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

Jacqueline G. O'Leary,[*] K. Rajender Reddy,[‡] Florence Wong,[§] Patrick S. Kamath,[‖] Heather M. Patton,[¶] Scott W. Biggins,[#] Michael B. Fallon,[**] Guadalupe Garcia-Tsao,[‡‡] Ram M. Subramanian,[§§] Raza Malik,[‖‖] Leroy R. Thacker,[¶¶] and Jasmohan S. Bajaj,[##] on behalf of the North American Consortium for the Study of End-Stage Liver Disease

*Medicine, Baylor University Medical Center, Dallas, Texas; [‡]Medicine, University of Pennsylvania, Philadelphia, Pennsylvania; [§]Medicine, University of Toronto, Toronto, Ontario, Canada; [‖]Medicine, Mayo Clinic School of Medicine, Rochester, Minnesota; [¶]Medicine, University of California, San Diego, San Diego, California; [#]Medicine, University of Colorado, Denver, Colorado; [**]Medicine, University of Texas Health Science Center, Houston, Texas; [‡‡]Medicine, Yale University School of Medicine, New Haven, Connecticut; [§§]Medicine, Emory University, Atlanta, Georgia; [‖‖]Medicine, Beth Israel Deaconess, Boston, Massachusetts; [¶¶]Biostatistics, [##]Medicine, Virginia Commonwealth University and McGuire VA Medical Center, Richmond, Virginia

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.**

METHODS: **In a 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 up 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. After discharge, 45% had subsequent infections, but only 26% of the subsequent infections occurred at the same site. Compared with 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.**

CONCLUSIONS: **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.

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, which impairs bacterial elimination and facilitates bacterial translocation.[3–5] It also is clear that patients in the hospital with one infection are at risk for a second infection.[6] Although first infections increase the risk of adverse outcomes, second infections portend an even

Abbreviations used in this paper: **CARS, compensatory anti-inflammatory response system; CI, confidence interval; CTP, Child–Turcotte–Pugh; DRO, drug-resistant organism; MELD, model for end-stage liver disease; NACSELD, North American Consortium for the Study of End-Stage Liver Disease; OR, odds ratio; PPI, proton pump inhibitors; SBP, spontaneous bacterial peritonitis; SIBO, small intestinal bacterial overgrowth; UTI, urinary tract infection.**

1542-3565/$36.00
http://dx.doi.org/10.1016/j.cgh.2014.07.060

worse prognosis.[6] Recent data highlighted that some frequently used medications, such as proton pump inhibitors (PPIs), increase the risk of infections, whereas others, such as β-blockers, do not.[7–12] However, prospective studies are needed to confirm and quantify these risks.[13] In addition, we frequently discharge patients from the hospital on antibiotics, such as norfloxacin, for spontaneous bacterial peritonitis (SBP) prophylaxis, and rifaximin for the 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 use may result in altered strategies to improve outcomes.[14]

Although the risk for subsequent infections and death is important in all cirrhotic patients, infections in liver transplant candidates are of particular interest.[15] As model for end-stage liver disease (MELD) scores at liver transplant continue to increase,[16] 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.

To help identify patients at highest risk for subsequent infections, we prospectively followed up 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. Before data analysis, we hypothesized that PPIs would increase the risk of subsequent infections, rifaximin and SBP prophylaxis would decrease the risk of subsequent infections, and β-blockers would not change the risk of subsequent infections.

Methods

The 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 one during hospitalization. This study was approved by all participating centers' Institutional Review Boards. Data were managed using Research Electronic Data Capture, which is based at Virginia Commonwealth University. Research Electronic Data Capture is a secure, web-based application that provides the following: (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, radiologic, and endoscopic findings; or by liver biopsy. Infections were defined uniformly at all sites as described later. 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 was obtained, 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 up for up to 6 months to determine their outcome (alive with or without transplantation, or dead), and whether a subsequent infection that required hospitalization at any hospital had occurred. Follow-up data were acquired by study site coordinators from the patient or their caregiver by telephone. 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 telephone interview, patients' relevant medications (PPI, β-blocker, SBP prophylaxis, and rifaximin) also were updated. Patients' medications were known at discharge and at the 6-month follow-up evaluation; the differences between these 2 time points are detailed in Supplementary Tables 1 and 2.

We defined infections according to standard criteria,[6–17] as follows: (1) spontaneous bacteremia: positive blood cultures without a known source; (2) SBP: ascitic fluid polymorphonuclear cell count greater than 250/μL; (3) lower respiratory tract infections: new pulmonary infiltrate in the presence of the following: (a) at least one respiratory symptom (cough, sputum production, dyspnea, pleuritic pain), with (b) at least one finding on auscultation (rales or crepitation) or one sign of infection (core body temperature >38°C or <36°C, shivering, or leukocyte count >10,000/mm^3 or <4000/mm^3) in the absence of antibiotics; (4) *Clostridium difficile* infection: diarrhea with a positive *C difficile* assay; (5) soft-tissue/skin infection: fever with cellulitis; (6) urinary tract infection (UTI): urine white blood cell count greater than 15 per high-power field with either positive urine Gram stain or culture; (7) intra-abdominal infections: diverticulitis, appendicitis, cholangitis, and so forth, and bacterial enterocolitis; (8) other infections: diarrhea or dysentery with a positive stool culture for *Salmonella*, *Shigella*, *Yersinia*, *Campylobacter*, or pathogenic *Escherichia coli*, and (9) fungal infections as a special category.

The index infection was defined as the first infection that occurred during the hospitalization in which the patient consented to participate in the study. A second infection was defined as another infection that occurred during the same hospitalization in which the patient consented to participate. A subsequent infection was defined as an infection that occurred after discharge from the index-infection hospitalization. Infection resolution was defined as nonhospice hospital discharge.