High Prevalence of Antibiotic-Resistant Bacterial Infections Among Patients With Cirrhosis at a US Liver Center

PUNEETA TANDON,[*,‡] ANGELA DELISLE,[§] JEFFREY E. TOPAL,[‖] and GUADALUPE GARCIA–TSAO[‡]

*University of Alberta, Edmonton, Alberta, Canada; ‡Section of Digestive Diseases, ‖Section of Infectious Diseases, Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut; and §In-patient Liver Unit, Yale New Haven Hospital, New Haven, Connecticut

BACKGROUND & AIMS: There are limited data on the prevalence or predictors of antibiotic-resistant bacterial infections (AR-BI) in hospitalized patients with cirrhosis in North America. Exposure to systemic antibiotics is a risk factor for AR-BI; however, little is known about the effects of the increasingly used oral nonabsorbed antibiotics. **METHODS:** We analyzed data from patients with cirrhosis and bacterial infections hospitalized in a liver unit at a US hospital between July 2009 and November 2010. Multivariate logistic regression was used to determine predictors of AR-BI. Data were analyzed on the first bacterial infection of each patient (n = 115), and a sensitivity analysis was performed on all infectious episodes per patient (n = 169). **RESULTS:** Thirty percent of infections were nosocomial. Urinary tract infections (32%) and spontaneous bacterial peritonitis (24%) were most common. Of the 70 culture-positive infections, 33 (47%) were found to be antibiotic resistant (12 were vancomycin-resistant *Enterococci*, 9 were extended-spectrum β-lactamase–producing *Enterobacteriaceae*, 7 were quinolone-resistant gram-negative rods, and 5 were methicillin-resistant *Staphylococcus aureus*). Exposure to systemic antibiotics within 30 days before infection was associated independently with AR-BI, with an odds ratio (OR) of 13.5 (95% confidence interval [CI], 2.6–71.6). Exposure to only nonabsorbed antibiotics (rifaximin) was not associated with AR-BI (OR, 0.4; 95% CI, 0.04–2.8). In a sensitivity analysis, exposure to systemic antibiotics within 30 days before infection and nosocomial infection was associated with AR-BI (OR, 5.2; 95% CI, 1.5–17.7; and OR, 4.2; 95% CI, 1.4–12.5, respectively). **CONCLUSIONS:** The prevalence of AR-BI is high in a US tertiary care transplant center. Exposure to systemic antibiotics within 30 days before infection (including those used for prophylaxis of spontaneous bacterial peritonitis), but not oral nonabsorbed antibiotics, is associated with development of an AR-BI.

Keywords: Multidrug Resistance; SBP; Epidemiology; Bacteriology.

Watch this article's video abstract and others at http://tiny.cc/bz9jv.

Scan the quick response (QR) code to the left with your mobile device to watch this article's video abstract and others. Don't have a QR code reader? Get one by searching "QR Scanner" in your mobile device's app store.

Bacterial infections are a major cause of morbidity and mortality in cirrhosis.[1] Over the past decade, the treatment of these infections has become more challenging as a result of the development of antibiotic-resistant bacteria.

Studies performed mostly in Europe[2–6] have shown increasing rates of infections caused by antibiotic-resistant organisms in patients with cirrhosis, particularly in those acquired while hospitalized. In studies performed in a liver unit in Spain, the development of antibiotic-resistant infections was correlated to an increased mortality rate.[2,3] Because Spain has disproportionately high rates of antibiotic resistance,[7–11] this may not be representative of the situation in the United States. Although even within the United States the resistance patterns may vary from center to center based on infection control and antibiotic use practices, the prospective collection of data from patients with cirrhosis admitted to a North American hospital is a starting point to identify the rate of antibiotic-resistant organisms and the factors that predict their presence. Both exposure to systemic antibiotics and selective intestinal decontamination using oral norfloxacin have been identified as predictors of the development of antibiotic-resistant bacterial infections (AR-BI) in patients with cirrhosis.[2,12] The impact of the increasingly used oral nonabsorbed antibiotics such as rifaximin in the development of AR-BI, although theoretically low,[13] has not been established. Our aims were to investigate the prevalence of AR-BI in patients with cirrhosis hospitalized in a liver unit in a US hospital and to determine the predictors of the presence of these infections, including prior exposure to antibiotics, categorized by type (systemic or oral nonabsorbed).

Methods

Patients

In the period between July 1, 2009, and November 20, 2010, the names, date of admission, and type of infection of all patients with cirrhosis admitted to the Liver Unit at the Yale New Haven Hospital who either had a bacterial infection at admission or developed an infection during their admission were collected prospectively. Charts were reviewed retrospectively for the remaining data. Post–liver transplantation patients were excluded. The primary analysis was performed using only the first bacterial infection per patient, but for the pur-

Abbreviations used in this paper: AR-BI, antibiotic-resistant bacterial infections; CI, confidence interval; ESBL, extended-spectrum β-lactamase–producing *Enterobacteriaceae*; MELD, Model for End-Stage Liver Disease; MRSA, methicillin-resistant *Staphylococcus aureus*; OR, odds ratio; QRGNR, quinolone-resistant gram-negative rods; SBE, spontaneous bacterial empyema; SBP, spontaneous bacterial peritonitis; UTI, urinary tract infection; VRE, vancomycin-resistant *Enterococcus*.

1542-3565/$36.00
http://dx.doi.org/10.1016/j.cgh.2012.08.017

poses of further analysis, data on repeat infections occurring during the course of an admission or in the same patient on separate admissions also were collected.

Data Collection

Data collected at the time of bacterial infection included patient demographics, etiology and severity of liver disease, reason for the septic work-up, laboratory values, co-existing medical diagnoses (diabetes mellitus, human immunodeficiency virus), medication use, and antibiotic use within 30 days of diagnosis of the bacterial infection. In the case of culture-positive infections, all microorganisms and their antibiotic susceptibility patterns were recorded.

Definitions

Cirrhosis was identified by laboratory features of hepatic dysfunction or clinical features of portal hypertension in the presence of compatible radiologic and/or histologic findings. Nosocomial infections were defined as those developing more than 48 hours after admission to the hospital. We considered the following to be antibiotic-resistant organisms: methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), quinolone-resistant gram-negative rods (QRGNR) (isolated resistance to a quinolone), extended-spectrum β-lactamase–producing *Enterobacteriaceae* (ESBL) (resistance to ceftazidime or ceftriaxone), *Enterobacter* infection with an AmpC β-lactamase mutation and bacterial isolates resistant to 3 or more classes of antibiotics.[14] Because it is often a contaminant, coagulase-negative *Staphylococcus epidermidis* was not classified as an antibiotic-resistant organism. Cases of spontaneous bacterial peritonitis (SBP) caused by this organism were counted as culture-negative SBP and cases of line infection or endocarditis, for which this organism is known to be a pathogen, were counted as culture-positive infections. SBP and spontaneous bacterial empyema (SBE) were defined by a fluid polymorphonuclear cell count of 250/mm^3 or higher irrespective of culture results. Spontaneous bacteremia was defined by a positive blood culture in the absence of a secondary source of infection. Notably, our definition of a urinary tract infection (UTI) was adapted from the recent Centers for Disease Control guidelines[15] and required a positive urine culture in addition to either symptoms of a UTI, hepatic encephalopathy, or associated bacteremia. This is a more stringent definition than previously used definitions of either leukocytosis or positive urine culture.[2] Pneumonia was diagnosed in the setting of compatible clinical signs, symptoms, and radiologic findings (2 or more serial chest radiographs with a persistent infiltrate or consolidation). Cellulitis was defined by physical examination findings of swelling, erythema, heat, and tenderness irrespective of culture results. Other infections were defined per standard guidelines.[15]

Systemic antibiotics are those administered intravenously or those administered orally that are partially (eg, norfloxacin) or completely absorbed (eg, ciprofloxacin). Nonabsorbed antibiotics are those administered orally that are not absorbed (eg, rifaximin, neomycin). A patient on both a systemic and a nonabsorbed antibiotic was considered to have systemic antibiotic exposure.

Statistical Analysis

Statistical analysis was performed using SPSS version 17.0 (SPSS, Inc, Chicago, IL). Categoric values were described using percentages and compared using either the χ^2 or the Fisher exact test. Continuous values were described using the mean and standard deviation and were compared using the Student *t* test. Univariate and multivariate logistic regression modeling were used to determine predictors of antibiotic resistance. All variables with a *P* value of less than .05 on univariate analysis were entered into the multivariate model. Unless otherwise specified, on both univariate and multivariate logistic regression, antibiotic use was categorized into 3 groups: (1) no antibiotics, (2) oral nonabsorbed antibiotics only, and (3) systemic antibiotics (± oral nonabsorbed antibiotics). The primary analysis was performed for the first infectious episode per patient. Further sensitivity analysis was performed using multiple infectious episodes per patient.

Results

Primary Analysis: Data for First Bacterial Infection Only (n = 115)

Baseline characteristics. Of an estimated 746 patients with cirrhosis admitted to the Liver Unit at the Yale New Haven Hospital during the 17-month study period, 115 unique patients with bacterial infection were identified. Table 1 shows baseline characteristics of the patients. Sixty-eight percent (78 of 115) of the patients were men and had a mean age of 55.6 ± 10.3 years. Alcohol-related liver disease (31 cases), hepatitis C virus infection (40 cases), or a combination of the two (22 cases) accounted for 81% of the causes of cirrhosis. At the time of diagnosis of infection, the mean Child–Pugh score was 9.3 ± 1.6 and the mean Model for End-stage Liver Disease (MELD) score was 21.6 ± 10.0. The main reasons for pursuing a septic work-up were infectious symptoms in 47%, hepatic encephalopathy with or without infectious symptoms in 32%, acute kidney injury in 16%, and gastrointestinal bleeding in the remaining 5%.

Bacterial infections. Of the 115 bacterial infections, 40 (35%) were spontaneous infections (28 SBP, 2 SBE, and 10 spontaneous bacteremias), 37 (32%) were UTIs, 22 (19%) were pneumonias, and 12 (10%) were cases of cellulitis. Of the remaining cases, 2 were septic arthritis, there was 1 liver abscess, and 1 cerebritis/mastoiditis. Thirty percent (34 of 115) of the infections were nosocomial.

Culture-positive antibiotic-resistant infections. Sixty-one percent (70 of 115) of all infections were culture-positive. This included all of the UTIs and spontaneous bacteremias (by definition), 43% (13 of 30) of the SBP/spontaneous bacterial empyemas, 27% (6 of 22) of the pneumonias, and 8% (1 of 12) of the cellulitis cases. Fifty-four percent (38 of 70) of the culture-positive infections were caused by gram-negative organisms, 44% (31 of 70) were owing to gram-positive organisms, and 1 UTI case was caused by mixed gram-positive and gram-negative organisms (Table 2).

In 70 culture-positive infections, 33 antibiotic-resistant bacteria were identified: 12 VRE (36%), 9 ESBL (27%), 7 QRGNR (21%), and 5 MRSA (15%) (Table 2). Of the culture-positive infections, these AR-BIs occurred in 20 of 37 (54%) of the UTIs, 7 of 13 (54%) of the SBP/SBEs, 2 of 10 (20%) of the spontaneous