Original Article

Compliance with Antibiotic Prophylaxis Guidelines in Patients with Acute Variceal Bleeding

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Background: Bacterial infections are frequently encountered in cirrhotic patients with gastrointestinal hemorrhage. Antibiotic prophylaxis is regarded by practice guidelines as an integral part of therapy for cirrhotic patients presenting with upper gastrointestinal bleeding.

Objectives: The study aimed at comparing the compliance of our hospital staff between 2 study patient cohorts and assessing whether use of antibiotic prophylaxis may decrease the incidence of infections and variceal rebleeding.

Methods: Cirrhotic patients presenting with variceal bleeding at E-Da Hospital during two time periods (i.e., 2005-2006 and 2012) without bacterial infections were retrospectively reviewed to evaluate the compliance with the guidelines on antibiotic prophylaxis and its impact on rebleeding.

Results: The 2005-2006 cohort comprised 90 patients and the 2012 cohort comprised 113 patients. In the 2005-2006 cohort, only 6 of 90 (6.7%) patients received prophylactic antibiotics, whereas 94 of 113 (83.2%) patients in the 2012 cohort received prophylactic antibiotics ($p < 0.05$). The incidence of bacterial infections was 19% among patients without receiving prophylactic antibiotics and 24% in patients receiving prophylactic antibiotics ($p > 0.05$). The rebleeding rate was 14% among patients receiving prophylactic antibiotics and 6% among patients without using prophylactic antibiotics ($p = 0.54$). The survival at discharge was 88% among patients with prophylactic antibiotics and 91% in those without ($p = 0.45$).

Conclusions: The compliance with guidelines on antibiotic prophylaxis in patients with acute variceal bleeding has increased significantly in recent years. However, the use of antibiotic prophylaxis did not appear to reduce infection, rebleeding or mortality in patients receiving banding ligation instead of sclerotherapy.

Key words: banding ligation, antibiotic prophylaxis, variceal rebleeding

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Introduction

Bacterial infections are frequently encountered in cirrhotic patients with gastrointestinal hemorrhage.[1-5] The incidence ranging between 25% and 65% has been reported. The association of bacterial infections with variceal bleeding may increase the occurrence of variceal rebleeding and mortality.[6] A meta-analysis of 8 randomized trials investigation the use of prophylactic antibiotics in patients with variceal rebleeding showed that bacterial infections decrease from 42% to 18% and mortality decrease from 22% to 18% among patients receiving antibiotic prophylaxis. Significant decrease from bacteremia, spontaneous bacterial peritonitis, pneumonia and urinary tract infection were noted.[7] For years, oral nonabsorable antibiotics such as norfloxacin, a quinolone, has been widely adopted to prevent infections in these patients.[8-9] In recent years, cephalosporins are also widely employed in the prophylaxis against bacterial infections in cirrhotic patients with upper gastrointestinal bleeding.[10-11] International guidelines such as Baveno Consensus for portal hypertension 2005, 2010 and American Association Society for Liver Diseases (AASLD) all recommended that antibiotic prophylaxis is an integral part of therapy for patients with cirrhosis presenting with upper gastrointestinal bleeding and should be instituted from admission.[12-14] The compliance of the guidelines worldwide and the true impact of antibiotic prophylaxis remain unclear. Thus, we conducted this retrospective analysis to compare the compliance of our hospital staff with the guidelines in cohorts of two different time periods (i.e., 2005-2006 and 2012) to assess whether antibiotic prophylaxis may decrease the incidence of infections and variceal rebleeding.

Subjects and Methods

This retrospective study included 2 cohorts. The first cohort included patients admitted between January 2005 and December 2006. The second cohort included patients admitted between January and December 2012. Inclusion criteria were cirrhotic patients presenting with hematemesis and/or melena at our hospital with the diagnosis of acute variceal hemorrhage established by emergency endoscopy receiving endoscopic therapy with either glue injection or banding ligation. Acute gastro-esophageal variceal bleeding was defined as: 1) active spurting or oozing of blood from a varix; or 2) stigmata of recent hemorrhage such as blood clots coating on the varices or the presence of hematocystic spots, erosive spots or white nipples on a varix; or 3) presence of red color signs on varices and no other potential site of bleeding was identified.[15-16] Exclusion criteria were: 1) association with fever > 37.5˚C, bacterial infection, sepsis on admission for index bleeding; 2) patients were not hospitalized for index bleeding; 3) patients presented with variceal bleeding on admission for other co-morbidities; 4) incomplete clinical data; 5) presence of hepatocellular carcinoma. The diagnosis of cirrhosis was based on clinical history, biochemical and laboratory data, ultrasound or radiological findings, or histological examination.

After endoscopic therapy, the patients were generally hospitalized for further supportive management. Clinical evaluations unclear including blood cells count, Child-Pugh's classification, renal function, serum alpha-fetoprotein and ultrasound of upper abdomen were routinely performed. Standard therapy, including blood and frozen plasma transfusion, fluid and electrolyte replacement were initiated if clinically indicated. The use of vasoconstrictors was at physicians' discretion. All endoscopists were trained and had experience in both glue injection of gastric varices and ligation of esophageal varices. The size of esophageal varices was based on Beppu's

classification.[17] Endoscopic findings, treatment strategies, and chart records of eligible subjects including baseline data, amount of blood transfusion, use of vasoconstrictors and prophylactic antibiotics, treatment outcomes and complications were reviewed. The Child-Pugh's score was calculated from the data of initial presentation.[18] Our study was approved by the IRB of our hospital.

Our methods of endoscopic variceal ligation on esophageal varices and glue injection on gastric varices were similar to those described previously.[15-16] Briefly, premedication with 20 mg of buscopan was given intramuscularly. The pneumatic-active ligating device (Sumitomo, Tokyo, Japan) was attached to the endoscope (Olympus XQ 230, Tokyo, Japan) and an overtube was used. Ligation was performed on the active bleeding site, hematocystic spots, or erosive spots over the varices.

Commercial needles (Olympus NM-1k) were rinsed with distilled water and lipiodol before and after injection. The obturation agent was n-butyl-2-cyanoacrylate (Histoacryl; B.Braun, Melsungen AG, Germany) 0.5 mL mixed with 0.5 mL Lipiodol ultra-fluide (Guerbet, Bois Cedex, France). If active bleeding was encountered during endoscopic procedure, injections were focused on the bleeding sites. Among patients with gastric varices without active bleeding, injections were focused on the hematocystic spots or the erosive spots on the culprit varix.

Definitions of initial hemostasis, very early rebleeding, treatment failure, and infection

Initial hemostasis was defined as achieving a 24-hour bleeding-free period within the first 48 hours after treatment together with stable vital signs based on modified Baveno consensus criteria.[19] Very early rebleeding was defined as upper gastrointestinal bleeding that occurred after initial hemostasis and within 5 days after enrollment. Treatment failure was defined as failure to control acute bleeding episodes or very early bleeding. Patients were diagnosed as having cirrhosis based on history, physical examinations, image studies or histological examination.

Definitions of infection were: 1) bacteremia: positive blood culture, but no definite focus identified; 2) spontaneous bacterial peritonitis: ascitic polymorphonuclear cells > 250/ mm^3; 3) pneumonia, confirmed by pneumonic patches on chest X-ray; 4) urinary tract infection: urine leukocytes > 15/HPF and/or positive urine culture with colony > 10^5/mL; 5) other infections: suspected by clinical, radiological or other bacteriological examination; 6) possible infection: fever > 38˚C more than 24 hours or leukocytosis with WBC > 12000/ mm^3 with left shift, but with negative blood culture.[10]

Statistical analysis

The data are expressed as mean ± S.D. Statistical analysis was based on an intention-to-treat principle. Quantitative variables were compared according to Student's t-test, and qualitative variables were compared with the Chi-square test and Fisher's exact test when appropriate. All P values were two-tailed. P value < 0.05 was considered significant. Analyses were performed using SPSS 12.0 software (SPSS Inc., Chicago, IL).

Results

In the 2005-2006 cohort, a total of 252 patients were screened, and 90 patients were included. In the 2012 cohort, 210 patients were screened and 113 patients were included. Patients excluded from the study were mostly due to incomplete data or presence of hepatocellular carcinoma. The baseline clinical data of both cohorts are shown in Table 1. Both groups were comparable in baseline characteristics such as etiologies of cirrhosis, severity of liver disease as shown by Child-Pugh's scores, and use of vasoconstrictors. However,

Table 1. Baseline data of both groups

	2005-2006 cohort (n = 90)	2012 cohort (n = 113)	*p* value
Age	52.07 ± 11.90	53.7 ± 12.61	0.35
Sex			0.03
Male	83 (92.2%)	93 (82.3%)	
Female	7 (7.8%)	20 (17.7%)	
Systolic pressure (mmHg)	117.48 ± 20.41	125.42 ± 29.13	0.02
GPT (U/L)	69.22 ± 86.40	56.42 ± 104.42	0.35
Hemoglobin (g/dL)	9.28 ± 2.46	8.40 ± 2.22	0.01
WBC (10^3/μL)	8.70 ± 4.01	7.63 ± 3.42	0.05
Platelets (10^3/μL)	116.50 ± 72.82	114.27 ± 62.83	0.82
Creatinine (mg/dL)	1.24 ± 0.55	1.38 ± 1.00	0.22
Etiology of Cause			0.42
Alcohol	36 (40%)	35 (31%)	
HBV	27 (30%)	31 (27.4%)	
HCV	22 (24.4%)	39 (34.5%)	
HBV + HCV	3 (3.3%)	3 (2.7%)	
Others	2 (2.2%)	5 (4.4%)	
Child-Pugh score			0.77
A	19 (21.1%)	28 (24.8%)	
B	42 (46.7%)	48 (42.5%)	
C	29 (32.2%)	37 (32.7%)	
EV bleeding	53 (58.9%)	83 (73.5%)	0.03
GV bleeding	37 (41.1%)	30 (26.5%)	0.03
Vasoconstrictors	81 (90%)	107 (94.7%)	0.21
Blood transfusion before endoscopy (units)	0.97 ± 1.21	2.11 ± 2.69	< 0.05
Blood transfusion after endoscopy (units)	2.78 ± 5.36	4.45 ± 6.97	0.06
Hoppitalization (days)	8.46 ± 5.93	9.75 ± 8.84	0.23

GPT: Glutamic pyruvic transaminase; WBC: White blood cell; HBV: Hepatitis B virus; HCV: Hepatitis C virus; EV: Esophageal varices; GV: Gastric varices

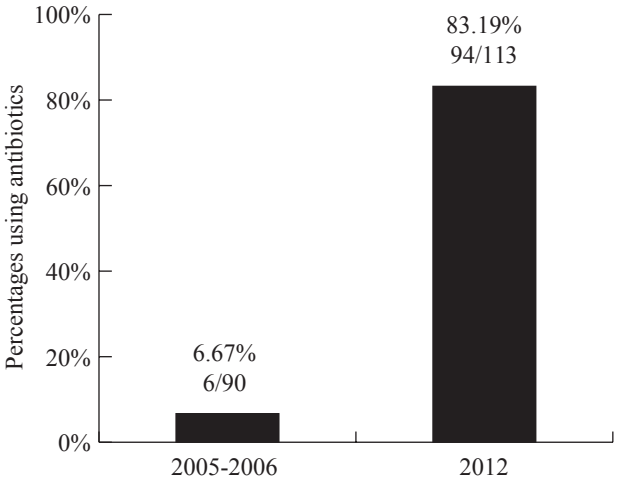

Fig. 1 A comparison of compliance to use antibiotic prophylaxis between 2005-2006 cohort and 2012 cohort ($p < 0.05$).

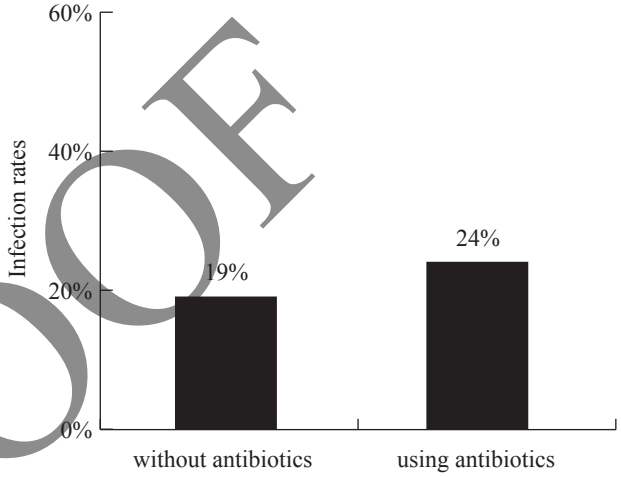

Fig. 2 A comparison of bacterial infection rates among patients receiving antibiotic prophylaxis and patients without antibiotic prophylaxis ($p > 0.05$).

the 2005-2006 cohort had a higher percentage of male patients and hemoglobin concentration, a higher incidence of gastric variceal bleeding, whereas a higher systolic blood pressure and amount of blood transfusion prior to endoscopic therapy were noted in the 2012 cohort.

In the 2005-2006 cohort, only 6 of 90 (6.7%) patients received prophylactic antibiotics, whereas 94 of 113 (83.2%) patients in the 2012 cohort received prophylactic antibiotics (Fig. 1). The difference is statistically significant ($p < 0.05$). In the 2005-2006 cohort, bacterial infections were encountered in 17 of 84 (20%) patients without receiving prophylactic antibiotics and 1 of 6 (17%) patients receiving prophylactic antibiotics ($p > 0.05$). Among the 2012 cohort, bacterial infections were encountered in 2 of 19 (10%) patients without receiving prophylactic antibiotics and 16 of 94

(17%) patients receiving prophylactic antibiotics (p = 0.73). If both cohorts were pooled together the incidence of bacterial infections was 19% among patients without receiving prophylactic antibiotics and 24% patients receiving prophylactic antibiotics (Fig. 2) (p = 0.43).

Table 2. Relationship between bacterial infections and Child-Pugh class (n = 44)

	Child-Pugh class			Total
	A	B	C	
Using antibiotics	3/20	9/45	12/35	24/100
Without antibiotics	1/27	9/45	10/31	20/103
Total	4/47 (8.5%)	18/90 (20%)	22/66 (33%)	44/203

Bacterial infections were significantly associated with severity of cirrhosis as shown by Child-Pugh class (p < 0.05)

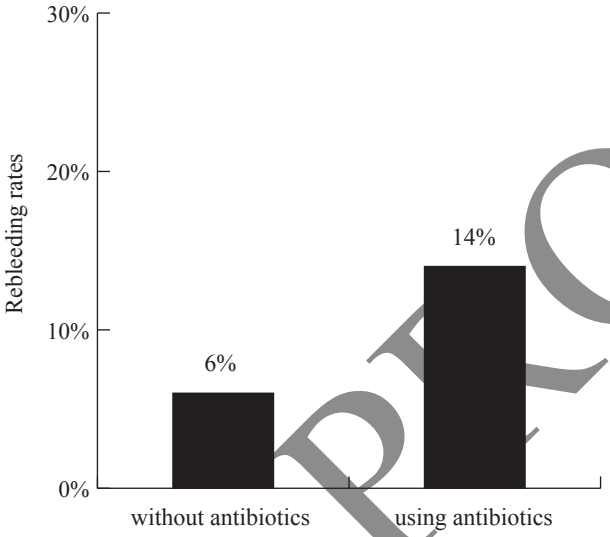

Fig. 3 A comparison of variceal rebleeding rates among patients receiving antibiotic prophylaxis and patients without antibiotic prophylaxis (p > 0.05).

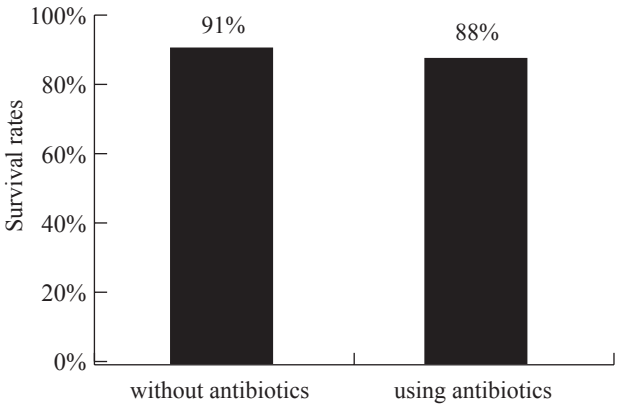

Fig. 4 A comparison of survival rates among patients receiving antibiotic prophylaxis and patients without antibiotic prophylaxis (p > 0.05).

Table 2 shows the relationship between bacterial infections and Child-Pugh's class among the 2 cohorts. Irrespective of the use of prophylactic antibiotics, the incidence of bacterial infections was significantly correlated with severity of liver disease shown by Child-Pugh's class (p < 0.05). The rebleeding rate was 14% among patients receiving prophylactic antibiotics and 6% among patients without prophylactic antibiotics (Fig. 3, p = 0.54).

The survival at discharge was 88% among patients receiving prophylactic antibiotics and 91% among patients without prophylactic antibiotics (Fig. 4, p = 0.45).

Discussion

Hemorrhage from gastro-esophageal varices is a devastating complication of portal hypertension. Although the in-hospital mortality of acute variceal bleeding was up to 40% about 20 years ago, it was decreased to about 15-20% in recent years.[20] One of the main reasons in the decrease of mortality has been ascribed to the alertness of clinicians in the treatment and prophylaxis of associated bacterial infections. The prevalence of bacterial infections in cirrhotic patients with gastrointestinal hemorrhage has been up to 52%-66%.[1-5] In 1985, Rimola et al was the first to perform a controlled trial to assess the role of prophylactic antibiotics among cirrhotic patients with gastrointestinal hemorrhage.[1] This study showed that bacterial infection was 34.7% in control patients and 16.2% in patients receiving prophylactic antibiotics. Since then a lot of controlled studies using different formula of prophylactic antibiotics to prevent bacterial infections have been reported. A meta-analysis of 8 randomized trials comparing patient outcomes with and without antibiotic

prophylaxis showed that bacterial infections decreased from 42% to 18% and mortality decreased from 22% to 18%.[7] Thus, international guidelines including Baveno Consensus for portal hypertension 2005, 2010 and American Association Society for Liver Diseases (AASLD) all recommended that antibiotic prophylaxis should be instituted for cirrhotic patients associated with upper gastrointestinal bleeding.[12-14] It is interesting to know whether clinicians are compliant with practice guidelines of antibiotic prophylaxis. The true impact of antibiotic prophylaxis on clinical outcomes has been largely unknown. The compliance with practice guidelines on screening esophageal varices and antibiotic prophylaxis during first variceal bleeding has been shown to reduce variceal bleeding.[21] The compliance with practice guidelines on antibiotic prophylaxis has rarely been studied.

Our study included 2 cohorts. Taking into consideration the increasing number of patients with variceal bleeding, the first cohort enrolled patients treated between 2005 and 2006 and the second cohort included patients treated in 2012 to make the sample sizes comparable. The incidence of gastric variceal bleeding was higher in the 2005-2006 cohort than that in the 2012 cohort. The amount of blood transfused was higher in the cohort 2012 than that in cohort 2005-2006. This may be owing to an increased severity of hemorrhage in the cohort 2 as shown by a lower hemoglobin level prior to endoscopy.

Our study showed that the use of prophylactic antibiotics was up to 83% in cohort 2, significantly higher than the figure of 6.7% in cohort 1 (Fig. 1). These data suggested high compliance of our clinicians with the practice guidelines on the use of prophylactic antibiotics among cirrhotic patients with variceal bleeding in recent years. However, the infection rates were similar between cohort 1 and cohort 2. When pooled together, the bacterial infection rates were 19% in patients without prophylactic antibiotics and 24% in patients receiving prophylactic antibiotics (Fig. 2). Moreover, the rebleeding rates were similar between patients with prophylactic antibiotics and those without. Our results are in sharp contrast to previous findings showing that bacterial infections were lower in patients receiving prophylactic antibiotics than those without prophylactic antibiotics and that rebleeding rates were lower in patients with prophylactic antibiotics than those without.[7,22-27] A few factors may be responsible for the discrepancy. First, this is a retrospective study, a lot of patients were excluded due to incomplete data collection or presence of hepatocellular carcinoma. Blood cultures were not routinely performed. Some patients with bacterial infection may be missed clinically. Second, patients with apparent infection on index hemorrhage were excluded. As shown in the study by Bernard, patients with variceal bleeding usually got infections on the first day of bleeding. The use of prophylactic antibiotics after first day of bleeding would hamper its effectiveness. Third, bacterial infection rate was up to 62% in the study of Goulis. This may be attributed to the presence of indwelling central venous and urinary catheters in almost all patients in that study.[5] Variceal rebleeding was only 14% in our study, which was apparently lower than the figure of 47% in Goulis's study. It has been demonstrated that bacterial infections were associated with failure to control bleeding but not mortality.[4] Therefore, a lower incidence of bacterial infections would be expected in patients with a higher success rate in the control of hemorrhage as well as avoidance of routine use of central venous catheters and urinary catheters. Fourth, the proportion of alcoholic cirrhosis in our study patients was lower than the figures in western studies. Lastly and most importantly, patients here with esophageal variceal bleeding were usually treated with endoscopic variceal ligation instead of sclerotherapy, while sclerother-

apy was still the preferred endoscopic treatment strategy in some European countries. A study from Lo et al. suggested that the incidence of bacterial infections was significantly higher in patients receiving sclerotherapy than those undergoing banding ligation.[28]

The present study showed that most clinicians at our hospital were compliant with the practice guidelines on prophylactic antibiotics in cirrhotic patients with variceal bleeding. Although high compliance with guideline generally represents good health care quality management, this does not always mean improved clinical outcomes.[29] Previous studies on the relationship between guidelines on the use of prophylactic antibiotics and incidences of bacterial infections had contradictory clinical outcomes.[29-30] Further prospective study is still required to evaluate the correlation between compliance with guidelines of antibiotic prophylaxis and bacterial infections and hemostasis in cirrhotic patients with variceal bleeding.

In conclusion, our study showed that compliance with the practice guidelines on the use of prophylactic antibiotics in cirrhotic patients with variceal bleeding has been significantly enhanced at our hospital in recent years. Probably due to highly effective hemostasis and a low incidence of bacterial infection associated with banding ligation, the incidences of bacterial infections and rebleeding were not affected by the use of prophylactic antibiotics in the current study. Prospective study is still required to clarify the issue regarding the use of prophylactic antibiotics and bacterial infections among patients with high hemostatic rate achieved by banding ligation alone.

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