte imbalances and constipation, infection, prerenal azotemia, hypokalaemic alkalosis, constipation, hypoxia, hypovolemia or the use of sedatives and tranquilizers.⁶ For both acute and chronic HE, the mainstay of treatment has been the use of non-absorbable disaccharides,⁷ since they decrease the absorption of ammonia through cathartic effects and by altering the colonic pH. Lactulose treatment may be complicated by excessive diarrhea and abdominal pain.^{8,9} Care should be taken to avoid diarrhoea resulting in dehydration and electrolyte abnormalities which can worsen HE and lead to renal dysfunction.⁶ Several oral antibiotics such as neomycin, paromomycin, metronidazole, vancomycin and rifaximin have shown some degree of effectiveness in lowering serum ammonia concentration by reducing the intestinal flora responsible for its production.¹⁰ With the exception of rifaximin, all other antibiotics have been associated with some side effects such as ototoxicity and nephrotoxicity (neomycin)^{11,12} and neurotoxicity (metronidazole).^{13,14} Vancomycin may be a safer option, however, its use has been associated with the development of bacterial resistance.¹⁵ On the other hand, rifaximin is a poorly-absorbed broad spectrum antibiotic with very few

systemic side effects and at low risk of inducing bacterial resistance.^{16,17} These properties make rifaximin an ideal antibiotic for the treatment of patients with HE as several studies have shown a significant decrease in plasma ammonia levels¹⁸⁻²⁰ with minimal impact on the normal gastrointestinal flora.¹⁶

Many small studies have suggested that rifaximin is effective in treating acute HE and is extremely well tolerated.¹⁸ In randomized studies, rifaximin was more effective than that of other antibiotics used in the treatment of acute hepatic encephalopathy.²¹ In patients who have not achieved optimal control of HE with lactulose monotherapy, consider combination of rifaximin and lactulose therapy.²²

Rifaximin is a derivative of rifamycin, which acts by inhibiting bacterial ribonucleic acid (RNA) synthesis. Rifaximin is virtually unabsorbed after oral administration and exhibits broad spectrum antimicrobial activity against both aerobic and anaerobic gram-positive and gram-negative microorganisms within the gastrointestinal tract.²³ During the past decade, several European studies have proved the efficacy of rifaximin for the treatment of HE in Caucasian patients. However, no similar investigation has been performed in Bangladeshi patients.

It has been reported that ethnicity can affect therapeutic response to anti-bacterial therapies and the long-term prognosis of patients with advanced liver diseases.²⁴⁻²⁶ In particular; it is not known whether ethnic background affects the effectiveness of rifaximin in the treatment of HE. In Bangladesh, hepatitis B is the major cause of decompensated liver cirrhosis presenting with hepatic encephalopathy. In contrast, in western countries, liver cirrhosis secondary to alcohol abuse predominates.^{27,28} Alcohol overdose often leads to intestinal bacterial overgrowth which is one of the important precipitating factors of HE.²⁸ Thus etiologic differences may affect the therapeutic efficacy of rifaximin in Bangladeshi patients with HE. Therefore, we conducted this randomized, prospective, placebo controlled, single blind study to evaluate the efficacy of rifaximin among hepatic encephalopathy with CLD patients by comparing with placebo.

Methods

This randomized, prospective, placebo controlled, single blind study was conducted in the Department of GHPD,

BIRDEM to compare outcome of hepatic encephalopathy patients with or without rifaximin therapy from 1st August, 2012 to 30th April 2013. Patient enrollment and follow up was done during this period.

Patients of chronic liver disease were eligible if they were at least 18 years old, had at least one episodes of overt HE (Conn score of 1 or more). Patients must have had a Model for End-Stage Liver Disease (MELD) score of 25 or lower.

Patients who had conditions known to precipitate HE such as active gastrointestinal bleeding, anemia (hemoglobin <7.0.g/dl), electrolyte abnormalities (sodium, <125mmol/l, potassium, <2.5mmol/l) renal insufficiency (serum creatinine, >2.0mg/dl) were excluded. Patients who had active spontaneous bacterial peritonitis or septicemia, regular alcohol consumption (>21 units/week in woman, >28units/week in man for more than 5 years), severe comorbidity such as heart failure, pulmonary disease, neurological and psychiatric problems impairing quality of life, others metabolic encephalopathy were also excluded from the study.

CLD patients of hepatic encephalopathy admitted in department of GHPD, BIRDEM who were receiving tab. rifaximin and oral lactulose were included in Group-A and who were receiving oral lactulose and placebo were included in Group-B. Every member of the sample had been selected by convenience sampling technique. The 1st patient was included in group A and next patient on group B. Group A was put on tab .rifaximin 550 mg twice daily and Group B was put on placebo for 10 days or earlier before discharged from hospital. Total 66 patients were first enrolled in the study. All patients were affected by CLD and HE which were diagnosed based on clinical and laboratory findings. Patients who showed signs of the first to third degree HE and had serum ammonia levels more than normal were included in this study.

All data were collected by preformed structured questionnaire from the patient with fulfillment of inclusion and exclusion criteria. Total 66 patients were first enrolled in the study. But 6 patients had developed other cirrhotic complications such as hepatorenal syndrome, variceal bleeding, spontaneous bacterial peritonitis, taking some medication that could potentially interfere with the course of HE. So at the end of the study, we got 60 patients- 31 in Group A and

29 in Group B. To evaluate reversibility of hepatic encephalopathy, all patients had been again examined on 10th day or if improved earlier up to discharged from hospital or died. Efficacy was assessed by changes in psychometric parameters of hepatic encephalopathy and conn score/HE grade at the end of treatment. Some laboratory data done initially and repeated specially complete blood count, serum bilirubin, serum creatinine, serum electrolytes, serum ammonia, prothrombin time, serum albumin etc. Grade of mental state is examined semi-quantitatively using Conn's modification of the Parsons-Smith classification.

Based on these measurements, portosystemic encephalopathy index was calculated for each patient at baseline and at the end of therapy. Efficacy was graded as 'improved', 'unchanged', or 'worsened'. A decreased of PSE index by at least one point was defined as 'improved', and increment of the PSE index by one point or more was defined as 'worsened'

Appropriate statistical analysis of collected data were done using computer statistical package SPSS 17 version and appropriate statistical method were used. Result for numerical data had been expressed as mean standard deviation (SD) with their respective t-value, degree of freedom (df) and p-value. Results for categorical data had been expressed as frequency (number) and percentage (%) with their respective p-value. For the statistical analysis unpaired numerical data had been expressed by unpaired student's 't' test and unpaired categorical data had been expressed by chi- square test as appropriate. P -value<0.05 was considered as significant (at the 95% confidence interval of the difference). Some of the results had been shown by bar diagram or pie diagram with their respective value (in percentage).

Ethical Clearance: It was taken from ethical committee of Bangladesh Diabetic Samity. Informed written consent had been taken from every patient prior to data collection.

Operational definition

Grade of mental state (Conn score) ¹¹

This is examined semi quantitatively using Conn's modification of the Parson's Smith classification.

Grade 0: no abnormality;

Grade 1: trivial loss of awareness, euphoria and anxiety, shortened attention span, impairment of addition and subtraction performance.

Grade 2: lethargy, disorientation with respect to time, obvious personality change, and inappropriate behavior.

Grade 3: somnolence to semi stupor, responsive to stimuli, confusion, gross disorientation, bizarre behavior.

Grade 4: coma, unable to test mental function.

Results

A total of sixty (60) patients fulfilling inclusion criteria were included in this study. Patients were divided into two groups: group A (31) and group B (29). Among the study subjects, mean age was (54.55 ± 7.67) years in group A and (52.86±7.86) years in group B. There was no significant age difference between two groups (P value=0.404).

Male patients were 22 (71.0%) and female were 9(29.0%) in group A. On the other hand, male were 21(75.9%) and female were 8(24.1%) in group B. Statistically this difference was not significant (P value=0.668).

In this study, there was no significant difference of HE grade or PSE index between two groups at enrollment. There was no significant difference of means of CTP score and MELD score between two groups (p=0.552, p=0.613)

But at the end of treatment, there was significant improvement of HE grade and PSE index in both groups. On the other hand, improvement in group A is significantly better than group B (Table I, II, III).

Table I. Comparison of Conn score (HE grade) at enrollment and at final follow up between two groups

Visit	Group	Conn score	χ ²	df	P- value
HE grade (0/1/2/3/4) at enrollment	A	(0/10/19/2/0)	0.652	2	0.772
	B	(0/11/15/3/0)			
HE grade (0/1/2/3/4) at the end of treatment	A	(23/5/2/1/0)	8.06	3	0.045
	B	(11/12/04/2/0)			

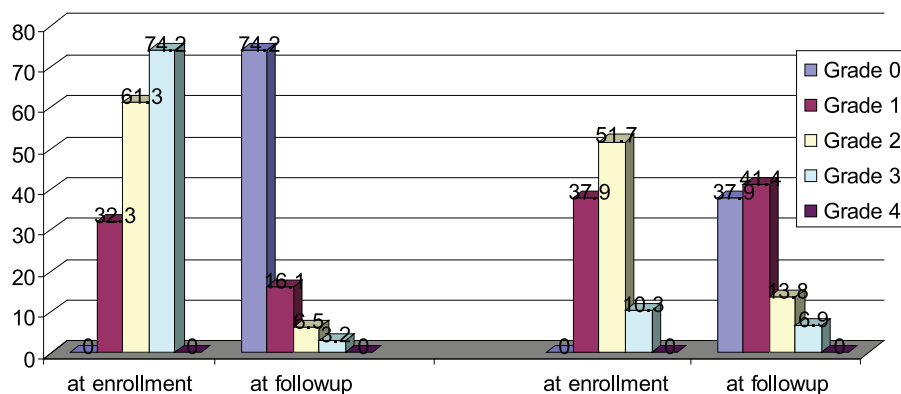


Figure 1. Comparison of HE grade at enrollment and at final follow up

Table II. CTP score and MELD score at enrollment and at final follow up

Variables	Visit	Group A (n=31)	Group B (n=29)	P - value
CTP score	Enrollment	10.06±2.36	9.68±1.73	0.489
	Final follow up	8.25±2.17	8.58±2.06	0.552
MELD score	Enrollment	13.25±3.27	12.93±3.64	0.716
	Final follow up	12.00±3.06	12.55±5.144	0.613

Table III. Changes in neuropsychiatric parameters of HE and PSE index at enrollment and at final follow up

Variables	Group / <i>P</i> -value	Enrollment	Final follow up	<i>P</i> -value
Blood ammonia level (mol/L)	Group A(n=31)	101.67±25.78	66.56±32.47	<0.001
	Group B (n=29)	93.03±29.49	84.24±23.28	0.142
	<i>P</i> -value	0.231	0.019	
Blood ammonia grade	Group A(n=31)	1.06±0.24	0.32±0.54	<0.001
	Group B (n=29)	1.06±0.25	0.65±0.48	<0.001
	<i>P</i> -value	0.872	0.132	
Mental status (HE) grade	Group A(n=31)	1.74±0.57	0.39±0.76	<0.001
	Group B (n=29)	1.72±0.64	0.90±0.90	<0.001
	<i>P</i> -value	0.778	0.045	
Grade of flapping tremor	Group A(n=31)	2.58±0.56	1.23±0.56	<0.001
	Group B (n=29)	2.59±0.50	1.31±0.89	<0.001
	<i>P</i> -value	0.968	0.659	
Grade of Number Connection Test(NCT)	Group A(n=31)	2.77±0.61	0.74±0.85	<0.001
	Group B (n=29)	2.86±0.69	1.38±1.14	<0.001
	<i>P</i> -value	0.605	0.017	
PSE index	Group A(n=31)	11.71±2.22	3.35±1.81	<0.001
	Group B (n=29)	11.76±2.34	6.10±4.82	<0.001
	<i>P</i> -value	0.934	0.017	

Table III compares the therapeutic effect of rifaximin plus lactulose and placebo plus lactulose at enrollment and at final follow up within the groups and between the groups.

The mean PSE index at enrollment was 11.71±2.224 in group A and 11.76±2.340 in group B. There was no significant difference of means of PSE index between two groups ($p=0.934$). The mean PSE index at final follow up was 3.355±3.817 in group A and 6.103±4.828 in group B. There was significant difference of means of PSE index between two groups ($p=0.017$). There was significant difference of mean PSE index from enrollment to final follow up within the group A and within the group B.

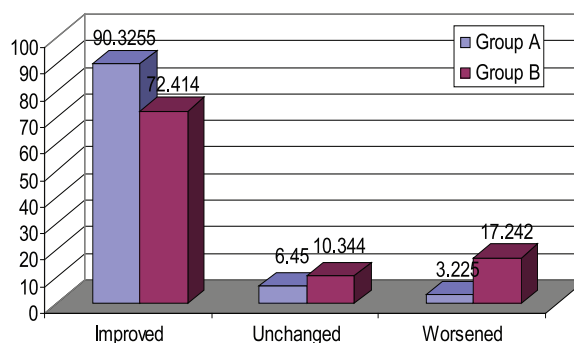


Figure 2. Portosystemic encephalopathy index at final follow up between two groups.

Figure 2 shows, PSE index more improved at final follow up in group A than group B which was (90.325 % and 72.414 % respectively)

The mean duration of hospital stay (days) 9.42 ± 2.527 in group A and 11.93 ± 4.350 in group B. There was significant difference of means of duration of hospital stay between two groups ($p=0.008$).

Discussion

The mean age and gender difference between two groups were not significant. Another study conducted by Paik et al. also showed no significant age and gender difference.³¹

At enrollment there was no significant difference of means of mean PSE index between two groups. At the end of treatment, there was significant difference of means of PSE index between two group ($p= 0.017$). Another study conducted by Paik et al. showed the mean PSE index was 5.0 ± 4.1 in group A and 4.2 ± 2.7 in group B.³¹ This result similar to another study conducted by Mas et al. where there was significant difference of means of PSE index at the end of treatment.³⁰

At enrollment, there was no significant difference of HE grade between two groups ($p=0.772$). At the end of treatment, there was significant difference of mean HE grade between two groups ($p=0.045$). This result similar to two other studies conducted by Festi et al.¹⁹ and Massa et al.²⁰ where rifaximin treated patients more significantly improved HE grade than lactulose treated patients. But, this result differ with other study conducted by Paik et al. showed the mean HE grade was similarly decreased within the study group ($p < 0.001$).³¹

At the end of treatment, the mean PSE index was also more decreased in group A (11.71 ± 3.35 , $p = < 0.05$) than in group B (11.76 ± 6.10 , $p = < 0.05$). There was significant difference of mean of PSE index in both groups. This result differ with other study conducted by Paik et al.³¹ where PSE index were similarly decreased in both group ($p = < 0.001$).

At enrollment and at follow up there was no significant difference of CTP score mean between two groups ($p = 0.0489$ and 0.552 respectively). Study conducted by Paik et al. also showed no significant difference of CTP score mean between two groups ($p = 0.404$, 0.505 respectively).³¹

There was significant difference of means of duration of hospital stay between two groups ($p=0.008$). This results support two retrospective review studies, where

rifaximin and lactulose reduced risk and duration of hospitalization.^{29, 32}

Conclusion

This study results suggest that there is more improvement of HE grade, reduced portosystemic encephalopathy index and mean duration of hospital stay among CLD patients with hepatic encephalopathy treated by combination of rifaximin plus lactulose therapy than lactulose therapy alone. Thus the combination rifaximin plus lactulose therapy may reduce morbidity and overall costs associated with hepatic encephalopathy. The significant success rate of combination of rifaximin and lactulose therapy may be considered in patients refractory to lactulose alone therapy among CLD patients with recurrent HE. It is reasonable to consider combination Rifaximin and lactulose therapy for patients after a single bout of HE as it has more therapeutic benefit and decreases duration of hospital stay.

Recommendation: Similar type of study with large sample size in multiple centers in Bangladesh should be conducted to establish therapeutic benefit of combination therapy of rifaximin and lactulose for CLD patient with hepatic encephalopathy.

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Conflict of interest: None.

References

1. Mullen K. Hepatic encephalopathy. In: Zakim D, Boyer TD, editors. *Hepatology: A Textbook of Liver Disease*. 5th Ed. Philadelphia, PA: WB Saunders; 2006. p. 311–31.
2. Abou-Assi S, Vlahcevic ZR. Hepatic encephalopathy. Metabolic consequence of cirrhosis often is reversible. *Postgrad Med* 2001; 109:52–65.
3. Fitz G. Hepatic encephalopathy, hepatopulmonary syndrome, coagulopathy and other complications of chronic liver disease. In: Feldman M, Friedman LS, Sleisenger MH, editors. *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*. 9th ed. Philadelphia: Saunders Elsevier; 2010. p. 1543–55.
4. Schiano TD. Complications of chronic liver disease. In: Friedman S, Grendell J, McQuaid K, editors. *Current Diagnosis and Treatment in Gastroenterology*. 2nd ed. Lange Current Series; 2002. p.536–45.
5. Ferenci P, Lockwood A, Mullen K, Tarter R, Weissenborn K, Blei AT, et al. Hepatic encephalopathy definition,

- nomenclature, diagnosis, and quantification: final report of the working party at the 11th World Congresses of Gastroenterology, Vienna, 1998. *Hepatology*, 2002; 35:716–21.
6. Blei A, Cordoba J. Practice Parameters Committee of the American College of Gastroenterology: Hepatic encephalopathy. *Am J Gastroenterol*, 2001; 96:1968–76.
 7. De Melo RT, Charneski L, Hilas O. Rifaximin for the treatment of hepatic encephalopathy. *Am J Health Syst Pharm*, 2008; 65:818–22.
 8. Clausen MR, Mortensen PB. Lactulose, disaccharides and colonic flora. Clinical consequences. *Drugs* 1997; 53: 930–42.
 9. Weber FL. Jr Lactulose and combination therapy of hepatic encephalopathy: the role of the intestinal microflora. *Dig Dis* 1996; 14(Supple 1): 53–63.
 10. Zeneroli ML, Avallone R, Corsi L, Venturini I, Baraldi C, Baraldi M. Management of hepatic encephalopathy: role of rifaximin. *Chemotherapy*, 2005; 51(Supple 1):90–95.
 11. Conn HO, Leevy CM, Vlahcevic ZR, Rodgers JB, Maddrey WC, Seeff L, et al. Comparison of lactulose and neomycin in the treatment of chronic portal-systemic encephalopathy. A double blind controlled trial. *Gastroenterology*, 1977; 72:573–83.
 12. Mullen KD, Dasarathy S. Hepatic encephalopathy. In: Schiff ER, Sorrell MF, Maddrey WC, editors. *Schiff's diseases of the liver*. 8th ed. New York: Lippincott-Raven; 1999:p590-617.
 13. Tarao K, Ikeda T, Hayashi K, Sakurai A, Okada T, Ito T, et al. Successful use of vancomycin hydrochloride in the treatment of lactulose resistant chronic hepatic encephalopathy. *Gut* 1990; 31:702–706.
 14. Morgan MH, Read AE, Speller DC. Treatment of hepatic encephalopathy with metronidazole. *Gut* 1982; 23:1–7.
 15. Phongsamran PV, Kim JW, Cupo Abbott J, Rosenblatt A. Pharmacotherapy for hepatic encephalopathy. *Drugs*, 2010; 70:1131–48.
 16. Debbia EA, Maioli E, Roveta S, Marchese A. Effects of rifaximin on bacterial virulence mechanisms at supra- and sub-inhibitory concentrations. *J Chemother* 2008; 20:186–94.
 17. Gerard L, Garey KW, DuPont HL. Rifaximin: a nonabsorbable rifamycin antibiotic for use in non systemic gastrointestinal infections. *Expert Rev Anti Infect Ther* 2005; 3:201–11.
 18. Leevy CB, Phillips JA. Hospitalizations during the use of rifaximin versus lactulose for the treatment of hepatic encephalopathy. *Dig Dis Sci*, 2007; 52:737–41.
 19. Festi D, Mazzella G, Orsini M, Sottili S, Sangermano A, Li Bassi S et al. Rifaximin in the treatment of chronic hepatic encephalopathy; results of a multicenter study of efficacy and safety. *Current Therapeutic Research* 1993; 54:598–609.
 20. Massa P, Vallerino F, Dodero M. Treatment of hepatic encephalopathy with rifaximin: Double-blind, double-dummy study versus lactulose. *Eur J Clin Res* 1993; 4:7–18.
 21. Williams R, Bass N. Rifaximin. A nonabsorbed oral antibiotic, in the treatment of hepatic encephalopathy: Antimicrobial activity, efficacy, and safety. *Rev Gastroenterol Disord* 2005;5(Supple): 10–18.
 22. Gillis JC, Brogden RN. Rifaximin. A review of its antibacterial activity, pharmacokinetic properties and therapeutic potential in conditions mediated by gastrointestinal bacteria. *Drugs* 1995; 49:467–84.
 23. Testa R, Efimiadi C, Sukkar GS, De Leo C, Rovida S, Schito GC, et al. A non-absorbable rifamycin for treatment of hepatic encephalopathy. *Drugs Exp Clin Res* 1985; 11:387–92.
 24. Reddy KR, Hoofnagle JH, Tong MJ, Lee WM, Pockros P, Heathcote EJ, et al. Racial differences in responses to therapy with interferon in chronic hepatitis C. Consensus Interferon Study Group. *Hepatology*, 1999; 30:787–93.
 25. Nguyen MH, Whittemore AS, Garcia RT, Tawfeek SA, Ning J, Lam S, et al. Role of ethnicity in risk for hepatocellular carcinoma in patients with chronic hepatitis C and cirrhosis. *Clin Gastroenterol Hepatol* 2004; 2:820–24.
 26. Nair S, Eustace J, Thuluvath PJ. Effect of race on outcome of orthotopic liver transplantation: a cohort study. *Lancet* 2002; 359:287–93.
 27. Huh K, Choi SY, Whang YS, Lee DS. Prevalence of viral hepatitis markers in Korean patients with hepatocellular carcinoma. *J Korean Med Sci* 1998; 13:306–10.
 28. Mandayam S, Jamal MM, Morgan TR. Epidemiology of alcoholic liver disease. *Semin Liver Dis* 2004; 24:217–32.
 29. Mantry PS, Munsaf S. Comparison of tolerability of adjunctive rifaximin treatment versus lactulose monotherapy for hepatic encephalopathy *Hepatology*, 2008; 48: 472-74.
 30. Mas A, Rodes J, Sunyer L, Rodrigo L, Planas R, Vargas V, et al. Comparison of rifaximin and lactitol in the treatment of acute hepatic encephalopathy: results of a randomized, double-blind, double-dummy, controlled clinical trial. *J Hepatol* 2003; 38:51-58.
 31. Paik YH, Lee KS, Han KH, Song KH, Kim MH, Moon BS, et al. Comparison of rifaximin and lactulose for the treatment of hepatic encephalopathy: a prospective randomized study. *Yonsei Med J* 2005; 46:399-407.
 32. RA Mahammad, RE RegAL, CA Ianiz. Combination therapy for the treatment and prevention of Hepatic encephalopathy. *Annals of Pharmacotherapy* 2012; 46(II):1559-63.