

The impact of rifaximin in the prevention of bacterial infections in cirrhosis

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Abstract. – OBJECTIVE: Bacterial infections are a leading factor in the progression from compensated to decompensated cirrhosis, with consequent worsening of the prognosis, and concerted efforts have been made to reduce infections and improve the survival rate of these patients. We retrospectively investigated the rate of infections in hospitalized cirrhotic patients under treatment with rifaximin.

PATIENTS AND METHODS: We enrolled 649 patients whose clinical and personal data, prescribed therapy, microbiological findings and laboratory tests were collected from previous discharge letters and our institution database. The efficacy of rifaximin in preventing several types infection was evaluated by comparing outcomes for rifaximin-treated patients vs patients receiving no antibiotic treatment.

RESULTS: The risk of developing selected bacterial infections was significantly lower in patients treated with rifaximin (OR 0.29; 95% CI 0.20-0.40, $p < 0.001$).

CONCLUSIONS: Continuous treatment with rifaximin may prevent bacterial infections in cirrhotic patients.

Key Words:

Cirrhosis, Bacterial infections, Rifaximin.

Introduction

Cirrhotic patients are prone to bacterial infections¹, a leading factor in the progression from the compensated to the decompensated stage of cirrhosis². Bacterial infections are known to lead to a fourfold increase in the probability of death in patients with advanced or decompensated cirrhosis, with a mortality rate of 30% at 1 month and of 63% at 1 year after the infection³. This proneness is multifactorial, and several studies

indicate that the cirrhotic patient should be considered an immunocompromised host⁴.

The causes of immune dysfunction in cirrhotic patients are mainly linked to decreased bactericidal activity and low serum levels of complement factors^{5,6}. However, several other factors also play an important role. These include impaired reticuloendothelial system (RES) functioning. Also, in physiological conditions, the liver is the first line of defence against gut-derived pathogens through the activation of Kupffer cells, but in the cirrhotic patient, the antigen-rich portal blood is not processed by these macrophages, whose functionality is significantly compromised. The presence of portosystemic shunts, through which blood reaches the systemic circulation directly, bypassing the liver filter, is another important factor in these patients' vulnerability to infection. In addition to this, in liver cirrhosis, homeostasis between the intestinal microbiota and gut-associated lymphatic tissue is unbalanced. The prevalence of pathogens among the normal components of the intestinal flora is higher than in healthy individuals, and bacterial translocation from the intestinal lumen to mesenteric lymph-nodes has been shown in mice models^{7,8}. Together, these factors lead to a higher rate of spontaneous bacterial peritonitis (SPB) and spontaneous bacteremia among patients affected by chronic liver disease^{9,10}.

Norfloxacin has been advanced as a prophylactic treatment of bacterial infections in cirrhotic patients due to its high efficacy against gram-negative gut-derived bacilli¹¹. However, the use of this class of antibiotics cannot be extensive because of the risk of selecting resistant pathogens¹². We focused our research on another antibiotic proposed as an alternative to the first

generation fluoroquinolone: rifaximin. The recent EASL position paper on spontaneous bacterial infections in cirrhosis¹³ stated that the efficacy and safety of this drug should be explored. As a better selection of patients who should undergo prophylactic treatment is another future goal, we retrospectively investigated the effects of this antibiotic treatment in patients with both early-stage and severe liver disease.

Rifaximin has a broad antimicrobial spectrum¹⁴⁻¹⁶ and nowadays is commonly used as an empirical therapy in preventing episodes of hepatic encephalopathy (HE)¹⁷: a large study published in 2010 reported that administration of this minimally-absorbed antibiotic at a dose of 550 mg BID significantly reduces the risk of HE recurrences¹⁸.

The main aim of the current study is to assess the association between rifaximin prophylaxis and subsequent infection in a cohort of cirrhotic patients admitted to hospital for any reason, after adjusting for potential confounders. The secondary aim was to assess the association between rifaximin prophylaxis and rates of infection for specific sites (bloodstream infections, urinary tract infections, respiratory tract infections, skin and soft tissues infections, gastrointestinal and abdominal infections, febrile diseases, meningitis, and endocarditis) and with specific aetiologies.

Patients and Methods

This study was conducted according to the STROBE Statement indications.

(<http://www.strobe-statement.org/>)

Study Design

Retrospective cohort study. Cohorts were *with infection vs no infection*. Infectious events recorded at or during hospital admission from patient records were counted.

Settings

We examined the clinical charts of all cirrhotic patients admitted to the Division of Infectious and Tropical Diseases of the Policlinico San Matteo, in Pavia, between January 1994 and March 2014.

Our study received the approval of the Ethical Committee of IRCCS Policlinico San Matteo Pavia (Italy) for the collection and the use of patient charts for scientific publication. Because of the retrospective design, patients did not sign any specific consent but they gave their written consent to the use of clinical data for scientific use.

Population

Inclusion criteria were: age at least 18, with HBV-related chronic hepatitis, HCV-related chronic hepatitis, HBV-HCV coinfection, HIV-HCV coinfection, alcoholic cirrhosis and autoimmune cirrhosis. We collected data of patients of all cirrhotic patients admitted for any medical reasons to the Division of Infectious and Tropical Diseases of the Policlinico San Matteo, in Pavia, Italy, between January 1994 and March 2014. Subjects included in the with infection cohort were those who had had a bacterial infection at admission or during their hospital stay. Those included in the without infection cohort had been admitted for liver-related disorders other than bacterial infections. For both groups, patients who were currently on continuous Rifaximin therapy following previous admissions for hepatic encephalopathy diagnosed according to AASLD and EASL criteria (http://www.aasld.org/sites/default/files/guideline_documents/141022_AASLD_Guideline_Encephalopathy_4UFd_2015.pdf) and were included in the Rifaximin prophylaxis condition. Patients in the no prophylaxis condition were those who were not currently on antibiotic prophylaxis at the time of admission.

Criteria for diagnosis of cirrhosis were evidence of cirrhosis on laboratory or radiologic testing with or without stigmata of chronic liver disease discovered on physical examination; and/or evidence of decompensated cirrhosis, characterized by the presence of severe and life-threatening complications such as variceal hemorrhage, ascites, or hepatic encephalopathy.

Exclusion criteria were age under 18, liver transplantation, acute hepatitis or reactivation of chronic hepatitis during patients' stay in hospital (because of possible worsening of liver function, resulting in a sudden increase in Child or MELD score).

Liver disease stage was determined by MELD, MELD-Sodium, Child-Pugh score and the recently validated CLIF-C ADs score¹⁹⁻²⁵.

Variables

Patients underwent the same diagnostic work-out which is detailed below.

We collected:

- Clinical and personal data: etiology of liver disease, age, sex, days of hospitalization.
- Prescribed therapy and use of Rifaximin (all patients who had been hospitalized for previous decompensating events had also been discharged with this prophylaxis).

- Microbiological data: Gram-positive pathogens and drug resistance.
- Laboratory tests: C-reactive protein, white blood cell count, platelet count, bilirubin, creatinine, international normalized ratio (INR), aspartate aminotransferase, alanine aminotransferase, and sodium.

The following infections were documented during the study. The diagnostic criteria adopted in our hospital are:

- Bloodstream infections: fever, positive blood culture or presence of sepsis²⁶.
- Urinary tract infections: fever, urinary symptoms (dysuria, pollakiuria, strangury) or positive urine cultures.
- Respiratory tract infections: fever, dyspnea, chest pain or pleural effusion with compatible radiographic signs. Urine antigen results positive for *Legionella pneumophila* or *Streptococcus pneumoniae* or positive cultures from bronchoalveolar lavage.
- Skin and soft tissue infections: physical findings (pain, tenderness, swelling, redness, warmth) on a distinct area of skin; and/or positive blood or skin cultures.
- Abdominal infections: gastrointestinal symptoms (pain, diarrhoea), fever, positive fecal culture or presence of spontaneous bacterial peritonitis (SBP)²⁷.
- Febrile diseases: fever with non-specific findings, exclusion of non-infectious aetiologies.
- Meningitis: meningeal signs, diagnostic cerebrospinal fluid test, and culture, resolution of symptoms after empiric antimicrobial therapy.
- Endocarditis: Duke criteria for infectious endocarditis²⁸.
- All patients with fever and ascites underwent blood culture and culture of ascites fluid.

Urine culture was performed on all patients. Urine tests for *Legionella* antigen and *Pneumococcus* were carried out where radiological signs of pneumonia were present; as well as sputum culture in some cases.

Data Sources

We collected microbiological findings, and blood analysis results from the central laboratory database of IRCCS Policlinico San Matteo, Pavia, Italy. Personal data and prescribed therapy were retrieved from discharge letters.

Statistical Analysis

Descriptive statistics were produced for demographic, clinical and laboratory characteristics of

patients in the with infection group vs. without infection group. Mean and standard deviation (SD) are presented for normally distributed variables, and median and interquartile range (IQR) for non-normally distributed variables, number, and percentages for categorical variables. For the patient characteristics, groups were compared with parametric or nonparametric tests, according to data distribution, for continuous variables, and with Pearson's χ^2 -test (Fisher exact test where appropriate) for categorical variables. In all cases, 2-tailed tests were used. The association between infection and a number of potential explanatory variables was assessed by means of univariable and multivariable logistic regression models (taking into account repeated admissions per patient). In multivariable models, we retained clinically relevant variables or those significant at the 0.01 level at univariable analysis, excluding co-linear variables, and no further selection was carried out. Results are expressed as Odds Ratios (OR), 95% Confidence Intervals and *p-values*.

Results

Participants

We enrolled 649 patients (232 females and 417 males), admitted a total of 1029 times over the course of the study. Mean age was 53 years (range 21 to 93). Average MELD score was 13 (range 8 to 18), MELD-Sodium 15 (range 9 to 21), Child-Pugh 9 (range 7 to 10) and CLIF score 50 (range 43 to 58).

Demographic and clinical characteristics of patients with and without infections are reported in Table. Decontaminating therapy with lactulose and rifaximin was administered at a standard dosage in 26.8% of admissions (276/1029). The median time on Rifaximin therapy was 57 days (25°-75° percentile 35-113 days). None of our patients received Norfloxacin as prophylactic therapy. We registered 410 infectious episodes (39.8% of total hospitalizations).

Pathogens were isolated in 210 cases (51.2%): 102 Gram-positive bacteria, 64 Gram-negative, and both Gram-positive and Gram-negative in 22 cases. There were 21 drug-resistant species: 11 Gram-positive and 10 Gram-negative.

Factors associated to infection at univariate analyses are reported in Table I. Of note, the risk of developing bacterial infections was significantly lower in patients treated with rifaximin (OR 0.287; 95% CI 0.202-0.407, *p* < 0.001) compared to those not treated.

Table I. Patient data, with univariate and multivariate logistic regression analysis of factors associated with infection.

Variable	Category (description)	Pts without infection N°-%	Pts with infection N°-%	Univariate			Multivariate			
				OR	95% CI	p-value	OR	95% CI	p-value	
Prophylaxis	No treatment	399-64.5	354-86.3	1	1-1	---				
	Rifaximin	220-35.5	56-13.6	0.287	.202-.407	< 0.001	0.25	0.16-0.39	< 0.001	
Age category	18-25	3-0.48	1-0.24	1	1-1	---				
	25-44	147-23.8	107-26.1	2.184	.223-.21.427	0.503				
	45-64	252-40.7	136-33.2	1.619	.166-15.774	0.678				
	65-84	205-33.1	147-35.9	2.151	.22-21.016	0.51				
	Over 85	12-1.9	19-4.6	4.75	.425-53.105	0.206				
Gender	Female	181-29.2	159-38.8	1	1-1	---				
	Male	438-70.8	251-61.2	0.652	.481-.885	0.006	0.75	0.51-1.08	0.124	
Length of hospitalization in days	Median (IQR)	10-(6-16)	15-(10-23)	1.05	1.034-1.065	< 0.001	1.05	1.02-1.07	< 0.001	
MELD score		15-(11-19)	12-(6-16)	0.944	.922-.966	< 0.001	0.95	0.93-0.97	< 0.001	
MELD-Sodium		18-(11-24)	14-(8-20)	0.952	.932-.973	< 0.001				
Child-Pugh		9-(7-10)	9-(7-10)	0.917	.833-1.01	0.079				
CLIF score		49-(43-58)	51-(43-58)	1.007	.991-1.023	0.41				
Aetiology of cirrhosis	Autoimmune	3-0.6	1-0.4	0.649	.067-6.288	0.709				
	Alcoholic	87-15.9	40-14.2	0.876	.573-1.338	0.539				
	HBV	39-6.3	26-6.3	1.007	.589-1.72	0.98				
	HCV	498-80.5	288-70.2	0.574	.413-.797	0.001				
	Others	15-2.8	8-2.9	1.041	.403-2.687	0.934				
Comorbidities	Diabetes	102-18.7	51-18.2	0.967	.635-1.474	0.877				
	HIV	226-36.5	157-38.3	1.079	.798-1.46	0.621				
	Hepatocellular carcinoma	142-22.9	31-7.6	0.275	.181-.418	< 0.001				
	Multifocal hepatocellular carcinoma	29-4.7	10-2.4	0.509	.228-1.133	0.098				
	Solid neoplasia	45-7.3	18-4.4	0.586	.314-1.092	0.092				
	Lymphatic neoplasia	22-3.6	12-2.9	0.818	.375-1.785	0.614				
	Creatinine (mg/dL)	Median (IQR)	1-(0.80-1.37)	0.96-(0.73-1.26)	0.975	.831-1.143	0.752			
	Total bilirubin (mg/dL)		2.73-(1.61-5.64)	1.49-(0.69-3.27)	0.902	.859-.947	< 0.001			
NR		1.47-(1.25-1.8)	1.28-(1.1-1.54)	0.732	.443-1.208	0.222				
Sodium (mEq/L)		134-(131-139)	136-(133-139)	1.037	1-1.076	0.047				
ALT (mU/mL)		56-(38-88)	37-(19-63)	0.999	.997-1.001	0.474				
AST (mU/mL)		85-(52-128)	49-(28-81)	0.996	.991-1.001	0.117				
Platelet count (x10 ⁹ /L)		73.5 - (51-106)	121-(68-214)	1.01	1.008-1.013	< 0.001				
C reactive protein (mg/dL)		0.8-(0.32-1.8)	2.49-(0.84-8.45)	1.186	1.067-1.318	0.001				
White blood cell count (units/mm ³)		4025-(3030-6500)	6870-(3820-10430)	1	1-1	< 0.001				
Deaths	Number of cases	63-10.18	26-6.34	0.598	0.373-0.958	0.033				

Note: descriptive statistics are presented at the “admission episode” level, obtained from 649 patients with a median 1 (IQR 1-2, min-max range 1-10) admissions.

Table continued

Table I (Continued). Patient data, with univariate and multivariate logistic regression analysis of factors associated with infection.

Number of admissions	Frequency	Percent	Cumulative
1	470	72.42	72.42
2	95	16.64	87.06
3	39	6.01	93.07
4	18	2.77	95.84
5	9	1.39	97.23
6	4	0.62	97.84
7	7	1.08	98.92
8	2	0.31	99.23
9	4	0.62	99.85
10	1	0.15	100.00
Total	649	100.00	

Rifaximin Efficacy: Subgroup Analyses

The association between rifaximin and specific infections is reported in Table II. The strongest protective associations were found for respiratory tract and abdominal infections.

Treatment with rifaximin showed a protective role both in patients with MELD > 15 and in those with MELD < 15; with ORs of 0.46 (95% CI, 0.31-0.68) and 0.16 (95% CI, 0.09-0.29) respectively.

We observed (Table II) 36 bacterial identifications in the treated group (15 Gram-positive and 21 Gram-negative) vs. 174 in the non-treated group

(109 Gram-positive and 65 Gram-negative). A lower OR for Gram-positive infections was found in patients undergoing rifaximin treatment than in the non-treated group (0.34; 95% CI, .19-.60).

Discussion

Key Results

This work indicates that prophylactic treatment of cirrhotic patients with rifaximin is protective against bacterial infections.

Table II. Rifaximin treatment in specific infections site.

Variable	Category (description)	Non decontaminated		Decontaminated		OR	95% CI	Z	p > b IZI
		n	%	n	%				
Infection site	Urinary tract	31	4.1	14	5.1	1.24	.66-2.36	0.671	0.502
	Abdominal	30	4	2	0.7	0.18	.04-.75	-2.351	0.019
	Febrile disease	37	4.9	4	1.5	0.28	.10-.80	-2.388	0.017
	Tuberculosis	8	1.1	0	0	—	—	—	—
	Endocarditis	10	1.3	0	0	—	—	—	—
	Meningitis	12	1.6	1	0.4	0.23	.03-1.74	-1.428	0.153
	Respiratory tract infection	122	16.2	9	3.3	0.17	.08-.37	-4.604	<0.001
	Prosthesis infection	12	1.6	1	0.7	0.24	.03-1.77	-1.419	0.156
	Abscess	19	2.5	0	0	—	—	—	—
	Sepsis	60	8	17	6.1	0.76	.43-1.33	-0.968	0.333
	Atypical mycobacterial disease	4	0.5	0	0	—	—	—	—
	Skin and soft tissues infection	39	5.1	9	3.3	0.62	.27-1.41	-1.144	0.253
	Microbiological diagnosis	Gram-positive	109	14.5	15	5.4	0.34	.19-.60	-3.691
Gram-negative		65	8.6	21	7.6	0.87	.51-1.50	-0.499	0.618
Drug-resistant pathogen		15	2	6	2.2	0.60	.37-3.19	0.163	0.870

Rifaximin in the Non-decompensated Phase of Cirrhosis

Rifaximin is already used to prevent and treat hepatic encephalopathy^{17,18}, a commonly occurring complication in the decompensated phase of cirrhosis²: for this reason, it is mainly adopted in patients with a high MELD score (13-15 or more). Our findings suggest that Rifaximin also gives outstanding benefits in non-decompensated cirrhosis; and that we should, therefore, consider starting this treatment independently of liver impairment stage.

Efficacy of Rifaximin in Protecting Against Specific Infections

Intestinal decontamination was protective to some degree against all specific infection types (see Table II). Nevertheless, abdominal and respiratory tract infections and febrile diseases were significantly less frequent in treated than in non-treated patients, suggesting that rifaximin had a particularly strong impact on these infections. The abdomen was a common infection site in our patients. However, of 32 episodes in 30 cases, only 2 occurred in patients who had undergone intestinal decontamination. This is noteworthy, given that SPB is one of the most frequent clinical challenges in cirrhotic patients.

The effects for sepsis and urinary tract infections were not significant, but the data are suggestive: of 77 episode of sepsis, 60 occurred in the non-decontaminated group and only 17 in decontaminated patients. We observed a similar trend for urinary tract infections: of a total of 45 episodes, 31 occurred in decontaminated and 14 in non-decontaminated patients.

Interpretation of the Results

The success of Rifaximin antibiotic prophylaxis could depend on its strong effectiveness against Gram-positive and Gram-negative gut-derived bacteria^{16,29}. Indeed, this rifamycin-derivate reaches a high concentration in the gastrointestinal tract and has minimal systemic bioavailability. Given its demonstrated role in reducing ammonia-producing enteric bacteria, rifaximin could be effective against pathogens commonly involved in cirrhosis-related infections: *E. coli*, *Shigella*, *Salmonella*, *Staphylococcus spp*, *Streptococcus spp*, and *Enterococcus spp*.

In these patients, infectious events are common because of increased intestinal permeability and cirrhosis-associated immune dysfunction (CAID). Continuative treatment with rifaximin

could maintain a low bacterial count or even eradicate gut-growing pathogens, leading to less intense bacterial translocation¹³. Therefore, in patients with small intestine bacterial overgrowth (SIBO) syndrome, rifaximin should be considered to improve symptom severity³⁰.

One interesting finding was that rifaximin is a risk factor for the development of a Gram-negative infection. Differences in microbial prevalence between treated and non-treated patients have also been described in other studies³¹. Consideration of the *in-vitro* and *in-vivo* efficacy of this antibiotic suggests the reason for this only partially unexpected behaviour: fecal levels of rifaximin are very high, reaching 4000-8000 $\mu\text{g/g}$ stool³², making this drug remarkably effective against both Gram-positive and Gram-negative bacteria. However, in another *in-vitro* study, the MIC₅₀ of rifaximin appeared to be much lower for Gram-positive than for Gram-negative bacteria (< 0.015-2 $\mu\text{g/ml}$ for Gram-positive; 12.5-128 $\mu\text{g/ml}$ for Gram-negative)³³. This different susceptibility could induce changes in intestinal microbiota and account for the difference in bacterial aetiologies in treated versus non-treated patients. Interesting data in support of the rifaximin-induced changes in intestinal microbiota was described in an interesting study of Ciobanu et al³⁴: they considered that rifaximin could limit necroinflammatory lesions determined by NSAIDs on guinea pig small bowel.

Physicians choosing an empirical antibiotic therapy for cirrhotic patients who have undergone long-term rifaximin treatment should consider this finding.

The positive correlation at the univariate analysis of infectious events with lower but not with higher MELD scores is to be explained by the characteristics of our population: admission of patients with the less severe liver disease was more likely to be related to external decompensating factors, among which infections play a major role. On the other hand, patients with advanced cirrhosis were usually hospitalized and died of complications related to the underlying liver disease (i.e. encephalopathy, variceal bleeding, ascites).

Study Limitations

We collected data on hospitalized patients retrospectively. One limitation of this type of study is that not all biological and clinical data are available for some patients. We also enrolled only hospitalized patients and with the available data we could not differentiate between those admitted

because of an infectious event and those who developed infections during their hospital stay. No follow-up was possible, also because of the retrospective design of the study and because access to patient data was limited to what was available in our hospital. For this reason, the long-term outcome of patients is beyond the aim of the study.

Conclusions

Long-term treatment with rifaximin may be an effective tool in the prevention of bacterial infections in cirrhotic patients. The protective effect seems to be present for every etiology and stage of cirrhosis, but varies for different types of infections. As a prophylaxis, rifaximin may reduce the rate of hospitalization of patients with liver disease and lead to a global shortening of hospital stay.

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Conflict of Interest

The Authors declare that there are no conflicts of interest.

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