Cirrhotic Patients Are at Risk for Health Care–Associated Bacterial Infections

MANUELA MERLI,* CRISTINA LUCIDI,* VALERIO GIANNELLI,* MICHELA GIUSTO,* OLIVIERO RIGGIO,* MARCO FALCONE,‡ LORENZO RIDOLA,* ADOLFO FRANCESCO ATTILI,* and MARIO VENDITTI‡

*Division of Gastroenterology, Department of Clinical Medicine, ‡Department of Infectious Diseases and Tropical Medicine, "Sapienza" University of Rome, Rome, Italy

BACKGROUND & AIMS: Bacterial infections are a frequent and serious burden among patients with cirrhosis because they can further deteriorate liver function. We assessed the epidemiology, risk factors, and clinical consequences of bacterial infections in hospitalized cirrhotic patients. **METHODS:** In a cohort of hospitalized cirrhotic patients (n = 150) referred to a tertiary care setting, all episodes of bacterial infections were recorded prospectively. Infections were classified as community-acquired (CA), health care–associated (HCA), or hospital-acquired (HA). Site of infection, characteristics of bacteria, and prevalence of antibiotic resistance were reported; consequences for liver function and patient survival were evaluated. **RESULTS:** Fifty-four infections were observed among 50 patients (12 CA, 22 HCA, and 20 HA). Bacterial resistance was more frequent among patients with HCA or HA infections (64% of isolates). Mortality was 37% from HA, 36% from HCA, and 0% from CA infections. Independent predictors of infection included a previous infection within the past 12 months ($P = .0001$; 95% confidence interval [CI], 2.2–10.6), model of end-stage liver disease score ≥15 ($P = .01$; 95% CI, 1.3–6.1), and protein malnutrition ($P = .04$; 95% CI, 1.5–10). Infectious episodes worsened liver function in 62% of patients. Patients with infection more frequently developed ascites, hepatic encephalopathy, hyponatremia, hepatorenal syndrome, or septic shock. Child class C ($P = .006$; 95% CI, 1.67–23.7), sepsis ($P = .005$; 95% CI, 1.7–21.4), and protein malnutrition ($P = .001$; 95% CI, 2.8–38.5) increased mortality among patients in the hospital. **CONCLUSIONS: In hospitalized cirrhotic patients, the most frequent infections are HCA and HA; these infections are frequently resistant to antibiotics. As infections worsen, liver function deteriorates and mortality increases. Cirrhotic patients should be monitored closely for infections.**

Keywords: Sepsis; Survival; Multidrug Resistance; Nutritional Status.

Bacterial infections are a frequent and severe complication in cirrhotic patients.[1] Episodes of infection are reported in 40% of hospitalized cirrhotic patients.[2] Infections are associated with a longer hospital stay and a higher risk of death; infection-related mortality rate, in fact, ranges between 15% and 19%.[2,3] Most of the infections in cirrhotic patients are caused by enteric bacteria.[4] This suggests that the defense mechanisms of these patients fail to prevent the microorganisms present in the intestinal lumen from reaching the systemic circulation. Sepsis favors acute decompensation of cirrhosis and may lead to hepatic encephalopathy, renal insufficiency, shock, and "acute on chronic liver failure."[1]

The possible risk factors for infections have been scarcely evaluated in chronic liver disease and a recent review indicated that a Child–Pugh C score can be considered the only independent predictor.[5] In most of the studies, bacterial infections in cirrhotic patients are caused, in large prevalence (70%–80%), by gram-negative cocci. In the past decade, however, infections induced by gram-positive bacilli have increased, owing to long-term antibiotic prophylaxis with quinolones recommended for those patients with previous spontaneous bacterial peritonitis (SBP) episodes,[6,7] which prevents infections caused by gram-negative bacilli but not those caused by gram-positive cocci. It recently has been proposed that infections occurring in patients who have had previous recent contact with the health care system can be classified as health care–associated (HCA) and may have a worse prognosis.[8] Patients with advanced liver disease frequently need to be hospitalized and therefore may be included in this risk category. No information is available about the prevalence and consequences of HCA infections in cirrhotic patients.

The current study consists of a prospective investigation aimed at determining, in a large cohort of hospitalized cirrhotic patients, the following: (1) the prevalence and etiology of community-acquired (CA), HCA, and hospital-acquired (HA) bacterial infections; (2) the risk factors associated with the development of bacterial infections; (3) the short-term clinical consequences of infection; and (4) patient survival 6 months after hospital discharge.

Patients and Methods

Patients

From October 2008 to June 2009, we consecutively enrolled all cirrhotic patients hospitalized at our University Hospital (a tertiary referral center). Diagnosis of cirrhosis was based on liver biopsy, when available, or on obvious clinical, biochemical, or ultrasonographic and endoscopic features. Exclusion criteria were a concomitant human immunodeficiency virus infection, high-dose corticosteroid treatment, and immunosuppressive therapy. The study was approved by the local

Abbreviations used in this paper: CA, community-acquired; CI, confidence interval; HA, hospital-acquired; HCA, health care–associated; HCC, hepatocellular carcinoma; HRS, hepatorenal syndrome; MDR, multidrug resistant; OR, odds ratio; SBP, spontaneous bacterial peritonitis; SIRS, systemic inflammatory response syndrome.

1542-3565/$36.00
doi:10.1016/j.cgh.2010.06.024

Ethical Committee Review Board, and written informed consent was signed by all the participants.

Clinical Evaluation and Management

Demographic, clinical, and biochemical parameters were recorded for each patient in a preformed digitalized dataset. At admission, previous relevant clinical data, such as origin of liver disease, history of alcohol abuse, ascites, encephalopathy, gastrointestinal bleeding, acute or chronic renal failure, and coexistence of other diseases, were recorded. Previous hospitalizations (within 6 mo), episodes of infections diagnosed within the past 12 months, and therapy administered during the past 4 weeks also was noted. The main cause of hospitalization was identified and basal clinical and biochemical parameters were assessed to define the severity of liver disease, renal function, and electrolyte imbalance. Mean arterial pressure, heart rate, respiratory rate, and body temperature were measured and the presence of systemic inflammatory response syndrome (SIRS) was investigated.[9] The severity of liver disease was assessed using the Child–Pugh score[10] and the model of end-stage liver disease (MELD) score.[11] Hepatorenal syndrome (HRS) was diagnosed according to international criteria.[12] The nutritional status was assessed in all the patients by anthropometric measurements.[13] Complications of cirrhosis were treated according to recent guidelines.[14] Antibiotic prophylaxis was administered in patients with previous SBP or recent gastrointestinal bleeding.[15,16] Overt hepatic encephalopathy was diagnosed according to the West Haven criteria[17] and treated only when the symptoms were clinically evident.

Diagnosis and Management of Infection

Bacterial infections were actively looked for in all patients based on the following assessment: (1) medical history reporting symptoms of infection; (2) physical examination focused on symptoms and signs suggestive of infection; (3) laboratory tests including erythrocyte sedimentation rate, C-reactive protein level, polymorphonucleater cell count, hepatic and renal function tests, and urinary sediment; (4) analysis of the ascitic fluid when present; (5) chest radiograph; and (6) abdominal ultrasound. When a bacterial infection was suspected, further investigations (cultures of blood, urine, sputum, ascitic fluid, or purulent secretions) were performed.

SBP was defined as a polymorphonucleater cell count greater than 250/mm^3 in the ascitic fluid ± a positive culture; pneumonia was defined as the presence of radiologic evidence of consolidation plus at least 2 of the following criteria: fever higher than 38°C or hypothermia less than 35°C, dyspnea, cough and purulent sputum, pleuritic chest pain, or signs of consolidation on physical examination. Urinary tract infections, biliary tract infections, cellulitis, and gastroenteritis were all diagnosed according to congruent symptoms and biochemical and imaging parameters following standard criteria.[18] The evidence of a positive blood culture without a recognized site of infection was defined as spontaneous bacteremia.

Study Design, Follow-Up Evaluation, and Outcomes

A complete patient assessment was performed at hospital admission and at discharge. If a diagnosis of infection was made during hospitalization, the patient assessment was repeated at that time. Main outcomes were modifications of the liver function, development of kidney dysfunction, development of hepatic encephalopathy, gastrointestinal bleeding, ascites, hyponatremia, length of hospital stay, and in-hospital survival. Patients were re-evaluated as outpatients at 1, 3, and 6 months or until death or liver transplant. The study was closed when the last patient enrolled had completed at least the 6-month follow-up evaluation.

Definitions

Infections were classified as follows.

Infections were classified as HA if the diagnosis of infection was made after more than 48 hours of hospital stay.

Infections were classified as HCA if the diagnosis was made within 48 hours of hospitalization in patients with any of the following criteria: (1) had attended a hospital or a hemodialysis clinic, or had received intravenous chemotherapy during the 30 days before infection; or (2) were hospitalized for at least 2 days, or had undergone surgery during the 180 days before infection; or (3) had resided in a nursing home or a long-term care facility.[8]

Infections were classified as CA if the diagnosis of infection was made within 48 hours of hospitalization and the patient did not fulfill the criteria for HCA infection[8] (ie, had no recent contact with the health care system and was not hospitalized in the past 6 months).

Patients with infections were treated immediately with empiric large-spectrum antibiotics, based on the site of infection and according to standard guidelines and local epidemiology. The antibiotic treatment then was modified according to the results of cultures (if available) and in case of treatment failure. All patients with infection underwent a consultation by an infectious diseases specialist with expertise in nosocomial infections.

Patients were considered to have SIRS when they fulfilled the criteria established by the most recent international guidelines. Sepsis was diagnosed in the presence of SIRS and a known or highly suspected infection. Septic shock was defined as sepsis with hypotension refractory to intravascular volume loading, associated with perfusion abnormalities that required the use of inotropes.[9]

The definition of a *multidrug resistant* (MDR) pathogen was used to describe a methicillin-resistant *Staphylococcus aureus*, an *Acinetobacter baumannii*, an extended-spectrum β-lactamases–producing gram-negative strain, or any bacterial isolate resistant to at least 3 classes of antimicrobial agents.[19,20] Protein malnutrition was diagnosed when the midarm muscle circumference was below the fifth percentile of the referral standard.[13]

Statistical Analysis

Each patient was considered only once during the first hospitalization.

To evaluate liver function modifications induced by the infection, the tests performed at the time of diagnosis were compared either with recent previous results (when available) or with the liver function test at the first outpatient control after discharge (1 month), when the infection had completely resolved.

All the values are reported as means ± standard deviations; P values less than .05 were considered significant. Data were analyzed as continuous or categoric by using the Student t test for parametric data and the Mann–Whitney U test or the Wil-