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Long-term Use of Antibiotics and Proton-Pump Inhibitors Predict Development of Infections in Patients with Cirrhosis

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Abstract

Background & Aims—Bacterial infections, particularly repeated infections, are significant causes of morbidity and mortality among patients with cirrhosis. We investigated and characterized risk factors for repeat infections in these patients.

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Methods—In prospective study, we collected data from 188 patients hospitalized with cirrhosis and infections and enrolled in the North American Consortium for the Study of End-Stage Liver Disease (12 centers). Patients were followed for 6 months after hospital discharge and data were analyzed on type of infections and factors associated with subsequent infections.

Results—Six months after hospital discharge, 14% of subjects had received liver transplants, 27% died, and 59% were alive without liver transplantation. Following discharge, 45% had subsequent infections, but only 26% of the subsequent infections occurred at the same site. Compared to patients not re-infected, patients with repeat infections were older and a higher proportion used proton-pump inhibitors (PPIs, $P=.006$), rifaximin ($P<.001$), or prophylactic therapy for spontaneous bacterial peritonitis (SBP, $P<.001$). Logistic regression showed that SBP prophylaxis (odds ratio [OR], 3.44; 95% confidence interval [CI], 1.56–7.63), PPI use (OR, 2.94; 95% CI, 1.39–6.20), SBP at hospital admission (OR, 0.37; 95% CI, 0.15–0.91), and age (OR, 1.06; 95% CI, 1.02–1.11) were independent predictors of subsequent infections.

Conclusion—Patients hospitalized with cirrhosis and infections are at high risk for subsequent infections, mostly at different sites, within 6 months of index infection resolution. Those at highest risk include previously infected older patients receiving PPIs and/or SBP prophylaxis, although these associations do not prove that these factors cause the infections. New strategies are needed to prevent infections in patients with cirrhosis.

Keywords

NACSELD; decompensation; antibiotic; complication

Introduction

Bacterial infections are one of the most significant complications that can occur in patients with cirrhosis; infections increase the cirrhotic patient's risk for intensive care unit admission, sepsis, development of acute kidney injury, hepatorenal syndrome, hepatic decompensation, multiorgan system failure, and death^{1,2}. The heightened susceptibility to a first infection likely results from the cirrhotic patient's compromised immune system that impairs bacterial elimination and facilitates bacterial translocation³⁻⁵. It is also clear that patients in the hospital with one infection are at risk for a second infection⁶. Although first infections increase the risk of adverse outcomes, second infections portend an even worse prognosis⁶. Recent data highlighted that some frequently used medications, such as proton pump inhibitors (PPIs), increase the risk of infections, while others, such as beta-blockers, do not⁷⁻¹². However, prospective studies are needed to confirm and quantify these risks¹³. In addition, we frequently discharge patients from the hospital on antibiotics, such as norfloxacin for spontaneous bacterial peritonitis (SBP) prophylaxis, and rifaximin for prevention of recurrent hepatic encephalopathy. It remains uncertain if these medications alter the risk for future infections. Therefore, a particular focus on the infectious risks associated with medication utilization may result in altered strategies to improve outcomes¹⁴.

Although the risk for subsequent infections and death is important in all cirrhotic patients, infections in liver transplant candidates are of particular interest¹⁵. As MELD scores at liver

transplant continue to increase¹⁶, patients are waiting for transplant longer, with increased risk of infectious complications further highlighting the need to identify and change modifiable risk factors to maintain candidacy for transplant and increase survival.

Toward the goal of identifying patients at highest risk for subsequent infections, we prospectively followed infected cirrhotic patients who were enrolled in the North American Consortium for the Study of End-Stage Liver Disease (NACSELD) for 6 months after hospital discharge for subsequent infections and their outcome. Prior to data analysis, we hypothesized that PPIs would increase the risk, rifaximin and SBP prophylaxis would decrease the risk, and B-blockers would not change the risk of subsequent infections.

Methods

NACSELD consists of 12 hepatology referral sites throughout North America that prospectively collect data on hospitalized patients with cirrhosis who are admitted with a bacterial infection or develop it during hospitalization. The study was approved by all participating centers' Institutional Review Boards. Data were managed using REDCap (Research Electronic Data Capture), which is based at Virginia Commonwealth University. REDCap is a secure, web-based application that provides: 1) a portal for validated data entry; 2) an audit trail for ease of tracking data manipulation and export procedures; 3) an effortless data download into several statistical packages; and 4) the ability to import data from external sources.

Admitted cirrhotic patients who had or developed an infection were approached for consent. Cirrhosis was diagnosed by a combination of biochemical, radiological, and endoscopic findings; or by liver biopsy. Infections were uniformly defined at all sites as described below. Exclusion criteria included patients with additional independent risk for infection such as those with human immunodeficiency virus infection, prior solid organ transplant, or disseminated malignancies.

After informed consent, data collection included patient demographics, vital signs, baseline biochemistry, liver and renal function, full blood count, and details of the infection including antibiotic treatment. Data collection also included intensive care unit admission, organ failure, liver transplantation, and length of hospitalization. Patients who were discharged without a liver transplant were followed to 6 months to determine their outcome (alive with or without transplantation, or dead), and if a subsequent infection that required hospitalization at any hospital had occurred. Follow-up data was acquired by study site coordinators from the patient or their caregiver by phone. If an infection occurred during the 6-month follow up period, records were obtained to validate the type of infection and the resistance pattern of the organism(s) diagnosed. During the phone interview, patients' relevant medications (PPI, Beta-blocker, SBP prophylaxis, and rifaximin) were also updated. Patients' medications were known at discharge and at 6-month follow-up; the differences between these 2 time points are detailed in Supplemental Table 1.

We defined infections according to standard criteria^{6, 17}: (a) spontaneous bacteremia: positive blood cultures without a known source; (b) SBP: ascitic fluid polymorphonuclear

cells >250/ μ L; (c) lower respiratory tract infections: new pulmonary infiltrate in the presence of: (i) at least one respiratory symptom (cough, sputum production, dyspnea, pleuritic pain) with (ii) at least one finding on auscultation (rales or crepitation) or one sign of infection (core body temperature >38°C or less than 36 °C, shivering or leucocyte count >10,000/mm³ or <4,000/mm³) in the absence of antibiotics; (d) *Clostridium difficile* Infection: diarrhea with a positive *C. difficile* assay; (e) soft-tissue/skin infection: fever with cellulitis; (f) urinary tract infection (UTI): urine white blood cell >15/high power field with either positive urine gram stain or culture; (g) intra-abdominal infections: diverticulitis, appendicitis, cholangitis etc and bacterial entero-colitis; (h) other infections: diarrhea or dysentery with a positive stool culture for *Salmonella*, *Shigella*, *Yersinia*, *Campylobacter*, or pathogenic *E. coli*, and (i) fungal infections as a special category.

Index infection was defined as the first infection that occurred during the hospitalization in which the patient was consented for the study. Second infection was defined as another infection that occurred during the same hospitalization in which the patient was consented. Subsequent infection was defined as an infection that occurred after discharge from the index-infection hospitalization. Infection resolution was defined as non-hospice hospital discharge. Index and subsequent infections were diagnosed based on the same criteria. Drug resistant organisms (DRO) were defined as methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus*, and quinolone-resistant gram-negative rods.

Statistical Analysis

Categorical data are presented as a percentage; continuous data are presented as a mean $\pm$ standard deviation, and discrete data are presented as a median with an inter-quartile range. Categorical variable analysis was performed with the χ^2 test, and group comparisons were done with either a two-sample t-test or a one-way ANOVA (>3 groups were compared). Group comparisons for discrete data were done with the Wilcoxon Rank-Sum test (Mann-Whitney U test) for two groups or the Kruskal-Wallis for >2 groups. For all statistical analyses, SAS 9.1 was used, and a p-value <0.05 was considered statistically significant.

Multivariable logistic regression modeling using stepwise elimination was employed. The dependent variable was subsequent infection within 6 months of hospital discharge with an index infection. Variables read into stepwise regression included age, gender, alcoholic etiology, laboratory values at admission of index hospitalization, Child-Turcotte-Pugh (CTP) score (at index hospitalization), and separately serum albumin and sodium; second infection during the index hospitalization; the type of infection (SBP vs. non-SBP infection); number of infections in the six months prior to index hospitalization; and medication use at 6-month follow-up (PPI, rifaximin, SBP prophylaxis, and non-selective beta-blocker use). All final models only included variables that remained statistically significant (p<0.05) with the exception of MELD score that was forced into the final model.

Results

NACSELD enrolled 337 cirrhotic inpatients with infections. During the index hospitalization 68 patients died and 14 patients underwent liver transplantation (Figure 1). Of the 255 patients who were discharged without transplant, 22 have not reached 6-months

of follow-up and 45 were lost to follow-up. Six-month follow-up with infection outcomes reported was available on the remaining 188 patients; 27%(51/188) died, 14%(26/188) were transplanted, and 59%(110/188) experienced transplant-free survival. During follow-up, 45%(84/188) of patients experienced at least one subsequent infection requiring hospitalization (90 total infections). This occurred in 6% in <2 weeks, 28% in 2 to <6 weeks, 17% in 6 weeks to <3 months, 28% in 3-6 months, and 21% in an unknown time after discharge. Patients with second infections during their index hospitalization that survived to the 6-month follow-up had a 54% (19/35) risk of a subsequent infection. As also shown in Table 1, there were no significant differences regarding demographics, etiology of cirrhosis, liver tests, MELD score and CTP score between those who developed subsequent infection and those that did not. There was a tendency for age to be greater in those who developed a subsequent infection (57.7 vs. 55.1, $p=0.06$).

Infection type was not statistically significantly different between the index and subsequent infection respectively (Table 2). Similarly, there was no difference between culture results of index and subsequent infections. Additional illness severity-related factors from the index hospitalization were separately analyzed (Table 3) to determine their predictive power for subsequent infections. Only mechanical ventilation was statistically significantly associated with a risk of subsequent infections.

Despite the similar distribution of infection types, the vast majority of subsequent infections were different than the primary infection (74%). Figure 2 details the 26% (22/84) of patients with subsequent infections at the same site by type; *C. difficile* had the highest risk (40%, 2/5), followed by UTIs (32%, 9/28), and skin/soft tissue infections (22%, 2/9). Although 33% (4/12) of patients with other infections had subsequent other infections, we cannot confirm these occurred in the exact same location.

DRO were equally likely in patients with index (16%, 34/188) and subsequent (17%, 14/84) infections (Supplemental Table 2). However, DRO were most commonly found in patients with SBP as a subsequent infection than as an index infection (42%, 8/19 vs. 7%, 3/46; $p=0.02$). The risk of a DRO in subsequent infections was lower in patients with UTIs (11%, 3/28), and spontaneous bacteremia (7%, 1/14).

Medication utilization rates at hospital discharge were confirmed at 6-months of follow-up and differed between patients with and without subsequent infections. Patients with subsequent infections had a higher rate of PPI (72.6% vs. 52.9%, $p=0.006$), rifaximin (52.4% vs. 27.9%, $p<0.001$), and SBP prophylaxis (53.6% vs. 21.2%, $p<0.001$) usage, and a similar rate of beta-blocker utilization (31.0% vs. 39.4%, $p=NS$) than those not prescribed these medications. However, patients taking rifaximin had higher index admission MELD scores (20 vs. 18, $p=0.04$) and higher index admission CTP scores (10 vs. 9, $p=0.03$) than patients not prescribed the medication. On the other hand, MELD scores were not significantly different during index admission between PPI and SBP prophylaxis users and non-users, but in both groups, medication users had higher CTP scores (PPI: 10 vs. 9, $p=0.02$; SBP: 10 vs. 9, $p=0.03$) than non-users respectively. Beta-blocker utilization was not associated with any marker of disease severity.

Although the unadjusted risk of all types of subsequent infections was higher in patients taking SBP prophylaxis, rifaximin, and PPI, the individual types of infections did not statistically significantly differ between patients, as highlighted in supplemental table 3. Of note, the risk of SBP was similar between patients whose index hospitalization was for recurrent SBP, and those with recurrent SBP during the 6-month follow up period [22% (2/9) vs. 11% (5/45), $p=0.6$]

The multivariable stepwise logistic regression model (table 4) demonstrated that SBP prophylaxis (OR=3.66, CI 1.60-8.37), PPI (OR=2.72, CI 1.30-5.71), SBP as the index infection (OR=0.37, CI 0.15-0.91), and age (OR=1.06, CI 1.02-1.11) were the only independent predictors of subsequent infections after forcing MELD (OR=1.02, CI 0.96-1.07) into the model.

We did experience 18% loss to follow-up despite multiple attempts to find all patients. We did not find any statistically significant differences in MELD score, age, or use of medications studied between those with and those without follow-up. However, patients who were lost to follow-up had a lower Child score than those with follow-up (8.7 +/-2.4 vs. 10.0 +/- 2.0, $p=0.002$).

Discussion

In our multi-center, prospective study, we found that cirrhotic patients discharged after adequate control of their index infection remain at high risk of subsequent infections. The subsequent infection was usually different from the infection at index hospitalization: the type of subsequent infection 74% of the time was different from the primary infection, and 17% were caused by DRO. This risk was independent of liver disease severity, possibly due to the relatively high median MELD and CTP score seen in our patients and, and was associated with type of index infection, older age, PPI use and SBP prophylaxis.

In non-cirrhotic patients, reports in the literature consistently document an increased risk of death after discharge in patients with sepsis^{18, 19}. Only one small study has shown an increased longer-term risk of subsequent infections in discharged non-cirrhotic intensive care unit patients²⁰. Our study is arguably the first multi-center study to extend this observation to cirrhotic patients. This is important because the subsequent infection risk may be even greater in cirrhosis than in patients without cirrhosis because it leads to increased bacterial translocation that is often coupled to small intestinal bacterial overgrowth (SIBO), dysbiosis, and immunodeficiency^{3, 21}. Cirrhosis not only increases access of intestinal bacteria to the portal circulation, but these translocated bacteria and resultant cytokines are even less likely to be cleared by the liver because of impaired reticuloendothelial cell phagocytosis and increased collateral blood flow. Patients with cirrhosis are also immunodeficient³, thereby impairing the host's ability to clear translocated bacteria. Several known mechanisms of immunodeficiency in cirrhosis include but are not limited to: polymorphonuclear impairment in migration to infected sites and phagocytosis once there, low complement and interleukin levels; altered macrophage Fc binding, adhesion, and function; opsonization impairment; and altered antibody mediated bactericidal capability³.

It is less clear how immune regulation may be altered in the longer term once infection occurs in a cirrhotic host. During severe infection, the systemic inflammatory response syndrome (SIRS) is activated, which involves innate immune activation and secretion of pro-inflammatory cytokines²². During infection or its resolution, the compensatory anti-inflammatory response syndrome (CARS) may also be activated²³⁻²⁶. CARS can include down-regulation of antigen presentation, macrophage deactivation, production of anti-inflammatory cytokines, and ultimate anergy. Of note, changes that result from CARS increase susceptibility to other pathogens. The duration of these changes that may result in "immunologic paralysis" remains unknown. While we did not directly investigate these risks from an immunological standpoint, the continued susceptibility to infections, especially those unrelated to the index infection type, points towards an impaired immune response as the likely culprit.

In addition to an inherent increased risk to subsequent infection posed by the index infection, medications may further modulate this propensity. This prospective study has confirmed most of the prior retrospective studies documenting no alteration in the risk of infection with beta-blocker administration^{10-12, 27}. Further, our data confirm prior work showing PPIs are associated with an increased risk of subsequent infections in cirrhotic patients^{7, 28-31}. PPIs' direct effects on the immune system include blockade of neutrophil's oxidative burst through inhibition of the H⁺ pump required for the rapid release of toxic reactive oxygen species, inhibition of IL-8 production decreases inflammatory cell recruitment, and limitation of oxidation³². In addition, PPIs' indirect effects include exacerbation of the cirrhotic host's predisposition to SIBO and preferential growth inhibition of nonpathogenic microorganisms leaving room for potential pathogens³³. Our and others' data documenting association coupled to the direct and indirect effects of PPIs on immune function and SIBO make us believe there is a causal relationship between PPIs and subsequent infections.

While much is known about the increased infectious risks of cirrhotic patients taking PPIs, it is less clear how SBP prophylaxis may be associated with infectious outcomes. It is more likely that the need for this class of medications, rather than the medications themselves, may be associated with subsequent infections. A higher CTP score was seen in patients on SBP prophylaxis, which may explain the risk for subsequent infections. Alternatively the simple need for SBP prophylaxis may indicate a high risk of bacterial translocation or selection of microbiota resistant to the prophylaxis agent over time. This potential selection of resistant pathogens could also explain why the first SBP episode was protective against subsequent infections while SBP prophylaxis was associated with a higher risk of subsequent infections.

We have not only documented an increased risk of subsequent infections in cirrhotic patients after hospital discharge with an infection, but a significant risk that the subsequent infection will be caused by a DRO in patients with SBP. Although the overall DRO rates were similar between index (16%) and subsequent (17%) infections, there was a high rate of DRO in patients whose subsequent infection was SBP (42%). Fortunately, there was a low risk of recurrent SBP in patients whose first infection was SBP. Others have seen the disturbing trend in cirrhotic patients in single-center studies that more infections are being caused by

DRO^{4, 41-44}. We hypothesize that the use, and possible overuse, of antibiotics in the hospital and outpatient setting has likely resulted in this increase. Although antibiotic prophylaxis to prevent recurrent SBP and infections after variceal hemorrhage has been very successful; with the increased need to develop infection prevention strategies, it will be critical to find non-antibiotic means of preventing infections in patients with cirrhosis in order to avoid an even higher prevalence of DRO. If these findings are replicated, alternative infection prevention strategies will need to be sought.

Although bolstered by the prospective data collection, large sample size and multicenter approach, exact dates of subsequent infections were not collected limiting our ability to perform a time-to-event analysis. Another limitation included our 18% loss to follow-up. The only difference between the two groups was a lower Child score among those who were lost to follow-up than those followed-up. Given a similar MELD scores, medication utilization and other clinical criteria, it is unlikely that this small difference would have made an appreciable alteration in the ultimate outcome of the study.

In conclusion, infected cirrhotic patients discharged from the hospital have a 41% risk of death or liver transplantation within 6 months. In transplant-free survivors, the risk of subsequent infections remains high at 45%. The risk of subsequent infections cannot be predicted by just liver severity indices, but is increased in older patients with non-SBP index infections, especially if they are taking PPIs or SBP prophylaxis. Given the association with PPI use, its indication should be critically evaluated in all patients. In patients who require SBP prophylaxis further evaluation of bacterial species and a better understanding of the disease states' association with subsequent infections is needed. Since these infections represent a continued potential source of morbidity and mortality not adequately managed by current medications, novel (preferably non-antibiotic based) infection prevention strategies are needed for cirrhotic patients who survive an index hospitalization for infection.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

CARS	compensatory anti-inflammatory response system
CTP	Child-Turcotte-Pugh
DRO	drug resistant organisms
MELD	model for end-stage liver disease

NACSELD	North American Consortium for the Study of End-Stage Liver Disease
PPI	proton pump inhibitors
REDCap	Research Electronic Data Capture
SBP	spontaneous bacterial peritonitis
SIBO	small intestinal bacterial overgrowth
SIRS	systemic inflammatory response system
UTI	urinary tract infection

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Figure 1.
Outcome of patients enrolled in the NACSELD trial.

Figure 2.

Frequency of first and subsequent infections occurring in the same location within 6 months of hospital discharge with an infection.

Table 1

Demographics at the time of the index hospitalization of the patients with 6-month outcomes. P-values compare patients with and without subsequent infections.

		No Subsequent Infection	Subsequent Infections	P-value
Number		104	84	
Age		55.1 (9.6)	57.7 (9.2)	0.06
Male		56.9%	51.2%	0.44
Etiology of liver disease	HCV	31.7%	15.5%	0.13
	Alcohol	30.8%	34.5%	
	HCV + Alcohol	12.5%	14.3%	
	NASH/CC	15.4%	22.6%	
	Other	9.6%	13.1%	
MELD score		18.35 (7.59)	19.3 (6.8)	0.36
Child-Turcotte-Pugh Score		10 (8, 12)	10 (9,11.5)	0.37
Bilirubin mg/dL		5.4 (6.9)	5.1 (4.6)	0.7
INR		1.7 (1.4)	1.7 (0.9)	0.97
Creatinine mg/dL		1.42 (1.1)	1.45 (1.2)	0.86
Sodium mEq/L		132.0 (6.7)	132.6 (6.5)	0.57
Albumin g/dL		2.79 (0.7)	2.7 (0.7)	0.64
Platelets 10 ³ /uL		32.4 (69.8)	24.2 (58.7)	0.39
Mean arterial pressure (mmHg)		83.0 (14.3)	83.4 (15.9)	0.87
WBC 10 ³ /uL		8.6 (7.7)	7.6 (5.5)	0.34
SBP Prophylaxis		21.2%	53.6%	<0.001
Rifaximin		27.9%	52.4%	<0.001
Proton Pump Inhibitor		52.9%	72.6%	0.006
B-Blocker		39.4%	31.0%	0.23

HCV, hepatitis C, NASH, non-alcoholic steatohepatitis; CC, cryptogenic cirrhosis

Table 2

Site of infection and organisms isolated in the index vs. subsequent infection(s).

	Index Infection* (n=188)	Any Subsequent Infection** (n=84)
Infection Site		
UTI	28% (53/188)	33% (28/84)
SBP	24% (46/188)	23% (19/84)
Skin/soft tissue	13% (24/188)	11% (9/84)
Spontaneous bacteremia	16% (30/188)	17% (14/84)
Clostridium difficile	5% (9/188)	6% (5/84)
Respiratory	7% (14/188)	4% (3/84)
Other	10% (19/188)	14% (12/84)
Organism Isolated		
Gram + organisms	34% (64/188)	37% (31/84)
Gram - organisms	27% (50/188)	26% (22/84)
Fungal	1.5% (3/188)	0% (0/84)
No organism	37.5% (71/188)	37% (31/84)

* No significant differences found between the 2 groups overall.

** Ninety infections were found in 84 patients.

UTI, urinary tract infection; SBP, spontaneous bacterial infection

Table 3

Organ failures and patient disease course during the index hospitalization.

	No Subsequent Infection (n=104)	Subsequent Infections (n=84)	P-value
Mechanical ventilation	2.0%	8.5%	0.04
Acute kidney injury [^]	16.5%	25.9%	0.12
Hepatic encephalopathy ^{^^}	49.5%	59.5%	0.17
LOS of index hospitalization (days)	12.1 (11.7)	14.6 (24.5)	0.4
ICU during index hospitalization	26.9%	22.6%	0.5
Shock [#]	12.5%	10.7%	0.7

[^] Acute kidney Injury defined as a rise in serum creatinine >50% from baseline or 0.3 mg <48 hours.^{^^} Hepatic encephalopathy defined as West-Haven grade 2.[#] Shock defined as the need for vasopressor support.

LOS, length of stay; ICU, intensive care unit

Table 4

Univariate and stepwise multivariate logistic regression analysis of predictors of subsequent infections (with MELD forced into the final model).

Variable	Odds Ratio (95% CI)	P-value
PPI	2.65 (1.43, 4.90)	0.002
SBP Prophylaxis	2.17 (1.14, 4.11)	0.02
Age	1.03 (1.00, 1.06)	0.06
Rifaximin	1.87 (1.03, 3.38)	0.04
Heart Rate	0.99 (0.97, 1.01)	0.19
2 nd Infection	1.63 (0.78, 3.42)	0.19
MELD	1.02 (0.98, 1.06)	0.36
Platelets	1.00 (0.99, 1.01)	0.39
Child-Turcotte-Pugh	1.07 (0.92, 1.26)	0.38
Gender (Male)	0.80 (0.44, 1.42)	0.44
Sodium	1.01 (0.97, 1.06)	0.57
Etiology Alcohol	1.19 (0.64, 2.19)	0.59
Index SBP Infection	0.83 (0.43, 1.64)	0.59
Albumin	0.90 (0.59, 1.38)	0.64
Number of Infections	1.06 (0.82, 1.39)	0.65
Mean Arterial Pressure	1.00 (0.98, 1.02)	0.86
Beta-Blocker	1.01 (0.54, 1.88)	0.98

Variable	Odds Ratio (95% CI)	P-value
SBP Prophylaxis	3.66 (1.60-8.37)	0.002
Age	1.06 (1.02-1.11)	0.006
Proton pump inhibitor use	2.72 (1.30-5.710)	0.008
Index SBP Infection	0.37 (0.15-0.91)	0.03
MELD	1.02 (0.96-1.07)	0.54

SBP, spontaneous bacterial peritonitis; MELD, Model for End-Stage Liver Disease