Antibiotic Prophylaxis After Endoscopic Therapy Prevents Rebleeding in Acute Variceal Hemorrhage: A Randomized Trial

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Bacterial infection may adversely affect the hemostasis of patients with gastroesophageal variceal bleeding (GEVB). Antibiotic prophylaxis can prevent bacterial infection in such patients, but its role in preventing rebleeding is unclear. Over a 25-month period, patients with acute GEVB but without evidence of bacterial infection were randomized to receive prophylactic antibiotics (ofloxacin 200 mg i.v. q12h for 2 days followed by oral ofloxacin 200 mg q12h for 5 days) or receive antibiotics only when infection became evident (on-demand group). Endoscopic therapy for the GEVB was performed immediately after infection work-up and randomization. Fifty-nine patients in the prophylactic group and 61 patients in the on-demand group were analyzed. Clinical and endoscopic characteristics of the gastroesophageal varices, time to endoscopic treatment, and period of follow-up were not different between the two groups. Antibiotic prophylaxis decreased infections (2/59 vs. 16/61; $P < .002$). The actuarial probability of rebleeding was higher in patients without prophylactic antibiotics ($P = .0029$). The difference of rebleeding was mostly due to early rebleeding within 7 days (4/12 vs. 21/27, $P = .0221$). The relative hazard of rebleeding within 7 days was 5.078 (95% CI: 1.854–13.908, $P < .0001$). The multivariate Cox regression indicated bacterial infection (relative hazard: 3.85, 95% CI: 1.85–13.90) and association with hepatocellular carcinoma (relative hazard: 2.46, 95% CI: 1.30–4.63) as independent factors predictive of rebleeding. Blood transfusion for rebleeding was also reduced in the prophylactic group (1.40 ± 0.89 vs. 2.81 ± 2.29 units, $P < .05$). There was no difference in survival between the two groups. In conclusion, antibiotic prophylaxis can prevent infection and rebleeding as well as decrease the amount of blood transfused for patients with acute GEVB following endoscopic treatment. (HEPATOLOGY 2004;39:746–753.)

Patients with cirrhosis complicated by gastroesophageal variceal hemorrhage (GEVB) are characterized by high mortality and rebleeding rates.[1] About one-third of patients with conservative treatment die at the index bleeding.[1] Among those who survive, subsequent rebleeding occurs in another third within 6 weeks of the index bleeding, and more than 80% of the rebleeding episodes occur within 2 weeks.[1] In patients with concomitant hepatocellular carcinoma (HCC) or gastric varices, the bleeding morbidity and mortality is even higher.[2–5] In the past few years, endoscopic variceal ligation (EVL) and tissue glue injection (EVS) have resulted in significant reductions in the rate of variceal rebleeding.[6–11] EVL has recently evolved to become the optimal endoscopic method to treat hemorrhage from esophageal varices, while EVS is now the promising endoscopic method to treat hemorrhage from gastric varices.[12,13] However, the rebleeding rate following endoscopic treatment is still high, at around 25–50%.[6–11] Therefore, how to further reduce the rebleeding rate remains an important issue.

Patients with cirrhosis and gastrointestinal bleeding (GIB) are particularly vulnerable to infections[14] because of their immunocompromised state, increased bacterial translocation in cirrhotic patients, the disruption of the intestinal mucosal barrier, and the frequent invasive manipulations during hemorrhage.[15–18] Bacterial infections

Abbreviations: GEVB, gastroesophageal variceal bleeding; EVL, endoscopic variceal legation: EVS, tissue glue injection; GIB, gastrointestinal bleeding; HCC, hepatocellular carcinoma.

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are documented in up to 66% of cases in patients with cirrhosis and GIB; antibiotic prophylaxis may decrease the incidence of infection.[19–24] Bacterial infections were also found to have a negative impact on hemostasis.[25–27] However, no controlled trial has been conducted and no study published to clarify the advantage of antibiotic prophylaxis in decreasing gastroesophageal variceal rebleeding after endoscopic treatment. If the hypothesis is true, such a study would provide solid evidence to further justify the prophylactic use of antibiotics in these patients.

Patients and Methods

Patients

From January 2001 to February 2003, all patients with cirrhosis who presented to our hospital with acute GIB, or those already hospitalized developing acute GIB, received emergency endoscopy unless prevented by severe encephalopathy, severe hemodynamic instability, or the patient's refusal. Only patients who had endoscopy-proven GEVB without signs of infection were included. Informed consent from the patients or their families was obtained.

Patients were excluded from the study if they met the following criteria. First, the patient's age was younger than 18 years or older than 80 years. Second, the patient had a terminal illness of any major organ system, like heart failure, uremia, COPD, or nonhepatic malignancy. Third, the patient had a history of surgical or endoscopic treatment of gastroesophageal varices, or if the patient received antibiotics within the last 2 weeks. Patients were subsequently excluded when initial bacteriological sampling turned out positive (occult infection). The diagnosis of liver cirrhosis was based on needle liver biopsy findings or, if unavailable, the combination of clinical, biochemical findings and radiological findings of hepatic failure and portal hypertension as well as a known cause of cirrhosis. The diagnosis of HCC was based on cytohistological criteria or liver biopsy or, if unavailable, two coincident imaging studies as well as one imaging study associated with AFP more than 400 ng/mL.[28] The study was approved by the Clinical Research Committee of the Veterans General Hospital in Taipei.

Randomization

Patients who fulfilled the inclusion criteria were immediately randomized to the two treatment groups by using consecutively numbered envelopes that contained the treatment assignments, which were generated by a computer-allocated random digit number. Patients in the prophylactic group received antibiotic treatment right after randomization with intravenous ofloxacin 200 mg q12h for 2 days and followed by oral ofloxacin 200 mg q12h for 5 days. Patients in the on-demand group received antibiotic therapy only when infection was suspected or established. Antibiotics were changed according to the antibiotic sensitivity test of cultured microorganisms.

Infection Assessment

All patients were closely monitored with special emphasis on the detection of bacterial infection through the hospitalization period. A careful physical examination, complete white blood cell count, chest radiography, urine sediment, urine culture, ascitic fluid neutrophil count and culture, and blood culture were routinely performed before randomization. Physical examination was performed at least once per day during hospitalization. If a new infection was suspected, the same procedures to assess infection were performed at admission. New infections were suspected when there was fever (>38°C), hypothermia (<36°C), unexpected hemodynamic instability, tachypnea, new onset of chest symptoms, dysuria, abdominal pain, distention, as well as alteration of mental state. A central venous catheter or urinary catheter were inserted only when clinically indicated.

Endoscopic Treatment Procedures

Before endoscopic treatment, vasoactive agents including terlipressin, somatostatin or balloon tamponade were allowed. If active bleeding was found during endoscopy, endoscopic treatment was performed immediately. All of the EVL or EVS were performed as soon as possible, but were completed within 24 hours of admission or bleeding onset. After endoscopic treatment, vasoactive agents were discontinued. EVL was performed using an Olympus XQ-230 videoendoscope (Olympus Optical Co., Tokyo, Japan) with endoscopic ligating devices (Bard International Products, Tewksbury, MA), and an overtube, or multiband ligators (Wilson-Cook Medical, Winston-Salem, NC). No more than 10 rubber bands were used in each session.

EVS was performed using an Olympus XQ-230 videoendoscope and a 23-g disposable injection needle (EIS 01943, Top Co., Tokyo, Japan) by means of an intravariceal injection with the 1:1 mixture of 0.5 ml N-butyl-2-cyanoacrylate (Histoacryl blue, Braun-Melsungen, Germany) and 0.5 ml Lipiodol (Guerbet Laboratory, Aulnay-Sous-Bris, France) in each shot. No more than 4 shots were performed in each session.

Clinical Assessment and Follow-up

Information regarding presentation of GEVB was carefully gathered from the patients and their families. Vital signs and the amount of blood transfusion before and after endoscopic treatment were recorded. Endoscopic treatment was performed weekly for the first 3

weeks when possible, then treatment was performed every 3 weeks until the varices were eradicated. Follow-up endoscopy was subsequently performed every 3 months and, if unremarkable twice, was moved to every 6 months. If rebleeding occurred, vasoactive agents, including terlipressin or somatostatin, or balloon tamponade were allowed before performing emergency endoscopy to identify the bleeding site. Bleeding esophageal varices were ligated and bleeding gastric varices were injected with tissue glue again. If the rebleeding site was associated with extensive ulceration, which prevented further endoscopic treatment, conservative treatment or surgery was allowed. The outcomes assessed in this study were infection, rebleeding, and mortality. Patients were followed-up until death or 3 months after the last patient was included and the desired sample size was reached.

Definition

The severity of esophageal varices was graded based on the system suggested by Beppu et al.[29] The severity of cirrhosis was classified according to Pugh's modification of Child's classification.[30]

GEVB was diagnosed by: 1) clinical signs of hematemesis, coffee ground vomitus, hematochezia, or melena; 2) endoscopic signs of active bleeding, adherent blood clots, white nipple signs, or erosions on varices; and/or 3) large varices with a red-color sign without other bleeding sources.[31] Rebleeding was defined as a new onset of hematemesis, coffee-ground vomitus, hematochezia, or melena, with an increasing pulse rate over 110 bpm and decreasing blood pressure below 90 mm Hg after a 24-hour period of stable vital signs and hematocrit following endoscopic treatment. Rebleeding within 7 days of enrollment after initial control of bleeding was defined as early rebleeding. Treatment failure was defined as failure to control active bleeding after two attempts of endoscopic treatment, rebleeding more than twice, or bleeding death. Rebleeding index for each patient was calculated by dividing the months of follow-up by the number of rebleeding episodes plus one.

The diagnosis of spontaneous bacterial peritonitis was based on $\geq$250 neutrophils/μl in ascitic fluid.[32] The diagnosis of bacteremia was based on positive blood culture and clinical signs or symptoms of infection (such as fever $>$38°C, hypothermia $<$36°C, alteration in mental status, and a greater than expected hemodynamic instability and oliguria) without other recognized cause. Urinary tract infection was based on the positive urine culture of $\geq 10^5$ colonies/mL with urine neutrophil count of $>$10 neutrophils/μL and associated clinical pictures. Respiratory infections were diagnosed by clinical symptoms and signs and positive chest X-ray findings. Patients without any identified infection source but with fever $>$38°C and leukocytosis $>$11,000/μl with neutrophilia were considered as having possible infections and received on demand antibiotics. In analyzing the incidence of infection and determining the effect of antibiotic prophylaxis, only infectious episodes occurring from inclusion into the trial to 10 days or those occurring during the first hospitalization were considered. Therefore, the infection rate was compared by number of events in this period.

Statistical Analysis

The results were expressed as mean $\pm$ SD. Each continuous parameter between the two treatment groups was analyzed with two sample Student's t tests. Categorical data were examined using the χ^2 test with Yate's correction. A 95% confidence interval (CI) of their differences was computed using the assumption of Z distribution. Kaplan-Meier analysis was used to examine the time of first recurrent bleeding and the time to death and the log-rank test was used to compare differences between the groups. Univariate analysis and stepwise multivariate analyses were performed to assess the potential risk factors of recurrent bleeding and survival using the Cox proportion hazards regression with SPSS 11.0 for Windows (SPSS, Chicago, IL). Covariate of infection was considered a time-dependent event in the multivariate Cox regression. The significance level was $P < .05$.

The rebleeding rate of patients with liver cirrhosis or concomitant HCC and esophageal or gastric variceal bleeding after endoscopic treatment, without special emphasis on antibiotics treatment, is 30–50%. Estimates of sample size were based on a rebleeding rate assumed to be 20% for the prophylactic antibiotics group and 45% for the demand antibiotics group. The type I (alpha) error and type II (beta) error were set to 0.05 and 0.2, respectively. The proposed sample size was 54 per group calculated by SigmaStat (SigmaStat Statistical Software, Version II, Jandel Scientific, San Rafael, CA).

Results

Demographics

In all, 172 patients were recruited and randomized. Seventeen patients in the prophylactic group and 19 patients in the on-demand group were excluded from analysis due to occult infections. Nine patients in the prophylactic group and 7 patients in the on-demand group were further excluded due to the inability to attend follow-up or their refusal to continue in the study. Therefore, 59 patients in the prophylactic group and 61 patients in the on-demand group were included for analysis. Except for Child-Pugh's score appearing higher and serum creatinine appearing lower in the prophylactic group,

Table 1. Clinical Characteristics of Patients with Variceal Bleeding Following Endoscopic Treatment Regarding Prophylactic and On-demand Use of Antibiotics

	Prophylactic Antibiotics (n = 59)	On-demand Antibiotics (n = 61)	*P*-Value
Age (year)	60.02 ± 13.92	59.39 ± 14.85	0.813
Sex (M/F)	43/16	48/13	0.597
Viral/alcohol/mixed/others	29/6/10/14	34/10/10/7	0.297
Hepatocellular carcinoma (±)	16/43	14/47	0.757
Child-Pugh's A/B/C	10/35/14	19/29/13	0.196
Child-Pugh's score	8.54 ± 1.90	7.90 ± 2.04	0.071
Albumin (g/dL)	2.86 ± 0.42	3.99 ± 0.43	0.109
Bilirubin (mg/dL)	2.90 ± 3.48	2.19 ± 1.50	0.151
Prothrombin time ↑ (sec.)	3.50 ± 3.04	2.70 ± 2.60	0.125
Ascites (±)	33/26	29/32	0.465
Encephalopathy (±)	8/51	5/56	0.517
Hematocrit (%)	28.85 ± 7.02	27.89 ± 5.50	0.405
Creatinine (mg/dL)	1.05 ± 0.38	1.19 ± 0.47	0.076
Platelet (K/cumm)	106.19 ± 50.63	98.69 ± 50.26	0.417
WBC (/cumm)	7140.68 ± 3115.78	6814.10 ± 2995.73	0.559
Hematemesis or hematochezia (±)	53/6	53/8	0.834
Blood transfusion (unit)	3.49 ± 2.32	4.10 ± 2.94	0.213
Active spurting or oozing (±)	17/42	14/47	0.600
Bleeding from esophageal/gastric varices	49/10	50/11	0.937
Urinary catheterization (±)	4/55	6/55	0.786
Time, bleeding to endoscopic treatment (h)	8.27 ± 5.52	9.55 ± 5.82	0.219
Follow-up period (day)*	255 (22,843)	270 (6,851)	1.000

*Median (range).

both groups had otherwise similar demographic data, association of HCC, hepatic functional reserve, severity of bleeding, endoscopic characteristics of gastroesophageal varices, time to endoscopic treatment, and period of follow-up (Table 1).

Infection Outcomes and Bacteriology

The incidence of bacterial infection was lower in patients receiving antibiotic prophylaxis (2/59, 3.4% vs. 16/61, 26.2%) (Table 2). Similarly, bacteremia occurred more frequently in patients without antibiotic prophylaxis (0/59 vs. 9/61, $P < .01$). Urinary tract infection was the second most common source of infection. Enteric bacteria were more frequently identified in patients without antibiotic prophylaxis (0/59 vs. 12/61, $P = .001$).

Hemostatic Outcomes

Successful control of active bleeding of either spurting or oozing was not different between the two groups (17/17 vs. 13/14). More patients and more episodes of rebleeding occurred in patients without antibiotic prophylaxis (Table 3). The difference of rebleeding was mostly due to early rebleeding within 7 days (4/12 vs. 21/27, $P = .0221$). The relative hazard of rebleeding within 7 days was 5.078 (21/61 vs. 4/59; 95% CI: 1.854–13.908, $P < .0001$) and 4.449 within 14 days (23/61 vs. 5/59; 95% CI: 1.812–10.926, $P < .0001$). The cumulative rebleeding rate was also higher in patients without antibiotic prophylaxis (Fig. 1). The rebleeding sources were not different between the two groups. Thirteen of the 18 (72.2%) infected patients had rebleeding when compared to 26 of the 102 (25.5%) noninfected patients

Table 2. Infection Outcomes and Bacteriology in Patients With Variceal Bleeding Following Endoscopic Treatment in Relation to Prophylactic and On-demand Antibiotics Use

	Prophylactic Antibiotics (n = 59)	On-Demand Antibiotics (n = 61)	*P*-Value
Number of infection patients (events)	2	16 (18)*	0.0014
Source			
Bacteremia	0	7 (9)	0.0229
Pneumonia	0	2	0.492
Spontaneous bacterial peritonitis	1	2	0.977
Urinary tract infection	1	5	0.229
Enteric bacteria	0	12	0.001
Escherichia coli	0	4	0.145
Klebsiella pneumoniae	0	4	0.145
Enterobacter cloacae	0	2	0.492
Proteus mirabilis	0	1	0.988
Aeromonas hydrophila	0	1	0.988
Nonenteric bacteria	2	6	0.295
Streptococcus viridans	1	3	0.639
Streptococcus pneumoniae	0	1	0.988
Staphyllococcus aureus	1	2	0.977

NOTE. Two of 2 infected patients in prophylactic antibiotics group and 11 of 16 infected patients in demand antibiotics group have rebleeding.

*Two patients had different microorganisms cultured from different infection sites.

Table 3. Hemostatic Outcome in Patients With Variceal Bleeding Following Endoscopic Treatment in Relation to Prophylactic and On-demand Antibiotics Use

	Prophylactic Antibiotics (n = 59)	On-Demand Antibiotics (n = 61)	*P*-Value
No. of rebleeding patients (episodes)	12 (14)	27 (39)	0.0094
Time of rebleeding*			
24 to 48 hours	4 (4)	12 (12)	0.770
3 to 7 days	0	9 (13)	0.065
7 to 14 days	1 (3)	2 (3)	0.584
15 to 42 days	7 (7)	2 (7)	0.0029
> 6 weeks	0	2 (4)	0.894
Sources of rebleeding†			
Esophageal varices	4	14	0.875
Esophageal ulcers	4	12	0.861
Gastric varices	4	10	0.892
Portal hypertensive gastropathy	0	1	0.591
Rectal varices or hemorrhoid	1	0	0.591
Undetermined	1	2	0.694
Rebleeding index (months/episode)‡	9.33 (0.83-25.96)	6.85 (0.67-28.20)	0.450
Blood transfusion for rebleeding (unit)	1.40 ± 0.89	2.81 ± 2.29	0.030
Treatment failure	2	6	0.295

*Early (≤7 days) rebleeding rate is lower in the prophylactic group regardless of rebleeding patient's number (4/12 vs. 21/27, $P = 0.0221$) or rebleeding episodes (4/14 vs. 25/39, $P = 0.0485$).

†Rebleeding rate is still lower in prophylactic group (16/59 vs. 30/61, $P = 0.0226$) if bleeding from non-portal hypertension sources (such as peptic ulcer & Mallory-Weiss syndrome) were included.

‡Median (range).

($P < .001$). Early rebleeding also likely occurred in infected patients (9/18, 50% vs. 16/102, 15.7%; $P < .005$).

Univariate analysis showed the rebleeding risk significantly linked to antibiotic prophylaxis, presence of HCC, urinary catheterization and bacterial infection (Table 4). On multivariate analysis of significant risk factors on univariate analysis, bacterial infection (relative hazard: 3.85, 95% CI: 1.85–13.90) and the association of HCC (presence vs. absence of HCC, relative hazard: 2.46, 95% CI: 1.30–4.63) were the two independent determinants of rebleeding. The amount of blood transfused for each episode of rebleeding was increased in patients without antibiotic prophylaxis (Table 3). Two cases of treatment failure in the prophylactic group were due to bleeding death. Six cases of treatment failure in the on-demand group were due to bleeding death (4) and more than two episodes of rebleeding (2).

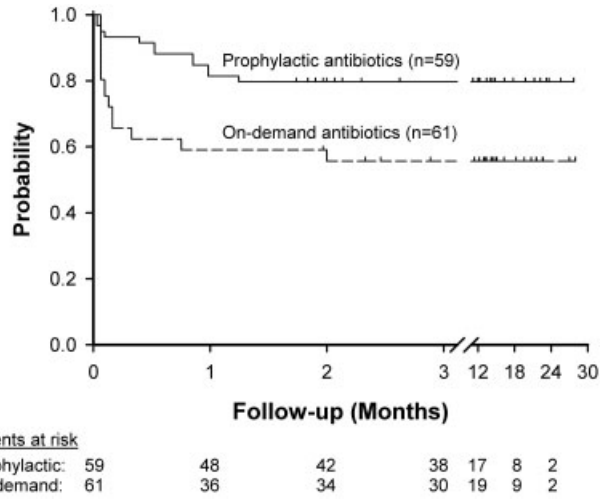

Fig. 1. Actuarial probability of remaining free of rebleeding in the liver cirrhotic patients with variceal bleeding following endoscopic treatment, in terms of prophylactic and on-demand antibiotics use. The difference between the two groups was significant ($P = .0029$).

Mortality and Survival

Sixteen patients and 13 patients died in the prophylactic and on-demand group, respectively. Hospital mortality and 30-day mortality were not different between the two groups (Table 5). End-stage liver disease with hepatic failure or multiorgan failure was the most common cause of death. The overall rate of survival was similar between the two groups even after excluding the patients with concomitant HCC (Fig. 2A,B). Univariate analysis showed that the survival was significantly linked to presence of HCC, Child-Pugh's score, urinary catheterization and first episode of rebleeding (Table 4). On multivariate analysis, the association of HCC (presence vs. absence of HCC, relative hazard: 19.11, 95% CI: 7.20–50.74) and hepatic reserve (each Child-Pugh's score, relative hazard: 1.33, 95% CI: 1.10–1.62) were two independent risk factors determining survival.

Table 4. Univariate Analysis of Potential Risk Factors for Rebleeding and Mortality in Patients With Variceal Bleeding Following Endoscopic Treatment

	Rebleeding			Mortality		
Variables	Relative Hazard	95% Confidence Interval	*P*-Value	Relative Hazard	95% Confidence Interval	*P*-Value
Antibiotic prophylaxis	0.378	0.191–0.747	0.005	0.786	0.612–2.645	0.519
Hepatocellular carcinoma	2.519	1.333–4.739	0.004	27.883	8.264–58.824	0.0001
Child-Pugh's score	1.051	0.889–1.244	0.557	1.393	1.178–1.648	0.0001
Creatinine (mg/dL)	1.358	0.371–1.464	0.383	1.872	0.827–4.235	0.172
Hematemesis or hematochezia	1.110	0.394–3.124	0.843	1.474	0.346–6.289	0.600
Active spurting or oozing	1.326	0.660–2.660	0.429	2.338	0.813–6.724	0.115
Bleeding from gastric varices	1.151	0.529–2.506	0.723	29.075	0.001–1.650	0.088
Blood units transfused	0.983	0.876–1.103	0.774	1.009	0.001–1.650	0.905
Urinary catheterization	3.745	1.553–9.091	0.003	7.692	2.747–21.277	0.0001
Bacterial infection	3.937	2.012–9.091	0.0001	1.294	0.492–3.401	0.601
Rebleeding	–	–	–	2.832	1.364–5.882	0.005

Discussion

Despite recent advances in the endoscopic and pharmacological treatment of variceal hemorrhage, the rebleeding rate is still high at around 25–35%.[6–9] The rebleeding rate is even higher in patients with concomitant HCC or gastric varices.[2–5] Upper GIB was associated with bacterial infection in up to 66% of patients with cirrhosis.[19–24] The close association of GIB with infection in cirrhosis is possible related to an interactive causal relationship. It is hypothesized that bacterial infection and endotoxemia trigger a cytokine cascade with release of vasoactive substances, leading to an increase of variceal pressure and impairment of primary hemostasis which in turn leads to variceal bleeding.[33] Indeed, bacterial infections were recently identified to be independently associated with failure to control GIB within 5 days and associated with early rebleeding.[25,26]

We also found that infection or the potential for infection is the only risk factor for rebleeding after endoscopic treatment of variceal bleeding.[27] Thus, the critical role of bacterial infection in determining the outcome of GEVB should never be overlooked. However, the main endpoints of most studies regarding antibiotic prophylaxis in cirrhosis with upper GIB were bacterial infections.[19–23] Neither special emphasis nor meticulous assessment of rebleeding was made.[19–23] Moreover, the population included in those studies was heterogeneous, usually mixed with diseases of highly variable rebleeding risk, such as variceal hemmorhage and peptic ulcer bleeding.[19–24] Furthermore, those populations with variceal bleeding were not controlled well by EVL or EVS, which also has an inherent impact on rebleeding.[19–24] Endoscopic treatment of acute GEVB, either by EVL for esophageal varices or by EVS for gastric varices, was suggested as a treatment choice and is becoming widely used.[6–13] This study is possibly the first randomized trial narrowing the heterogeneity of population to GEVB and a restriction to those undergoing standard endoscopic treatment.

Table 5. Mortality and Survival in Patients With Variceal Bleeding Following Endoscopic Treatment in Relation to Prophylactic and On-demand Antibiotics Use

	Prophylactic Antibiotics (n = 59)	On-Demand Antibiotics (n = 61)	*P*-Value
Mortality	16	13	0.597
Hospital mortality	2	3	0.799
30 days mortality	2	1	0.858
Causes of death			
Hepatic failure	9	5	0.566
Bleeding	2	4	0.459
Sepsis	2	2	0.756
Multiple organs failure	3	2	0.799

Consistent with previous studies, enteric aerobic Gram-negative bacteria are the most common causative organisms in patients with acute GIB.[19–23] This study further proved the effectiveness of a quinolone in preventing Gram-negative bacterial infection in these patients; however, Gram-positive bacterial infection appeared not to be prevented by quinolones.[20,21,23] This finding can be easily be explained by the antibacterial spectrum of olfloxacin, which is more active against Gram-negative bacilli.[34,35]

In addition, the overall rebleeding rate was lower and the amount of blood transfused for rebleeding was markedly decreased in patients with antibiotic prophylaxis. These results echo the findings of Burroughs and colleagues,[26] where bacterial infections were associated with failure to control bleeding within 5 days. It is noteworthy that the rebleeding events were particularly reduced in the early period. The findings further strengthen the critical

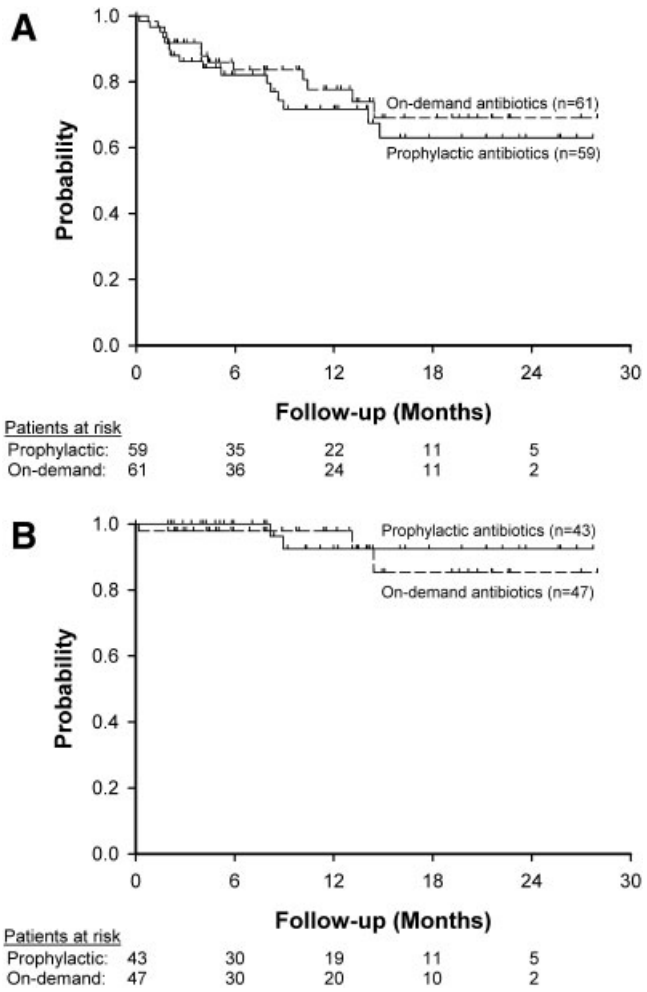

Fig. 2. (A) Actuarial probability of survival in the liver cirrhotic patients with variceal bleeding following endoscopic treatment, in terms of prophylactic and on-demand antibiotics use. The difference between the two groups was not significant ($P = .523$). (B) Actuarial probability of survival in the liver cirrhotic patients without concomitant hepatocellular carcinoma and with variceal bleeding following endoscopic treatment, in terms of prophylactic and on-demand antibiotics use. Sixteen patients of the prophylactic group and 14 patients of the on-demand group had concomitant hepatocellular carcinoma, and thus were not included in the survival comparison. The difference between the two groups was not significant ($P = .518$).

role of antibiotic prophylaxis as acute infection leads to an impairment of primary hemostasis and variceal rupture, which can be prevented and corrected. Other than antibiotic prophylaxis, the presence of HCC is another independent predictor of rebleeding. Historical studies have found that the rebleeding rate in patients with HCC and EVB following EVL is around 50–60%, which is almost double the rebleeding rate of those patients without HCC.[2,3,10] The mechanisms behind the high rate of recurrent bleeding associated with HCC are arterioportal shunting, portal vein thrombosis, as well as a more rapid deterioration of hepatic reserve, which leads to a higher portal vascular resistance and pressure.[36,37] Certainly, infection and the presence of HCC were not the only risk factors for rebleeding. Other well-known risk factors include continuous drinking in patients with alcoholic liver cirrhosis, poor hepatic reserve, as well as higher portal pressure or variceal pressure. Therefore, abstinence of alcohol should be encouraged and use of vasoactive agents to decrease portal pressure cannot be overemphasized.

Although the rebleeding events were reduced and the amount of blood transfusion for rebleeding was also decreased in patients who received prophylactic antibiotics, these beneficial effects are not reflected in terms of mortality and survival. The lack of influence of antibiotic prophylaxis on mortality is likely the result of infection not being an independent predictive factor for survival. That rebleeding is short of a significant impact on survival is possibly due to the fact that most rebleeding episodes can be further controlled by repeated endoscopic treatments and patients can finally be stabilized after resuscitation. Actually, most patients died of hepatic failure or multiorgan failure.

Although the use of short-term prophylactic antibiotics in patients with GEVB is merited by the reduction of bacterial infection and rebleeding, emergence of resistance is usually the major concern of antibiotic prophylaxis. Indeed, quinolone-resistant microorganisms are rapidly rising[38,39]; however, the development of quinolone resistance is found mostly in patients with long-term and outpatient prophylaxis.[40,41] Short-term and inpatient prophylaxis seems safe and the emergence of resistance in this group needs further evaluation.

In all, this study provided direct evidence that antibiotic prophylaxis and the early use of antibiotics are critically important in decreasing bacterial infection and rebleeding and, at the same time, decreasing the need for blood transfusion following rebleeding in patients with GEVB after endoscopic treatment. Although the results are promising, more evidence should be developed and further studies required on the cost–benefit analysis because these results are of prime importance in justifying the treatment strategy of patients with GEVB.

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References

1. Graham DY, Smith JL. The course of patients after variceal hemorrhage. Gastroenterology 1981;80:800–809.
2. Ng WD, Chan YT, HO KK, Kong CK. Injection sclerotherapy for bleeding esophageal varices in cirrhotic patients with hepatocellular carcinoma. Gastrointest Endosc 1989;35:69–70.
3. Lo GH, Lin CY, Lai KH, Malik U, Ng WW, Lee FY, Lee SD, et al. Endoscopic injection sclerotherapy versus conservative treatment for patients with unresectable hepatocellular carcinoma and bleeding esophageal varices. Gastrointest Endosc 1991;37:161–164.

4. Merican I, Burroughs AK. Gastric varices. Eur J Gastroenterol 1991;4: 511–520.
5. Sarin SK, Lahoti D, Saxena SP, Murthy N, Makwana UK. Prevalence, classification and natural history of gastric varices: a long-term follow-up study in 568 portal hypertension patients. HEPATOLOGY 1992;16:1343–1349.
6. Stiegmann GV, Goff JS, Michaletz-Onody PA, Korula L, Leiberman D, Saeed ZA, Reveille RM, et al. Endoscopic sclerotherapy as compared with endoscopic ligation for bleeding esophageal varices. N Engl J Med 1992; 326:1527–1532.
7. Hou MC, Lin HC, Kuo BIT, Chen CH, Lee FY, Lee SD. Comparison of endoscopic variceal injection sclerotherapy and ligation for the treatment of esophageal variceal hemorrhage: a prospective randomized trial. HEPATOLOGY 1995;21:1517–1522.
8. D'Amico G, Pagliaro L, Bosch J. The treatment of portal hypertension: a meta-analytic review. HEPATOLOGY 1995;22:332–354.
9. Laine L, Cook D. Endoscopic ligation compared with sclerotherapy for treatment of esophageal variceal bleeding. A meta-analysis. Ann Intern Med 1995;123:280–287.
10. Chen WC, Hou MC, Lin HC, Lee FY, Yeh YY, Chang FY, SD Lee. Feasibility and potential benefit of maintenance endoscopic variceal ligation in patients with unresectable hepatocellular carcinoma and acute esophageal variceal hemorrhage: a controlled trial. Gastrointest Endosc 2001;54:18–23.
11. Lo GH, Lai KH, Cheng JS, Chen MH, Chiang HT. A prospective, randomized trial of butyl cyanoacrylate injection versus band ligation in the management of bleeding gastric varices. HEPATOLOGY 2001;33:1060–1064.
12. Bosch J, Laine L, Burroughs AK, Macon N, Nevens F, Silvain C, Vinel JP. Baveno III consensus statements: treatment of the acute bleeding episodes. In: De Franchis R, ed. Portal hypertension III. Proceedings of the Third Baveno International Consensus Workshop on definitions, methodology and therapeutic strategies. Oxford: Blackwell Science, 2001:168–169.
13. Binmoeller K. Glue for gastric varices: some sticky issues. Gastrointest Endosc 2000;20:298–301.
14. Bleichner G, Boulanger R, Squara P, Sollet JP, Parent A. Frequency of infections in cirrhotic patients presenting with acute gastrointestinal hemorrhage. Br J Surg 1986;73:724–726.
15. Rimola A, Soto R, Bory F, Arroyo V, Piera C, Rodes J. Reticuloendothelial system phagocytic activity in cirrhosis and its relation to bacterial infections and prognosis. HEPATOLOGY 1984;4:53–58.
16. Rajkovic IA, Williams R. Abnormalities of neutrophil phagocytosis, intracellular killing, and metabolic activity in alcoholic liver cirrhosis and hepatitis. HEPATOLOGY 1986;6:252–262.
17. Garcia-Tsao G, Lee FY, Barden GE, Cartun R. West AB. Bacterial translocation to mesenteric lymph nodes is increased in cirrhotic rats with ascites. Gastroenterology 1995;108:1835–1841.
18. Deitch EA, Morrison J, Berg R, Specian RD. Effect of hemorrhagic shock on bacterial translocation, intestinal morphology, and intestinal permeability in conventional and antibiotics-decontaminated rats. Crit Care Med 1990;18:529–536.
19. Rimola A, Bory F, Teres J, Perez-Ayuso RM, Arroyo V, Rodes J. Oral nonabsorbable antibiotics prevent infection in cirrhotics with gastrointestinal hemorrhage. HEPATOLOGY 1985;5:463–467.
20. Soriano G, Guarner C, Tomas A, Villanueva C, Torras X, Gonzalez D, Sainz S, et al. Norfloxacin prevents bacterial infection in cirrhotics with gastrointestinal hemorrhage. Gastroenterology 1992;103:1267–1272.
21. Blaise M, Pateron D, Trinchet JC, Levacher S, Beaugrand M, Pourriat JL. Systemic antibiotic therapy prevents bacterial infection in cirrhotic patients with gastrointestinal hemorrhage. HEPATOLOGY 1994;20:34–38.
22. Pauwels A, Mostefa-Kara N, Debenes B, Degoutte E, Levy VG. Systemic antibiotic prophylaxis after gastrointestinal hemorrhage in cirrhotic patients with a high risk of infection. HEPATOLOGY 1996;24:802–806.
23. Hsieh WJ, Lin HC, Hwang SJ, Hou MC, Lee FY, Chang FY, Lee SD. The effect of ciprofloxacin in the prevention of bacterial infection in patients with cirrhosis after upper gastrointestinal bleeding. Am J Gastroenterol 1998;93:962–966.
24. Bernard B, Grange JD, Khac EN, Amiot X, Opolon P, Poynard T. Antibiotic prophylaxis for the prevention of bacterial infections in cirrhotic patients with gastrointestinal bleeding: a meta-analysis. HEPATOLOGY 1999;29:1655–1661.
25. Bernard B, Cadranel JF, Valla D, Escolano S, Jarlier V, Opolon P. Prognostic significance of bacterial infection in bleeding cirrhotic patients: a prospective study. Gastroenterology 1995;108:1828–1834.
26. Goulis J, Armonis A, Patch D, Sabin C, Greenslade L, Burroughs AK. Bacterial infection is independently associated with failure to control bleeding in cirrhosis patients with gastrointestinal hemorrhage. HEPATOLOGY 1998;27:1207–1212.
27. Hou MC, Chen WC, Lin HC, Lee FY, Chang FY, Lee SD. A new "sandwich" method of combined endoscopic variceal ligation and slcerotherapy versus ligation alone in the treatment of esophageal variceal bleeding: a randomized trial. Gastrointest Endosc 2001;53:572–578.
28. Bruix J, Sherman M, Llovet JM, Beaugrand M, Lencioni R, Burroughs AK, Christensen E, et al. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL Conference. J Hepatol 2001;35:421–430.
29. Beppu K, Inokuchi K, Koyanagi N, Nakayama S, Sakata H, Kitnao S, Kobayashi M. Prediction of variceal hemorrhage by esophageal endoscopy. Gastrointest Endosc 1981;27:213–218.
30. Pugh RN, Murray-Lyon IM, Dawson JL, Peitroni MC, Williams R. Transection of the esophagus for bleeding esophageal varices. Br J Surg 1973; 60:646–649.
31. Hou MC, Lin HC, Chen CH, Kuo BIT, Schmidt CM, Lee FY, Lee SD. Clinical implications of white nipple sign and its role in the diagnosis of esophageal variceal hemorrhage. Am J Gastroenterol 1996;91:2103–2109.
32. Rimola A, Garcia-Tsao G, Navasa M, Piddock LJV, Panas R, Bernard B, Inadomi JM, et al. Diagnosis, treatment and prophylaxis of spontaneous bacterial peritonitis: a consensus document. J Hepatol 2000;32:142–153.
33. Goulis J, Patch D, Burroughs AK. Bacterial infection in the pathogenesis of variceal bleeding. Lancet 1999;353:139–142.
34. Nord CK. Effect of quinolones on the human intestinal microflora. Drugs 1995;49:81–85.
35. Silvain C, Bouquet S, Breux JP, Becq-Giraudon B, Beauchant M. Oral pharmacokinetics and ascitic fluid penetration of ofloxacin in cirrhosis. Eur J Clin Pharmacol 1989;37:261–265.
36. Ho J, Wu PC, Kung TM. An autopsy study of hepatocellular carcinoma in Hong-Kong. Pathology 1981;13:409–416.
37. Morse SS, Sniderman KW, Galloway S, Rapoport S, Ross GR, Glickman MG. Hepatoma, arterioportal shunting and hyperkinetic portal hypertension: therapeutic embolization. Radiology 1985;153:77–82.
38. Campillo B, Dupeyron C, Richardet JP, Mangeney L, Leluan G. Epidemiology of severe hospital-acquired infections in patients with liver cirrhosis: effect of long-term administration of norfloxacin. Clin Infect Dis 1998; 26:1066–1070.
39. Fernandez J. Bacterial infections in cirrhosis: epidemiological changes with invasive procedures and norfloxacin prophylaxis. HEPATOLOGY 2002;35: 140–148.
40. Novella M, Sola R, Soriano G, Andreu M, Gana J, Ortiz J, Coll S, et al. Continuous versus inpatients prophylaxis of the first episode of spontaneous bacterial peritonitis with norfloxacin. HEPATOLOGY 1997;25:532–536.
41. Terg R, Llano K, Cobas SM, Brotto C, Barrios A, Levi D, Wasen W, et al. Effects of oral ciprofloxacin on aerobic gram-negative fecal flora in patients with cirrhosis: results of short- and long-term administration, with daily and weekly dosages. J Hepatol 1998;29:437–442.