A Prospective Study of the Role of Antibiotic Prophylaxis in Compensated Cirrhotic Patients after the First Variceal Bleeding

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Background and study aim: Current guidelines recommend antibiotic prophylaxis for all cirrhotic patients with variceal bleeding. However, the low infection rate in Child-A patients raises concerns about antibiotic overuse. This study investigates the impact of antibiotic prophylaxis in this population.

Patients and Methods: We conducted a prospective study of 312 patients with Child-A cirrhosis experiencing their first variceal hemorrhage. Patients received either standard treatment (n=152) or standard treatment plus seven days of intravenous ceftriaxone (n=160). All patients underwent upper endoscopy and band ligation.

Results: There were no significant differences between groups in baseline characteristics, infection rates, re-bleeding within 5 days, or 6-week mortality. Laboratory markers of infection and liver function were also similar.

Conclusion: Antibiotic prophylaxis did not improve outcomes in Child-A patients with first variceal hemorrhage. This challenges current recommendations and suggests a more nuanced approach to antibiotic use in this population.

INTRODUCTION

Gastroesophageal varices (GEV) are present in approximately 42% of patients with Child A cirrhosis and 72% with Child B and C cirrhosis[1]. Variceal hemorrhage is the second most common decompensating event in patients with cirrhosis. Acute variceal hemorrhage (AVH) can be complicated by bacterial infection, hepatic encephalopathy, and renal impairment [2]. Bacterial infections may occur in more than half of the cirrhotic patients and may be a precipitating factor for variceal hemorrhage in 20 % of these patients [3]. Therefore, all practice guidelines recommend antibiotic prophylaxis for all cirrhotic patients with variceal bleeding[2, 4, 5] .

However, the rate of infection among patients with cirrhosis Child A is very low. This may be attributed to the low incidence of ascites, and hypoalbuminaemia, which are risk factors for infection [6, 7]. Additionally, Antibiotic overuse is a significant health concern as it can lead to life-threatening complications [8, 9]. Therefore, an effective antibiotic stewardship program is necessary to restrict antibiotic use to high-risk cirrhotic patients, especially Child B and Child C patients. This study aims to evaluate outcomes regarding the incidence of infection, re-bleeding, and decompensation among Child A cirrhotic patients who did not receive antibiotics compared to those who received antibiotic prophylaxis after an episode of variceal hemorrhage.

PATIENTS/MATERIALS AND METHODS

Patients` selection :

This prospective study enrolled patients with upper gastrointestinal (UGI) bleeding who were admitted to the intensive care unit (ICU) at Tropical Medicine Department, Zagazig University Hospitals, between October 2021 and April 2022. Only patients with upper GI bleeding caused by variceal hemorrhage and those classified as cirrhosis Child A were included (refer to flow chart, figure 1). Exclusion criteria encompassed individuals with a history of ascites, hepatic encephalopathy, or previous variceal bleeding. Additionally, patients with upper GI bleeding not related to variceal hemorrhage, and those diagnosed with hepatocellular carcinoma (HCC) were excluded. Patients displaying signs of evident infection (e.g., temperature >38°C, WBCs count >10.000/ul, respiratory, gastrointestinal, urinary or skin symptoms) or occult infection (positive blood cultures within 48-72 hours after admission), as well as those who had received antibiotics before admission, were also excluded from the study .

Management of the variceal hemorrhage and patients` stratification:

Treatment of the acute variceal hemorrhage included initial resuscitation and vasopressors with either octreotide or terlipressin injection. Intravenous ceftriaxone (1 g) was empirically administered for 7 days as prophylactic antibiotic to 160 patients (2). The selection of patients who received the antibiotic was empirical, and neither the physician nor the patient was aware of whether the antibiotic was taken or not. Patients who received antibiotics (N = 160) and those who did not (N = 152) were followed up for 6 weeks. Upper endoscopy was performed after initial stabilization and within 12 hours of admission. Band ligation of the esophageal varices and injection of gastric varices were performed in all patients, accordingly.

Outcomes:

Follow-up was conducted during the hospital admission period to identify any infections. The diagnosis of the infection was based on the qSOFA score and sepsis-3 criteria (2). The patient follow-up included the following assessments ؛

- Monitoring of clinical symptoms and signs of infection and decompensation, such as chest symptoms (cough, phlegm, crackles on auscultation), abdominal distension, lower limb edema, cellulitis, jaundice among others.
- Laboratory evaluations, including Complete Blood Count (CBC), liver and kidney function tests, ESR, CRP, arterial blood gases (ABG), urine analysis and culture, and blood culture .
- Imaging studies comprised chest radiography, and abdominal ultrasonography .
- The report included the rate of bleeding control and the incidence of re-bleeding

Patients who developed infection, re-bleeding, or any signs of decompensation, during the follow-up period, were treated accordingly and antibiotics were administered as necessary. A follow-up endoscopy was scheduled for all patients after 6 weeks of the initial admission to confirm varices eradication and assess liver related-mortality rate .

Statistical analysis:

Statistical analyses were performed using the SPSS version 23. Continuous variables were analyzed as means and standard deviations. Categorical variables were expressed as medians. The chi-square or Fisher exact test was used for categorical parameters and the Student t test for continuous parameters. The different outcomes were assessed using the Odds ratio. All tests were two sided. P-value < 0.05 was considered statistically significant.

RESULTS

A total of 750 patients with UGI bleeding were evaluated for inclusion; 115 patients were excluded because they had non variceal bleeding, 25 patients with evident infections and 13 patients had positive blood cultures were excluded. Among the patients with acute variceal hemorrhage with no infection, we included 312 patients who fulfilled the inclusion criteria (flow chart), and 65% were male. The mean age of the patients was 54 ± 10.5 years. The cause of cirrhosis was chronic HCV (70%) and unknown in the others .

There were no statistically significant differences between the groups in terms of baseline clinical symptoms, comorbidities, signs of chronic liver disease, or Non selective B blockers/carvedilol

use (table 1). In addition, there were no differences in infection rate, laboratory parameters suggestive of infections (WBCs, ESR rate) or abnormal liver function tests (table 2) .

Assessment of the outcome was based on the rate of development of infection, re-bleeding within 5 days, and 6 weeks liver related-mortality (10). Regarding the first outcome, the number of patients who developed infections was not significantly different between the two groups, during the duration of admission (seven patients; four patients out of them were among those not receiving antibiotic prophylaxis (P value; 0.717). Of the four patients with infection, two had pneumonia, one had UTI and one had bacteremia. The incidence of re-bleeding within 5 days was not significantly different between both groups (5 patients versus two, P value: 0.272)

Regarding the mortality rate after 6 weeks of follow-up, there was no statistically significant difference between patients who received antibiotic prophylaxis (five patients) and those who did not (three patients) (P = 0.724). (Table 3, Figure 2). There was no significant reduction in the risk of developing infection in patients receiving antibiotic prophylaxis compared with those who did not (odds ratio = 0.71; confidence interval: 0.16 – 3.21) (Table 4)

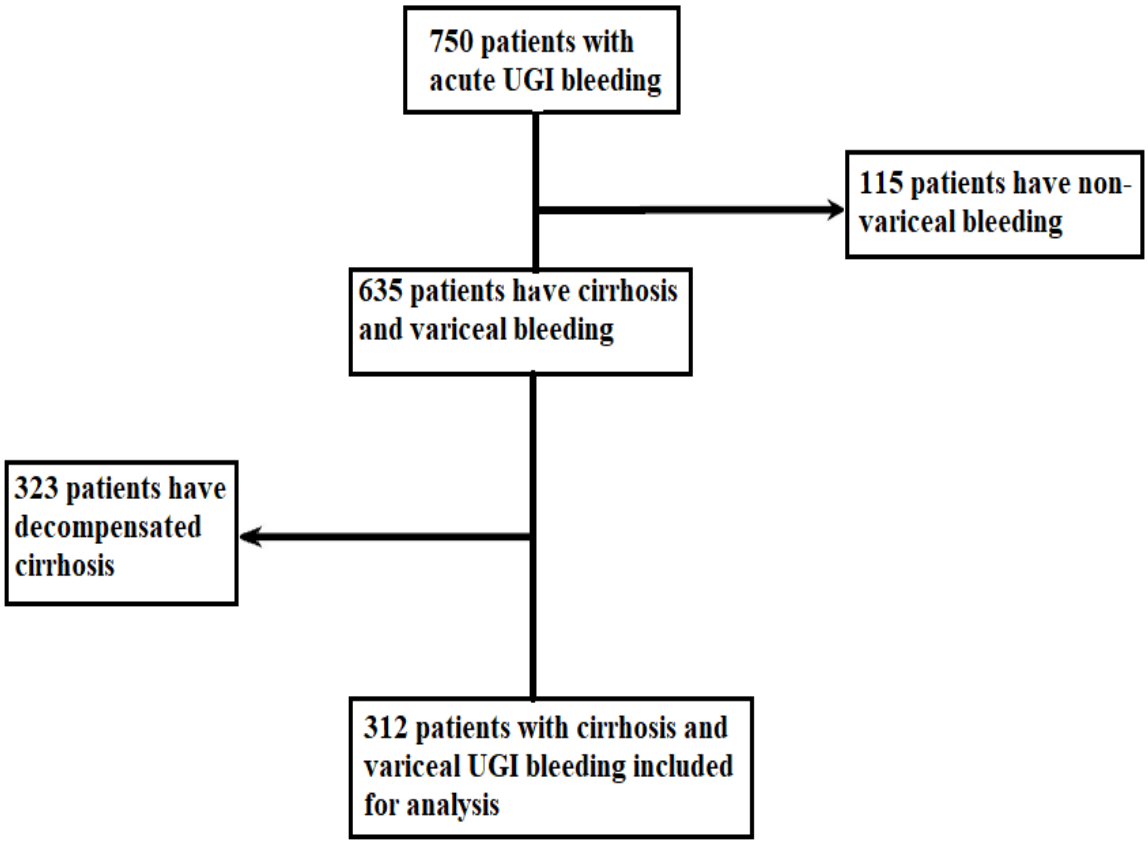

Figure 1: Flow chart

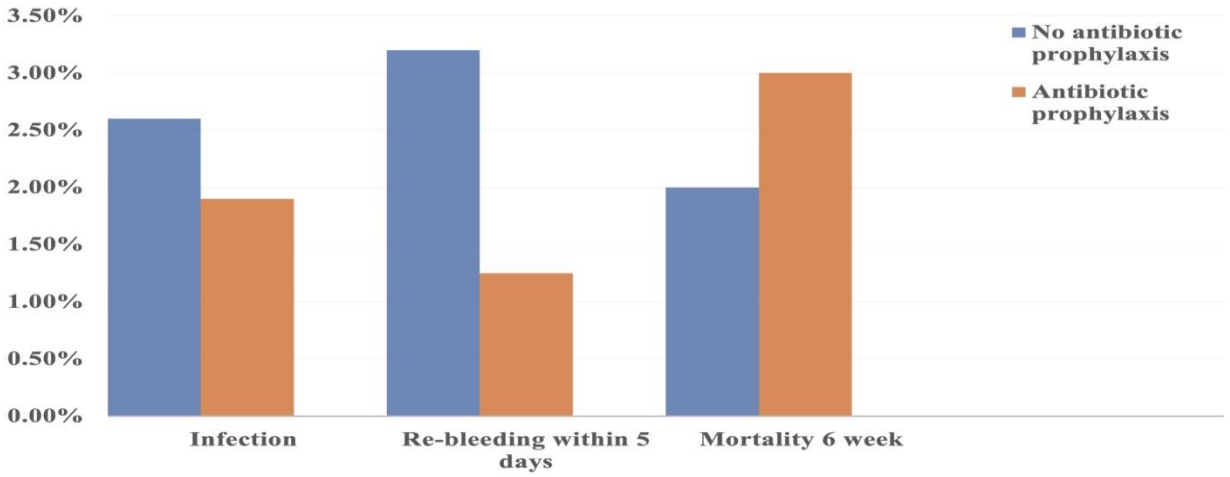

Figure 2: Outcomes of patients not given antibiotic prophylaxis and patients given antibiotic prophylaxis

Table 1: Comparison of clinical data between patients not given antibiotic prophylaxis with those given:

Patient`s characteristics	No antibiotic prophylaxis No. 152 (48.7%)	Antibiotic prophylaxis No. 160 (51.3%)	P Value
Age (mean±SD)	53 ± 11	55 ± 10	0.094
Gender (Male)	100 (66%)	110 (69%)	0.630
Fever	4 (2.6%)	3 (2%)	0.717
Jaundice	0	0	1.0
Abdominal pain	2 (1.3%)	0	0.237
Chest symptoms (cough, phlegm)	2 (1.3%)	1(0.62%)	0.614
Urinary symptoms (dysuria, frequency)	1 (0.66%)	1 (0.62%)	1
Comorbidities	20 (13%)	23 (14.3%)	0.870
Non selective BB/Carvedilol use	94 (62%)	109 (68%)	0.285
			Severity of bleeding:
Heart Rate	92 ± 7	90 ± 9	0.234
Systolic BP	101 ± 7	103 ± 12	0.064
Number of units of blood transfusion	2.6 ± 2.7	3.2 ± 3	0.064

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Table 2: comparison between the two groups regarding the laboratory tests:

Patient`s characteristics	No antibiotic prophylaxis No. 152 (48.7%)	Antibiotic prophylaxis No. 160 (51.3%)	P Value
WBC ($X10^3$/ul)	5.6 ± 3.2	6 ± 2.6	0.162
Hemoglobin (gm/dl)	8 ± 1.1	7.7 ± 1.5	0.109
Platelets ($X10^6$/ul)	99 ± 28.6	99.5 ± 16.3	0.792
ALT (U/L)	23 ± 8.6	22.2 ± 7.3	0.767
AST (U/L)	36.3 ± 18.4	33.8 ± 15.7	0.184
Bilirubin total (mg/dl)	0.7± 0.3	0.7 ± 0.2	0.403
Bilirubin direct (mg/dl)	0.2± 0.06	0.2± 0.05	0.078
Albumin	3.3 ± 0.4	3.3 ± 0.3	0.772
INR	1.1 ± 0.1	1.1 ± 0.1	0.086
Creatinine	1.1 ± 0.9	0.9 ± 0.7	0.029
BUN	20.1 ± 3.3	19.5 ± 3.7	0.094

Table 3: comparison between the two groups regarding the different outcomes:

Outcomes	No antibiotic prophylaxis No. 152 (48.7%)	Antibiotic prophylaxis No. 160 (51.3%)	P value
Infection N (%)	4 (2.6%)	3 (1.9%)	0.0.717
Re-bleeding within 5 days N (%)	5 (3.2%)	2 (1.25%)	0.272
Mortality (6-week) N (%)	3 (2%)	5 (3%)	0.724

Table 4: The risk of development of infection in patients not given antibiotic prophylaxis with those given.

	Infection	No infection	p-value	OR (CI)
Antibiotic prophylaxis No. 160 (51.3%)	3 (1.9 %)	157 (98.1 %)	0.6535*	0.71(0.16 – 3.21)
No antibiotic prophylaxis No. 152 (48.7%)	4 (2.6 %)	148 (97.4 %)		

Abbreviations: CI, confidence interval; OR, odds ratio.
*Statistically non -significant.

DISCUSSION

This prospective, single-center study investigated the impact of prophylactic antibiotic therapy on a cohort of 312 patients with Child-A cirrhosis experiencing their first variceal hemorrhage. We hypothesized that antibiotic prophylaxis would not significantly affect patient outcomes. Our findings demonstrated no significant differences in infection rates, re-bleeding within 5 days, or liver-related mortality within 6 weeks between patients who received antibiotics (n=160) and those who did not (n=152)

The routine use of antibiotic prophylaxis in patients with variceal hemorrhage and preserved liver function (Child-A) remains controversial, with existing guidelines advocating for its use in all patients [5, 6, 11]. This study aimed to determine the potential benefits of antibiotic prophylaxis specifically for Child-A patients with variceal hemorrhage.

Our results align with previous retrospective studies that reported no significant differences in infection rates, re-bleeding, or mortality with antibiotic prophylaxis in patients with varying Child-Pugh classifications, including Child-A [6, 7, 11]. Notably, Tandon et al. (2015) found the lowest infection rate in Child-A patients (2%), further decreasing with prophylaxis [6]. This observation underscores the inherently lower infection risk in this patient population.

A key strength of our study lies in its prospective design, mitigating selection bias inherent to previous retrospective studies. Additionally, our focus on Child-A patients with first-time variceal hemorrhage creates a more homogenous population, potentially reducing confounding factors that could influence outcomes. The most common infections observed (pneumonia and urinary tract infections) mirrored findings from prior studies [6, 7], further supporting the lower prevalence of spontaneous bacterial peritonitis (SBP) in patients without ascites.

Our study also highlights the potential role of advancements in endoscopic interventions and intensive care unit (ICU) management in improving patient outcomes. The low rate of re-bleeding (around 2%) and the limited number of blood transfusions required suggest that factors beyond antibiotic prophylaxis significantly impact outcomes in this patient group.

Current guidelines for antibiotic prophylaxis in patients with variceal hemorrhage often lack stratification based on disease severity. Our findings suggest that the routine use of antibiotic prophylaxis in Child-A patients with first-time variceal hemorrhage may not be necessary. This challenges current recommendations and highlights the need for a more nuanced approach based on disease severity and individual patient risk factors. Future studies with larger, multicenter cohorts could definitively determine the optimal approach to antibiotic prophylaxis in patients with Child-A cirrhosis experiencing variceal hemorrhage.

Limitations:

Our study was conducted at a single center, potentially limiting generalizability.

The relatively small sample size may limit the detection of statistically significant differences in some outcomes.

Future Directions:

Multicenter studies with larger patient cohorts are needed to confirm our findings.

Investigations into the cost-effectiveness of antibiotic prophylaxis in Child-A patients with variceal hemorrhage are warranted. Research exploring the role of biomarkers in guiding antibiotic prophylaxis decisions in this patient population could be valuable.

CONCLUSION:

This prospective study found no significant benefit of antibiotic prophylaxis in Child-A cirrhotic patients with first-time variceal

hemorrhage regarding infection rates, re-bleeding, or mortality. Our findings challenge current guidelines and suggest the need to re-evaluate the routine use of antibiotic prophylaxis in this specific patient group.

Conflict of interest: none

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Conflict of Interest: None.

Ethical consideration: The study was carried out in a manner consistent with the ethical principles of the Declaration of Helsinki, and it was approved by the Institutional Review Board of the Faculty of Medicine, Zagazig University (approval no. 8017/15-9-2021). Informed consent has been obtained from every participant.

HIGHLIGHTS:

- No significant benefit of antibiotic prophylaxis in Child-A cirrhotic patients with first-time variceal hemorrhage regarding infection rates, re-bleeding, or mortality.
- Our findings challenge current guidelines and suggest the need to re-evaluate the routine use of antibiotic prophylaxis in this specific patient group.

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