Universal antibiotic prophylaxis may no longer be necessary for patients with acute variceal bleeding

A retrospective observational study

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Abstract
A few decades ago, antibiotic prophylaxis for patients with acute variceal bleeding was reported beneficial. However, endoscopic and systemic therapy for variceal bleeding has dramatically improved since then, so the necessity of prophylactic antibiotics can be questioned. In this study, we reevaluated the efficacy of antibiotic prophylaxis in acute variceal bleeding, using the most recent data in our hospital.

We retrospectively analyzed the medical records of 150 patients with acute variceal bleeding who were admitted to Kurashiki Central Hospital between January 2012 and December 2016. We compared the rates of bacterial infection, in-hospital mortality, 5-day rebleeding rate, and 30-day emergency readmission between patients treated or not treated with antibiotic prophylaxis.

Forty-six patients (30.7%) received antibiotic prophylaxis; 104 (69.3%) did not. The rates of the outcomes in patients with antibiotic prophylaxis were 6.5% (bacterial infection), 4.3% (in-hospital mortality), 2.2% (5-day rebleeding), and 10.9% (30-day emergency readmission) and were not significantly different from the corresponding figures in those without antibiotic prophylaxis (1.9%, 7.7%, 1.9%, and 10.6%, respectively). Moreover, these rates in our patients, even without antibiotic prophylaxis, were much lower than rates reported in past years, perhaps because of improvements in care of patients with variceal hemorrhage.

Antibiotic prophylaxis was not associated with significantly better outcomes of bacterial infection, mortality, rebleeding or readmission rate in patients with acute variceal bleeding. Universal antibiotic prophylaxis for patients with acute variceal bleeding should be reconsidered.

Abbreviations: EIS = endoscopic injection sclerotherapy, EVL = endoscopic variceal ligation, HCC = hepatocellular carcinoma.

Keywords: antibiotic prophylaxis, bacterial infections, bleeding, cirrhosis, varices

1. Introduction
Variceal bleeding is a life-threatening complication of portal hypertension,[1,2] and efforts have been made to improve its outcomes. Variceal bleeding is a risk factor for hospital-acquired bacterial infections in cirrhotic patients.[3] In turn, bacterial infection is thought to increase sinusoidal pressure and inhibit platelet aggregation, which contribute to uncontrollability of variceal bleeding.[4-7] In 1990s, bacterial infection was observed in up to 66% of cirrhotic patients with gastrointestinal hemorrhage, and infection was associated with high mortality rates.[6] Therefore, prevention of bacterial infection has long been advocated as a means of improving survival outcomes in such patients.

Twelve randomized clinical trials have been conducted to assess the efficacy of antibiotic prophylaxis in cirrhotic patients with acute gastrointestinal bleeding (variceal and non-variceal).[2,7-16] A meta-analysis of these trials concluded that prophylaxis was associated with significantly lower rates of bacterial infection, mortality and rebleeding.[7] Thus, current guidelines recommend the use of prophylactic antibiotics for cirrhotic patients with variceal or other gastrointestinal bleeding.[18-20]

However, endoscopic and systemic therapy for variceal bleeding has improved over the past decades,[21] and the rate of bacterial infection after variceal bleeding has decreased.[22] The effects of antibiotic prophylaxis in the outcomes of patients with bleeding is difficult to quantify. In a French population, the 6-week mortality rate after variceal bleeding decreased to less than half, from 24.6% to 10.9%, in 10 years.[23] and a recent prospective trial conducted in Taiwan found the 28-day survival rate to be nearly 100%.[24] Thus, observations
have led to a hypothesis that universal antibiotic prophylaxis is no longer be necessary for patients with variceal bleeding. Therefore, in this study, we aimed to reevaluate the efficacy of antibiotic prophylaxis in cirrhotic patients with variceal bleeding by using the most recent data in our hospital.

2. Patients and methods

2.1. Patients and antibiotic prophylaxis

We conducted a retrospective observational study including 155 cirrhotic patients who were admitted to Kurashiki Central Hospital between January 2012 and December 2016 with acute variceal bleeding. Of these, 5 patients who had overt infection or aspiration pneumonia at admission were excluded. Among the remaining 150 patients, 46 were treated with prophylactic antibiotics, and 104 were not (Fig. 1). We defined antibiotic prophylaxis as one or more doses of any antibiotics administered to patients who had no evidence of bacterial infection within 48 hours from admission. The decision of whether to prescribe antibiotics was made by attending physicians.

2.2. Patients' characteristics and treatment for variceal bleeding

We evaluated baseline patients' characteristics, including age, sex, cause of liver disease, Child-Pugh score, MELD-Na score, past history of variceal bleeding, and presence of hepatocellular carcinoma (HCC). We also assessed initial vital signs, laboratory data, endoscopic findings, and treatment, such as hemostatic procedures and amount of blood transfused. All of these information were taken from electronic medical records. In our hospital, endoscopic intervention is always available regardless of the day and time. Thus, immediate endoscopy was performed for patients with suspected active bleeding and endoscopic variceal ligation (EVL) was the first choice of therapy for confirmed active bleeding or vascular plugs.

2.3. Study endpoints

We compared the following outcomes between patients who had received antibiotic prophylaxis and those who had not:

1) in-hospital bacterial infection;
2) in-hospital mortality;
3) rebleeding within 120 hours; and
4) emergency readmission within 30 days.

Diagnosis of bacterial infection was made on the basis of clinical assessments; detection of microorganism was not required. High body temperature without identified infection source was not considered bacterial infection.

2.4. Ethics

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Institutional Ethics Committee reviewed and approved this study (no. 2822). Informed consent was obtained from all patients for being included in the study in an opt-out system.

Figure 1. Flow diagram. A total of 150 patients were included in this study. Forty-six patients (30.7%) received antibiotic prophylaxis. The numbers of patients for each endpoint are described in the figure.
2.5. Statistical analysis

Baseline clinical background and outcomes were compared between the two groups based on administration of antibiotic prophylaxis. Continuous variables, expressed as median (interquartile range), were compared by use of the Mann-Whitney U test. Categorical variables, expressed as numbers (percentages), were compared by use of the chi-square test. Our sample size was thought to be sufficient because the power to detect the difference of the rates of bacterial infection between the 2 groups was calculated to be 93%, based on the rates reported in the most recent randomized trial (3.4% in prophylaxis group and 26.2% in non-prophylaxis group). As selection bias might have exist, rates of bacterial infection and in-hospital mortality were also analyzed with multivariate logistic-regression; all factors that had significant association with the objectives in univariate analysis and antibiotic prophylaxis were included as covariates. Because of the numerous covariates, a backward stepwise approach was used for analysis of in-hospital mortality. All tests were 2-tailed, and P values <.05 were considered significant. Missing data imputation or sensitivity analysis was not performed. The statistical analyses were performed with R version 3.5.1 (R Foundation).

3. Results

3.1. Patients’ characteristics

The patients’ baseline characteristics are presented in Table 1. Among the 150 patients, 116 (77.3%) were male, and the median age was 62.5 years. Forty-six patients (30.7%) had received antibiotic prophylaxis. The most commonly used antibiotic agents were cefazolin and ceftriaxone (20 patients each) for 5 to 7 days. The most common cause of cirrhosis was alcohol abuse. Medians of Child-Pugh score and MELD-Na scores were 8 and 11 respectively. Nearly half of the patients had a previous history of varical bleeding. Twenty-one patients (14%) had HCC present at the time of varical bleeding; 13 had been treated for HCC and were free of detectable cancer. All baseline characteristics of patients treated with antibiotics and those not treated were not significantly different.

About three-quarters of patients had arrived at our hospital within 24 hours from the onset of symptoms. Patients’ vital signs and laboratory data at admission are presented in Table 2; there were no significant differences between these variables and several more in the 2 patient groups.

3.2. Endoscopic findings and initial treatment

Table 3 lists the endoscopic findings and amount of blood transfused in patients who received antibiotic prophylaxis and those who did not. After admission, all but 2 patients underwent emergency endoscopy within 24 hours. Active bleeding was seen in 60 patients (40%), and 111 patients (74%) were treated with EVL. Endoscopic procedures controlled bleeding in most cases, but they failed in 2 (1.3%) of the 104 patients. Because of the availability of emergency endoscopic procedures and high success rate, no patient received vasoactive drugs for hemostasis. With the intent of reducing the risk of rebleeding, we performed endoscopic injection sclerotherapy (EIS) in 59 patients (39.3%) during the same hospital stay. The median volume of red blood cells transfused was 2 units per patient. No differences were found in the 2 populations in the numerous variables evaluated.

### Table 1

Baseline characteristics of patients with and without antibiotic prophylaxis.

|                | Prophylaxis (n = 46) | No prophylaxis (n = 104) | P value |
|----------------|----------------------|--------------------------|---------|
| Age            | 62.5 (51.3–70)       | 62.0 (52.8–70)           | .97     |
| Sex            |                      |                          | 1.00    |
| Male           | 36 (78.3%)           | 80 (76.9%)               |         |
| Female         | 10 (21.7%)           | 24 (23.1%)               |         |
| Etiology of cirrhosis |                     |                          | .51     |
| HBV           | 3 (6.5%)             | 9 (8.7%)                 |         |
| HCV           | 9 (19.6%)            | 19 (18.3%)               |         |
| Alcohol        | 19 (41.3%)           | 45 (43.3%)               |         |
| Alcohol and HBV/HCV |                   |                          |         |
| NASH          | 3 (6.5%)             | 5 (4.8%)                 |         |
| Others         | 2 (4.3%)             | 13 (12.5%)               |         |
| Child-Pugh score | 8 (7–9)             | 8 (7–9)                  | .53     |
| Child-Pugh class |                    |                          | .35     |
| Class A        | 9 (19.6%)            | 13 (12.5%)               |         |
| Class B        | 26 (56.5%)           | 71 (68.5%)               |         |
| Class C        | 11 (23.9%)           | 20 (19.2%)               |         |
| MELD-Na score  | 11 (10–13)           | 12 (10–16)               | .11     |
| Past history of varical bleeding | |                      | .06     |
| Twice or more  | 13 (28.3%)           | 30 (28.8%)               |         |
| Once           | 12 (26.1%)           | 25 (24.0%)               |         |
| Never          | 21 (45.7%)           | 49 (47.1%)               |         |
| History of HCC |                      |                          | .20     |
| HCC present    | 3 (6.5%)             | 18 (17.3%)               |         |
| Treated and free from recurrence | 5 (10.9%)          | 8 (7.7%)                  |         |
| None           | 38 (82.6%)           | 78 (75.0%)               |         |

### Table 2

Vital signs and laboratory data at admission of patients with and without antibiotic prophylaxis.

|                | Prophylaxis (n = 46) | No prophylaxis (n = 104) | P value |
|----------------|----------------------|--------------------------|---------|
| Time from onset to arrival |                     |                          | .52     |
| <24 hours       | 37 (80.4%)           | 77 (74.0%)               |         |
| ≥24 hours       | 9 (19.6%)            | 27 (26.0%)               |         |
| Vital signs at arrival |                   |                          |         |
| Systolic blood pressure, mmHg | 110 (98–129)   | 110 (96–127)             | .84     |
| Diastolic blood pressure, mmHg | 63 (54–71)     | 63 (51–71)               | .89     |
| Heart rate, per minute | 107 (91–114)   | 100 (87–115)             | .26     |
| Body temperature, degree | 36.6 (36.2–36.9) | 36.5 (36.2–36.8)         | .64     |
| Respiratory rate, per minute | 18 (16–20)       | 18 (16–20)               | .62     |
| Laboratory data |                      |                          |         |
| Hb, g/dl        | 8.8 (7.5–10.0)       | 8.6 (7.3–10.6)           | .94     |
| WBC, ×10^3/μl   | 7,400                | 7,000                    | .23     |
| Plt, ×10^9/μl   | 10.2 (7.0–12.6)      | 8.9 (7.0–12.5)           | .25     |
| PT-INR          | 1.28 (1.19–1.43)     | 1.35 (1.24–1.51)         | .09     |
| Alb, g/dl       | 3.0 (2.4–3.3)        | 2.8 (2.4–3.3)            | .51     |
| Bil, mg/dl      | 1.1 (0.7–1.9)        | 1.2 (0.7–2.0)            | .71     |
| ALT, U/l        | 28 (16–37)           | 31 (21–44)               | .23     |
| Cr, mg/dl       | 0.8 (0.7–1.3)        | 0.9 (0.7–1.2)            | .94     |
| BUN, mg/dl      | 23 (16–41)           | 23 (17–36)               | .99     |
| pH              | 7.42 (7.37–7.45)     | 7.42 (7.38–7.45)         | .93     |
| HCO3⁻, mmol/l   | 23.7 (21.9–43.6)     | 23.0 (19.4–25.2)         | .18     |
| Lactate, mmol/l | 3.1 (2.1–5.9)        | 3.5 (2.2–5.4)            | .71     |

Abb = albumin, ALT = alanine aminotransferase, Bil = bilirubin, BUN = blood urea nitrogen, Cr = creatinine, Hb = hemoglobin, pH = potential of hydrogen, Plt = platelets, PT-INR = prothrombin time-international normalized ratio, WBC = white blood cells.
3.3. Univariate analyses of study endpoints

The rates of bacterial infection, mortality, rebleeding and readmission in the 2 study populations are listed in Table 4. Bacterial infection was identified in a total of 5 patients (3.3% [95% confidence interval (CI), 1.1–7.6%]). The clinical diagnoses of infection were respiratory infection, urinary tract infection, catheter-related bloodstream infection, spondylitis, and febrile neutropenia (24 hours after variceal bleeding in a patient with malignant lymphoma) in one patient each. All the infections were treated successfully with antibiotics. In-hospital death occurred in 10 patients (6.7% [95% CI, 3.2–11.9%]); the deaths were associated with persistent gastrointestinal bleeding (n = 2), progressive organ failure despite hemostasis (n = 2), and rebleeding after temporary hemostasis (n = 3). Rebleeding within 120 hours and emergency readmission within 30 days occurred in 2 patients (1.3% [95% CI, 0.2–4.7%]) and 16 patients (10.7% [95% CI, 6.2–16.7%]), respectively. The reason for emergency readmission was variceal rebleeding in most cases (n = 10). None of the rates of these endpoints was significantly different between the 2 groups (P values were .34, .71, 1.00 and 1.00, respectively).

3.4. Multivariate analysis of the factors associated with in-hospital bacterial infection and mortality

In order to deal with confounding factors, we analyzed the factors associated with in-hospital bacterial infection and in-hospital mortality by using multivariate logistic-regression analysis. As illustrated in Table 5, impaired renal function (serum creatinine levels ≥1.2 mg/dl) was a significant risk factor for in-hospital bacterial infection (P = .02), and antibiotic prophylaxis was associated with a trend toward increased, not decreased, rate of infection (P = .08).

The data in Table 6 illustrate that there was no relationship between in-hospital mortality and antibiotic prophylaxis (P = .51). Impaired renal function (serum creatinine ≥1.2 mg/dl), presence of HCC, hypotension at admission (mean arterial pressure ≤65 mm Hg), and not performing EVL were significant and independent risk factors for in-hospital mortality (P values were .04, .02, .006, and .003, respectively).

4. Discussion

In this study of antibiotic prophylaxis in patients with acute variceal bleeding, we found that

1) the frequency of bacterial infection, in-hospital mortality, rebleeding within 120 hours, and emergency readmission within 30 days were not significantly associated with the use of prophylactic antibiotics, and

2) the incidence of these outcomes was much less than that reported in previous studies, irrespective of the use or nonuse of prophylactic antibiotics.[2,5,7–16]
Among the randomized controlled trials that have evaluated the efficacy of antibiotic prophylaxis for cirrhotic patients with acute gastrointestinal bleeding, five focused on variceal bleeding.[13,15,16] Among those studies, three reported lower rates of bacterial infection[13,15,16] and rebleeding[13,15,16] with prophylaxis. However, bacterial infection and early rebleeding occurred frequently in these trials and much more often than in this series: without prophylaxis, their rates were 15.5% to 45.0% and 20.7% to 44.3%, respectively,[13,15,16] whereas our rates were 3.3% and 1.3%, respectively. It is also noteworthy that none of the reported trials found significant reduction in mortality rates with antibiotic prophylaxis.[8,9,13,15,16]

We feel that the large differences between the past reports and our results in rates of infection and early rebleeding may be due to the progress that has been made in endoscopic treatment for acute variceal bleeding. EVL has been found better for immediate control of bleeding than are vasoactive drugs[25] or EIS,[26,27] and rebleeding rates with EVL have been lower than with EIS.[28] In our study, almost all patients underwent emergency endoscopy; immediate EVL was performed whenever possible; active bleeding was well controlled in all but two patients; and the median amount of blood transfusion was 2 units, nearly half of that in a previous report.[15] In view of these advances, we feel it unlikely that antibiotic prophylaxis alone was responsible for better outcomes.

There are other concerns about antibiotic prophylaxis in variceal bleeding: multi-drug resistance, Clostridium difficile infection, and drug toxicity.[29] Thus, we feel it is time to assess the balance of benefits and risks of antibiotic prophylaxis.[29] Some have proposed using risk-stratified strategies.[1,29] However, the risk factors of bacterial infection in patients with acute variceal bleeding have not been thoroughly defined. In our study, impaired renal function at admission was the only independent risk factor for bacterial infection. Although validation in other cohorts is needed, our findings may be useful for risk stratification.

Limitations of our study are these: First, the study is retrospective, and prescription of prophylactic antibiotics depended on physicians’ decisions, which could have introduced selection bias. Indeed, there was an imbalance in patient numbers between the 2 groups with or without antibiotic prophylaxis. Therefore, we evaluated numerous variables on the baseline characteristics of patients, and found that there were no significant differences between the 2 groups. In addition, with regard to the in-hospital bacterial infection and in-hospital mortality, we performed the multivariate analysis to see association of antibiotic prophylaxis with these outcomes to deal with confounders. Nonetheless, hidden confounders could have influenced our results. Second, the sample size of 150 might not be large enough. However, as far as the rate of bacterial infection concerns, the power to detect statistical difference between the two groups was calculated to be 93% with our sample size, which appeared enough to avoid the type 2 error. Third, minor episodes of bacterial infection may not have been detected, but, if so, we feel that under-detection would have had little effect on survival outcomes. Fourth, the accessibility to tertiary hospitals, levels of endoscopic skills, and protocols of treatment vary among countries and regions. We assume that the low incidence of bacterial infection in this study might depend, at least to some extent, on that immediate hemostasis was achieved in most cases and immediate and successful endoscopic procedures. Thus, we are not sure that our results are applicable to different settings. Validation of our results in other institutions, both within Japan and in other countries, is needed.

5. Conclusions

In conclusion, antibiotic prophylaxis in patients with cirrhosis and variceal bleeding was not associated with significantly better outcomes of bacterial infection, mortality, rebleeding or readmission rate in patients with acute variceal bleeding. The rates of these outcomes in our patients were substantially lower,
even without antibiotic prophylaxis, than in published rates, possibly because of improvements in the management of variceal bleeding in recent years. Given the improvement of these outcomes in recent practice, the recommendations for universal antibiotic prophylaxis in patients with variceal hemorrhage should be reconsidered, as prophylaxis may no longer be necessary.

Acknowledgments

The authors would like to thank William R Brown, MD (the director of International Medical Editing Service) for the English language review and statics consultation.

Author contributions

M Ueno and T Kayahara designed the study. M Ueno, T Sunami and H Takayama collected the data. M Ueno, T Kayahara, H Takabatake, Y Morimoto, H Yamamoto and M Mizuno analyzed and interpreted the data. M Ueno, T Kayahara and M Mizuno wrote the manuscript and all other authors approved it.

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