Bacteremia in cirrhotic patients with upper gastrointestinal bleeding

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ABSTRACT

Background/Aims: Increased risk of bacterial infection is common in cirrhotic patients with upper gastrointestinal bleeding (UGIB). Our study aimed to explore the association of the bacteremia with in-hospital mortality and risk factors of bacteremia in these patients.

Materials and Methods: In our retrospective cohort study, we collected data for cirrhotic patients with UGIB admitted to our hospital between August 2010 and December 2010. The primary outcome was in-hospital mortality. The secondary outcome was bacteremia. A multivariate logistic regression analysis was performed to determine risk factors for mortality and bacteremia.

Results: A total of 202 patients with cirrhosis presenting with UGIB at the emergency department (ED) were enrolled. Bacteremia was associated with a higher mortality rate (adjusted odds ratio [OR]: 9.7; 95% confidence interval [CI]: 1.9-50.6, p=0.007), whereas shock (systolic blood pressure <90 mmHg at ED triage) and bandemia (>0% immature neutrophils of band form) were associated with bacteremia in cirrhotic patients with UGIB (adjusted OR: 5.3; 95% CI: 2.3-12.7, p<0.0001 and adjusted OR: 4.0; 95% CI: 1.6-9.9, p=0.0003, respectively).

Conclusion: Bacteremia in cirrhotic patients with UGIB is one of the major risk factors leading to in-hospital mortality. On the basis of our findings, prevention of bacteremia in cirrhotic patients with UGIB, especially in those with shock and bandemia, is important; thus, adequate antibiotic treatment is suggested.

Keywords: Cirrhosis, upper gastrointestinal bleeding, antibiotics, bandemia, bacteremia, shock

INTRODUCTION

In patients with cirrhosis, upper gastrointestinal bleeding (UGIB) is a common complication resulting in critical morbidity and mortality (1-3). Variceal bleeding accounts for >50% cirrhotic patients with UGIB compared to peptic ulcer bleeding, which accounts for only approximately 20% (4). Many current studies have suggested that prophylactic antibiotic therapy decreases bacterial infection rate, rebleeding, and in-hospital mortality in cirrhotic patients with either variceal bleeding or peptic ulcer bleeding (5-7). The common antibiotic regimen prescriptions are third-generation cephalosporin and fluoroquinolones, but the choice of drug, duration, and dose are not clearly standardized (1,2,8). However, over time, the inappropriate use of antibiotics has led to emergence of multidrug-resistant (MDR) bacteria that pose a serious biological threat, particularly for cirrhosis patients with relatively immunocompromised conditions (9-11). A recent study suggests that prophylactic antibiotics prescribed for Child-Pugh (CP) classification A cirrhotic patients with UGIB did not significantly decrease in-hospital mortality and bacterial infection (12) but increased MDR bacteria incidence. Therefore, our study aimed to investigate the association of bacteremia with in-hospital mortality and the risk factors for bacteremia in cirrhotic patients with UGIB to assist decision-making for preventing complications, such as pneumonia and other infections, and treatment strategies of antibiotics use in the emergency department (ED).

MATERIALS AND METHODS

Study population

This was a retrospective cohort study. The study population included all patients with cirrhosis suffering from

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UGIB admitted at a medical center between August and December 2010. These patients initially presented at ED and were then admitted in the same hospital. We excluded patients with fever up to 38°C or obvious initial infection signs, such as a pneumonia patch on a chest X-ray and positive growth for ascites, blood, urine, and sputum cultures during the week before the ED visit. Patients who had taken antibiotics within 1 week before admission were also excluded. The study was approved by the Institutional Review Board of the hospital, and informed consent was waived because of the retrospective design.

Definitions

The diagnosis of liver cirrhosis was confirmed on the basis of compatible abdomen sonographic findings accompanied with laboratory findings of hepatic dysfunction or clinical findings of portal hypertension. CP classification was used to classify the severity of cirrhosis. UGIB was defined as initial chief complaints with at least one of the following: coffee ground vomitus, hematemesis, melena, or tarry stool passage. Peptic ulcer bleedings were treated by argon plasma coagulation or with hypertonic saline-epinephrine injection. Variceal bleedings were treated by endoscopic variceal ligation with overtube insertion or cyanoacrylate injection. Prophylactic antibiotic courses were defined as either a prescription for an oral fluoroquinolone as ciprofloxacin (ciproxin, Bayer Pharma AG, Leverkusen, Germany) 1000 mg/d (500 mg twice a day) or intravenous third-generation cephalosporin as ceftriaxone (Rocephin, Hoffmann-La Roche, Kaiseraugst, Switzerland) 2 g/d, whereas initial ED management with at least 3-day therapy. Shock was defined as systolic blood pressure <90 mmHg at ED triage. Bacteremia was defined as any evidence of positive blood culture results during hospital stay. Bandemia was defined as >0% immature neutrophils of band form. Spontaneous bacterial peritonitis (SBP) was defined as polymorphonuclear cell count >250 cells/mm^3 in ascitic fluid analysis. Pneumonia was diagnosed on the basis of clinical features including cough, fever, sputum production, pleuritic chest pain, rales, or bronchial breath sounds on lung examination and radiological features, including newly or progressive infiltration, consolidation, or cavity in the chest X-ray. The diagnosis of urinary tract infection (UTI) was confirmed by following positive urine culture (10^5 colony-forming units/mL). Hepatic encephalopathy (HE) was defined as neuropsychiatric abnormalities seen during hospital stay. Hepatorenal syndrome (HRS) was defined as the development functional renal failure during hospital stay. Rebleeding was defined as a new-onset UGIB diagnosed by repeated endoscopy within 48 h after initial successful endoscopic and medical management. Mortality was defined as in-hospital death during the same admission.

Statistical analysis

Statistical analysis was performed using MedCalc Statistical Software version 17.0.4 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org; 2017). Enrolled patients were divided into nonmortality and mortality groups. Normally distributed data were presented as mean with standard deviation (SD), and data with skewed distribution were expressed as median and interquartile ranges (IQR). Mann-Whitney U test, Student's t test, and chi-square test were used to test the differences between the two groups. The difference was considered significant if p value was <0.05. A logistic regression model was employed in the risk analysis of hospital mortality and bacteremia for cirrhotic patients with UGIB with a 95% confidence interval (CI) after adjustment for the variables mentioned. A two-tailed p<0.05 was considered statistically significant.

RESULTS

A total of 202 cirrhotic patients with UGIB were included in this retrospective cohort study. The mean age of the enrolled patients was 55.7±13.3 years, and males were predominant (80.2%). Endoscopy was performed for UGIB in all patients. The bleeding type observed were esophageal variceal (EV) bleeding (80.2%), gastric variceal (GV) bleeding (41%), gastric ulcer (GU) bleeding (25.7%), and duodenal ulcer (DU) bleeding (13.9%). HE was noted in 23 (11.4%) patients and HRS was noted in 11 (5.4%) patients (Table 1).

The multivariable logistic regression analysis for risk factors of hospital mortality (Table 2) showed that bacteremia (adjusted odds ratio [OR]: 9.7; 95% CI: 1.9-50.6, p=0.007), pneumonia (OR: 14.5; 95% CI, 2.5-84.3, p=0.003), CP classification C (OR: 8.9; 95% CI, 17-45.4, p=0.008), and HRS (OR: 11.4; 95% CI: 1.6-80.2, p=0.014) were major risk factors leading to in-hospital mortality. However, prophylactic antibiotic use and HE were not associated with mortality in our study (OR: 0.4; 95% CI: 0.1-2.9; p=0.3, OR: 1.1; 95% CI: 0.2-6.2, p=0.9, respectively).

Of the 202 patients, 172 (85.1%) did not develop bacteremia and 30 (14.9%) developed bacteremia. Of the

Table 1. Univariate analysis for risk factors of mortality in cirrhotic patients with UGIB

	Total patients (n=202) (%)	Nonmortality (n=188) (%)	Mortality (n=14) (%)	p
Age	55.7±13.3	55.5±13.1	58.9±15.4	0.35
Male	162 (80.2)	153 (81.4)	9 (64.3)	0.16
Prophylactic antibiotics in ED	122	111 (59)	11 (78.6)	0.15
EV bleeding	162 (80.2)	149 (79.3)	13 (92.3)	0.19
GV bleeding	83 (41.0)	79 (42.0)	4 (28.6)	0.41
GU bleeding	52 (25.7)	47 (25)	5 (35.7)	0.28
DU bleeding	28 (13.9)	28 (14.9)	0 (0)	0.12
Shock at ED triage	45	36 (19.1)	9 (64.3)	0.001
Rebleeding	45	37 (19.7)	8 (57.1)	0.004
Bacteremia	30	19 (10.1)	11 (78.6)	<0.0001
Spontaneous bacterial peritonitis	9	4 (2.1)	5 (35.7)	<0.0001
Pneumonia	15	6 (3.2)	9 (64.3)	<0.0001
Urinary tract infection	8	4 (2.1)	4 (28.6)	0.001
Hepatic encephalopathy	23	17 (9.0)	6 (42.9)	<0.0001
Hepatorenal syndrome	11	5 (2.7)	6 (42.9)	<0.0001
Child A	68	67 (35.6)	1 (7.1)	0.02
Child B	86	84 (44.7)	2 (14.3)	0.03
Child C	48	37 (19.7)	11 (78.6)	<0.0001
Creatinine (mg/dL)		1.4±1.4	2.7±1.3	0.001
Hemoglobin (g/dL)	8.6±2.5	8.8±2.5	7.0±1.8	0.01
Platelets (10^3/μL)	113.4±77.3	114.7±78.8	94.8±53.9	0.35

UGIB: Upper gastrointestinal bleeding; ED: emergency department; Prophylactic antibiotics in ED was defined as a prescription for an oral fluoroquinolone or intravenous third-generation cephalosporin while initial ED management with at least 3-day therapy; EV: esophageal varices; GV: gastric varices; GU: gastric ulcer; DU: duodenal ulcer; Shock at ED triage was defined as systolic blood pressure <90 mmHg at ED triage; Child A, B, C: Child-Pugh classification A, B, C; Child A denotes good hepatic function, Child B denotes intermediate hepatic function and Child C poor function Continuous variables are presented as mean ± SD or median (interquartile range)

30 patients developing bacteremia, 23 (76.7%) received prophylactic antibiotics. Of the 80 patients who did not receive prophylactic antibiotics, seven (8.8%) had bacteremia developed. Initial shock at ED triage (OR: 3.1; 95% CI: 1.1-9.3; p=0.0399), body temperature at ED triage (OR: 2.1; 95% CI: 1.2-3.6; p=0.0090), and CP classification C (OR: 2.2; 95% CI: 1.1-4.7; p=0.04) were associated with an increase of prophylactic antibiotic use. DU bleeding (OR: 0.3; 95% CI: 0.1-0.8; p=0.0180) and CP classification A (OR: 0.4; 95% CI: 0.2-0.9; p=0.0294) were associated with a decrease of prophylactic antibiotic use. Patients with bacteremia had a significantly higher proportion of initial shock at triage (56.7% vs. 16.3%, p<0.0001) and a higher rate of rebleeding (40.0% vs. 19.2%, p = 0.02) than those without bacteremia. Multivariate analysis for risk factors of bacteremia (Table 3) revealed that initial shock at triage (OR: 5.3; 95% CI: 2.3-12.7; p<0.0001) and bandemia (OR: 4.0; 95% CI: 1.6-9.9; p=0.0003) were associated with a higher rate of bacteremia.

Table 2. Multivariate analysis of risk factors of mortality in cirrhotic patients with UGIB

Risk factor	p	95% CI	Adjusted odds ratio
Bacteremia	0.007	1.9-50.6	9.7
Pneumonia	0.003	2.5-84.3	14.5
Child C	0.008	1.7-45.4	8.9
Hepatorenal syndrome	0.014	1.6-80.2	11.4

UGIB: Upper gastrointestinal bleeding; CI: confidence interval; Child C: Child-Pugh Classification C; Child-Pugh classification A, B, C; Child A denotes good hepatic function, Child B denotes intermediate hepatic function, and Child C poor function

Table 3. Multivariate analysis of risk factors for bacteremia in cirrhotic patients with UGIB

Risk factor	p	95% CI	Adjusted odds ratio
Shock at triage	<0.0001	2.3-12.7	5.3
Bandemia	0.0003	1.6-9.9	4.0

UGIB: Upper gastrointestinal bleeding; Shock at triage was defined as systolic blood pressure <90 mmHg at ED triage; Bandemia: presence of >0% immature neutrophils of band form in blood

DISCUSSION

In clinical practice, bacterial infections in cirrhotic patients with UGIB are very common and sepsis is the leading cause of hospitalization and death in intensive care units (1,12-14). Infections directly cause 30%-50% deaths in patients with cirrhosis (15,16); indeed, our study demonstrated that in-hospital mortality was associated with bacteremia (OR: 9.7; 95% CI: 1.9-50.6; p=0.007). The common bacterial infections in patients with cirrhosis include SBP, UTI, pneumonia, bacteremia, and soft-tissue infections (17-20). We observed that not only bacteremia but also the incidences of other infections, such as pneumonia, UTI, and SBP, was significantly higher in the mortality group than in the nonmortality group. In fact, bacterial infections may be also a triggering factor for HE and acute kidney injury, but the pathophysiology is still not completely understood. The organ failure of possible mechanism is that bacterial infection induces excessive production of proinflammatory molecule, and it causes cardiovascular and endothelial dysfunction (21,22). In our study, HE and HRS were significantly higher in the mortality group than in the nonmortality group (42.9% vs. 9.0%, p<0.0001, 42.9% vs. 2.7%, p<0.0001, respectively). HRS was associated with higher mortality rate (OR: 11.4; 95% CI: 1.6-80.2; p=0.014). A randomized controlled trial presented that prophylactic antibiotics for cirrhotic patients with bacterial infection could decrease the clinical course of HRS and increase survival, consistent with our findings (23).

Many studies and guidelines demonstrate that timely use of prophylactic antibiotics for cirrhotic patients with UGIB decrease not only bacterial infections but also mortality (5,6,24,25). The third-generation cephalosporin and quinolones have been recommended (1,2,8,26). However,78.6% patients in mortality group had prophylactic antibiotics, implying that the patients with prophylactic antibiotics were having relative higher mortality rate (presented in Table 1). This could be attributed to physicians' treatment selection bias, as patients receiving prophylactic antibiotics were associated with advanced liver disease with CP classification C (OR: 2.2; 95% CI: 1.1-4.7; p=0.04), initial shock at ED triage (OR: 3.1; 95% CI: 1.1-9.3; p=0.0399), and body temperature at ED triage (OR: 2.1; 95% CI: 1.2-3.6; p=0.0090). Although multivariable regression revealed that prophylactic antibiotic use was not associated with mortality (OR: 0.4; 95% CI: 0.1-2.9; p=0.3), a negative odds ratio suggested that prophylactic antibiotic use in our study still showed a beneficial trend of decreased mortality.

Patients with cirrhosis are not only immunocompromised but also exhibit excessive activation of proinflammatory cytokines and are thus prone to spontaneous bacterial infections, hospital-acquired infections, and a variety of infections from uncommon pathogens (20,27). Moreover, disequilibrium of intestinal bacterial translocation is common in these patients because UGIB exacerbates intestinal barrier function and local immune defense function (28,29). In this setting, endogenous bacteria, such as gram-negative enteric bacilli, anaerobes, and *Enterococcus* spp. from the gastrointestinal tract cause bacteremia by altering the intestinal barrier permeability (28,30).

In our multiple regression analysis, we observed that the rate of bacteremia increased when initial triage shock and presence of immature neutrophils of band form in blood (band >0%) were noted in ED. A retrospective cohort study consisting of 2342 patients admitted to an infection ward demonstrated that even with normal total white blood cell count, significantly increased rate of positive blood cultures and in-hospital mortality was noted in patients with bandemia on admission (31). Another study by Chase et al. (32) analyzing 5630 ED patients with suspected infection found that patients with bandemia and

vasopressor use for shock in ED had a significantly elevated gram-negative bacteremia rate.

It is well-determined that advanced CP classification has a strong association with bacterial infections and higher mortality rate in patients with cirrhosis (1,3).

Indeed, patients with CP classification C had a higher bacteremia rate and a higher mortality rate in our study. As we just discussed, the possible pathophysiology is that advanced patients with cirrhosis are immunocompromised and show dysregulation of intestinal bacterial translocation (20, 28). On the other hand, patients with CP classification A are at lower risk to develop bacteremia and mortality in our observation, but in reality, the benefits from the prophylactic antibiotics in these patients are still controversial. Several previous studies revealed that the risk of bacterial infection in patients with CP classification A with UGIB is negligible regardless whether prophylactic antibiotics were prescribed or not (6,12). In fact, prevalence of difficult-to-treat and MDR pathogens has substantially increased because of antibiotic overuse, such as β-lactams and quinolones as suggested by guidelines and frequent exposure to a healthcare environment for management of the complications of cirrhosis in these patients (13). This has been a challenging issue and may be fatal for these patients, and the use of broad-spectrum antibiotics (carbapenems or tigecycline) to treat MDR bacteria would be a vicious cycle (9-11). Therefore, the use of prophylactic antibiotics in these patients should be evaluated carefully.

Our report has several limitations. First, we did not enroll patients admitted with other initial diagnoses, but who developed UGIB during their hospital stay. Moreover, those admitted to the hospital through outpatient service were also not enrolled in our study. These limitations can cause selection bias.

In conclusion**,** in cirrhotic patients with UGIB, bacteremia, pneumonia, CP classification C, and HRS were the major risk factors leading to in-hospital mortality. Moreover, patients with initial shock and bandemia had a higher incidence of bacteremia and prophylactic antibiotics would be more beneficial to these specific patients.

Ethics Committee Approval: Ethics committee approval was received for this study from the Institutional Review Board of Chang Gung Medical Foundation (Decision Date: October 17, 2016; Decision No: 201601258B0).

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