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Antibiotic use in cirrhotic children with acute upper gastrointestinal bleeding

A retrospective study using the pediatric health information system (PHIS) database

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Abstract

Prior studies have demonstrated positive impacts of antibiotic use on reducing mortality, rebleeding events, and length of hospitalization in adult cirrhotic patients with acute upper gastrointestinal bleeding (UGIB). We aimed to investigate the use of antibiotics in cirrhotic children with acute UGIB and its impact on patient outcomes.

This was a retrospective study using the Pediatric Health Information System database. Cirrhotic patients aged 0 to 18 years with acute UGIB, admitted between October 2005 and September 2015, were identified based on ICD-9 codes. Patients with no documented endoscopy during admission were excluded.

Forty-four (23 females) cirrhotic children were eligible for data analysis. The median patient age was 6 years. Etiology of acute UGIB included esophageal varices (n = 37), non-variceal bleeding (n = 4), and both (n = 3). A significant proportion of cirrhotic children with acute UGIB (n = 30, 68%) were given intravenous antibiotics within 48 hours of admission. Among children who did not develop bacteremia, 68% received antibiotics vs. 32% who did not ($P = .6$). The rate of readmission within 30 days of discharge was 7% in patients with antibiotics vs. 21% in those without antibiotics ($P = .3$).

This study suggested that antibiotic use within 48 hours of admission in cirrhotic children with acute UGIB might have a positive impact on the percentage of children free of bacteremia and the readmission rate. A prospective study should investigate whether prophylactic antibiotics should be targeted only to a subgroup of cirrhotic children with acute UGIB who are particularly at high risk for bacterial infection.

Abbreviations: AASLD = American Association for the Study of Liver Disease; ASGE = American Society for Gastrointestinal Endoscopy; GI = gastrointestinal; ICD-9-CM = International Classification of Diseases, 9th Revision, Clinical Modification; IQR = interquartile range; PHIS = Pediatric Health Information System; PPIs = proton pump inhibitors; UGIB = upper gastrointestinal bleeding.

Keywords: antibiotic prophylaxis, bacteremia, children, cirrhosis, non-variceal bleeding, variceal bleeding

1. Introduction

Acute upper gastrointestinal bleeding (UGIB) is a potential life-threatening complication in patients with cirrhosis. Among adult patients with cirrhosis presenting with acute UGIB, bacterial infection has been associated with increased risks for early rebleeding and increased short-term mortality.[1–3] Prior studies have demonstrated positive impacts of antibiotic use on reducing mortality, rebleeding events, and length of hospitalization in adult cirrhotic patients requiring gastrointestinal (GI) procedures to control bleeding.[4–9] In fact, current guidelines published by the American Association for the Study of Liver Disease (AASLD) and the American Society for Gastrointestinal Endoscopy (ASGE) recommend short-term antibiotic prophylaxis in all cirrhotic patients with acute UGIB.[10,11] This practice has shown to reduce the incidence of bacteremia and improve survivals in adult cirrhotic patients with acute UGIB.[6,9,12] However, the use of antibiotic prophylaxis in cirrhotic children with acute UGIB is not well established and varies between institutions. The aims of this study were to investigate the use of antibiotics in cirrhotic children presenting with acute UGIB and to evaluate its impact on patient outcomes.

2. Methods

2.1. Study design and data source

This was a retrospective study using the Pediatric Health Information System (PHIS, Children's Hospital Association, Overland Park, KS).[13] The hospital's institutional review board

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waived approval for this study because the data were de-identified at the time of data submission and review.

The PHIS database is a comparative pediatric database containing clinical and resource utilization data for inpatient, ambulatory surgery, emergency department, and observation unit patient encounters for 44 not-for-profit children's hospitals in the United States. For the purposes of external benchmarking, participating hospitals provide discharge/encounter data, including demographics, International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnoses and procedures, length of stay, and discharge status (discharged to home, rehabilitation facility, nursing facility, or inpatient death). Data are de-identified at the time of data submission and are subjected to bimonthly coding consistency reviews and quarterly data quality reports to ensure data quality, through a joint effort between the Child Health Corporation of America and participating hospitals.

2.2. Patient population

The PHIS database was queried for cirrhotic patients aged 18 years old or younger who were admitted between October 2005 and September 2015 with a diagnosis of acute UGIB. Cirrhosis was defined based on ICD-9 codes for cirrhosis and common underlying cirrhosis etiology, such as primary diagnosis of cirrhosis (571.0), cirrhosis without mention of alcohol (571.5), biliary cirrhosis (571.6), other chronic nonalcoholic liver disease (571.8), cryptogenic cirrhosis (571.5), biliary atresia (751.61), autoimmune hepatitis (571.42), primary sclerosing cholangitis (576.1), alpha-1 antitrypsin deficiency (273.4), Wilson disease (275.1), cystic fibrosis with GI manifestations (277.03), congenital cystic disease of the liver (751.62), Alagille syndrome (759.89), and progressive familial intrahepatic cholestasis (576.8). Acute UGIB was defined based on ICD-9-CM diagnosis codes for hematemesis (578.0), melena (578.1), and hemorrhage of the GI tract (578.9). Acute UGIB was further classified into variceal bleeding, non-variceal bleeding, or both, using ICD-9 Current Procedural Terminology codes, such as endoscopy with sclerosis of varices (43243), esophagus endoscopy transoral with sclerosis (43204), esophagus endoscopy transoral with esophageal banding (43205), esophagus endoscopy with control bleeding (43227), upper GI endoscopy/ligation with banding (43244), upper GI endoscopy with ablation (43251), and upper GI endoscopy with control bleeding (43255). Patients with no documented endoscopy during admission were excluded.

2.3. Statistical analysis

Data were collected for baseline patient characteristics, hospitalizations, primary diagnosis, complications of cirrhosis (including ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, hepatorenal syndrome, hepatopulmonary syndrome), bacteremia, thrombocytopenia, use of blood products (packed red blood cells, platelets, fresh frozen plasma), and medications (intravenous antibiotics, proton pump inhibitors [PPIs], and octreotide). For patients who received antibiotics, timely administration of antibiotics was defined as antibiotics was given within 48 hours of admission, because the majority of infections were documented on admission or very shortly afterward, and prior studies have shown benefits from antibiotic prophylaxis administered within 48 hours of admission.[6,14–16] Antibiotic prophylaxis given on a regular basis before admission (i.e., oral sulfamethoxazole/trimethoprim, amoxicillin/clavulanate, or fluoroquinolone, etc.) was not considered as in-hospital antibiotic prophylaxis. If patients had multiple admissions, the analysis was limited to the first hospitalization. Patient outcomes were analyzed based on length of hospitalization, readmission within 30 days of discharge, recurrent bacteremia, and/or rebleeding following the first admission. Long-term survival outcome after discharge was not captured during this analysis; however, the 90-day survival outcome was computed if patients were subsequently readmitted.

Data were analyzed using SPSS version 25.0 (SPSS Inc, Chicago, IL), and were reported as the median (interquartile range [IQR]), or percentage. Groups of patients with and without antibiotic use were compared using chi-squared test or Fisher exact test, as appropriate, for categorical variables, and using *t* test or Mann–Whitney *U* test, as appropriate, for continuous variables. $P < .05$ was considered to be statistically significant for all tests.

3. Results

3.1. Patient characteristics

Among 152 cirrhotic children admitted during the study period, 44 patients (23 females, 53%) with acute UGIB had a documented endoscopy during admission and were eligible for data analysis. The median patient age was 6 years (IQR = 11). The majority of the patients were white (n = 36, 82%). The most common primary diagnosis was biliary atresia (n = 21, 48%), followed by alpha-1 antitrypsin deficiency (n = 5, 11%), and autoimmune hepatitis (n = 2, 5%). Etiology of acute UGIB included esophageal variceal bleeding (n = 37, 84%), non-variceal bleeding (n = 4, 9%), and both (n = 3, 7%). Most patients were started on PPIs (n = 35, 80%) on admission, but only 20 (45%) received octreotide in addition to PPIs. Thirty patients (68%) received intravenous antibiotics within 48 hours of admission. Table 1 summarizes patient and hospitalization characteristics according to antibiotic use.

3.2. Impact of antibiotic use on infectious complications

The majority (68%) of the patients received intravenous antibiotics timely after admission, and 10/30 (33%) of the patients received more than one class of antibiotics. The most common class of antibiotics given within 48 hours of admission was piperacillin/tazobactam (15 patients), followed by third-generation cephalosporin (14 patients), and fluoroquinolone (4 patients). The median duration of antibiotic use was 3 days (IQR = 6). Antibiotics were more commonly used in patients with complications of cirrhosis, such as hepatorenal syndrome (n = 3, 10%), and hepatic encephalopathy (n = 2, 7%) (Table 1). However, the only patient who had spontaneous bacterial peritonitis did not receive antibiotics during the first 48 hours of admission.

Among the patients receiving antibiotics, 24 (80%) presented with esophageal variceal bleeding, 4 (13%) with non-variceal bleeding, and 2 (7%) with both types of bleeding (Table 1). Overall, 26/40 (65%) of the patients presenting with esophageal variceal bleeding and 6/7 (86%) of the patients with non-variceal bleeding did receive antibiotics within the first 48 hours of admission. There was no statistically significant difference in the rate of bacteremia between children with and without antibiotics,

Table 1

Patient and hospitalization characteristics.

	With antibiotics (n = 30)	No antibiotics (n = 14)	P
Age (years), median (range)	5 (1–15)	12 (5–18)	.01
Female, n (%)	13 (43)	10 (71)	.08
Ethnicity, n (%)			.40
White	23 (77)	13 (93)	
Others	7 (23)	1 (7)	
Primary diagnosis, n (%)			.28
Biliary atresia	16 (53)	5 (36)	
Alpha-1 antitrypsin deficiency	4 (13)	1 (7)	
Autoimmune hepatitis	1 (3)	1 (7)	
Others	9 (31)	7 (50)	
Complications of cirrhosis, n (%)			.28
Hepatic encephalopathy	2 (7)	1 (7)	
Spontaneous bacterial peritonitis	0 (0)	1 (7)	
Hepatorenal syndrome	3 (10)	0 (0)	
Etiology of acute UGIB, n (%)			.36
Esophageal varices	24 (80)	13 (93)	
Non-variceal bleeding (i.e., gastric and/or duodenal ulcer)	4 (13)	0 (0)	
Both	2 (7)	1 (7)	
Blood products, n (%)			.06
Packed red blood cell	11 (37)	4 (29)	
Others	3 (10)	5 (36)	
Medications, n (%)			.97
PPIs	10 (33)	5 (36)	
PPIs + octreotide	14 (47)	6 (43)	

PPIs = proton pump inhibitors; UGIB = upper gastrointestinal bleeding.

4/30 (13%) vs. 2/14 (14%), respectively. However, among children who did not develop bacteremia, 68% received antibiotics vs. 32% who did not ($P = .6$).

3.3. Impact of antibiotic use on patient outcomes

The median hospital stay was 7 days (IQR = 9) in children with antibiotic use, vs. 5 days (IQR = 16) in those with no antibiotics ($P = .05$). Among 24 patients who were subsequently readmitted during the study period, the 90-day survival rate was 100% in both groups. Five patients were readmitted within 30 days of discharge due to recurrent UGIB, and none developed bacteremia. The rate of readmission within 30 days of discharge was lower in patients who received antibiotics, 2/30 (7%) vs. 3/14 (21%) in those who did not receive antibiotics ($P = .3$).

4. Discussion

Complications of cirrhosis in children include acute UGIB caused by gastroesophageal varices and/or portal hypertensive gastropathy, ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, renal dysfunction, and poor weight gain. Cirrhotic patients with acute UGIB are at risk of developing bacterial infections, including spontaneous bacterial peritonitis and/or other infections, that are associated with an increased risk for early rebleeding and increased short-term mortality.[2,14] Moreover, cirrhotic patients undergoing an endoscopic procedure to control bleeding are particularly at risk for infection,[5,6,9] and prior adult studies have shown that antibiotic prophylaxis reduced morbidity and mortality in cirrhotic patients with acute UGIB.[4,5,7–9,12] This improved survival was thought to be partially related to decreased incidence of early rebleeding in those who received antibiotics.[17] Although numerous studies have been performed in cirrhotic adults, there was no published pediatric study that addressed the question of whether antibiotic prophylaxis would be beneficial in cirrhotic children with acute UGIB. Furthermore, although current AASLD and ASGE guidelines recommend antibiotic prophylaxis in all cirrhotic patients who present with acute UGIB,[10,11] there is lack of consensus and experience on using antibiotic prophylaxis in cirrhotic children presenting with acute UGIB, probably due to limited number of cirrhotic children with acute UGIB, especially in a single center, and lack of a well-designed study examining the role of antibiotic prophylaxis in this patient population. The current study provided preliminary data on the current practice of using antibiotics in cirrhotic children with acute UGIB and its impact on patient outcomes.

The advantage of using the PHIS database is that it provides an opportunity to collect data on a number of cirrhotic children admitted with acute UGIB quickly and with little expense, and this may provide preliminary data that can be used to empower future studies. In line with adult studies,[6,12] our findings showed that a significant proportion (68%) of cirrhotic children with acute UGIB were given intravenous antibiotics timely within 48 hours of admission, and the use of antibiotics appeared to increase the percentage of children free of bacteremia and reduce the readmission rate, although it did not reach statistical significance due to small sample size. All patients who received antibiotics were given antimicrobial agents that were effective against gram-negative bacteria in the gut, although only 18/30 (60%) of these patients were given first-line choices as recommended by current guidelines,[10,11,18] specifically third-generation cephalosporins or fluoroquinolones. In addition, current guidelines[10,11,18] recommend short-term prophylactic antibiotics for up to 7 days in cirrhotic patients presenting with UGIB, but the median duration of antibiotics in the present study was only 3 days, which raised a question of whether these children have received the full benefit of antibiotic prophylaxis. Furthermore, current guidelines[10,11,18] recommend that somatostatin or its analogues (i.e., octreotide) should be initiated as soon as variceal bleeding is suspected, but only 20 patients in the present cohort received octreotide.

The limitation of using the PHIS database is that it relies on billing providers who enter ICD-9 codes for diagnoses and procedures. Because ICD-9 codes were used to identify the patients, we acknowledged that some patients with missing or incorrect coding might not have been captured. Among 152 cirrhotic children identified during the study period, there might be more than 44 children undergoing endoscopy during admission, but if billing providers did not enter ICD-9 codes for diagnosis and/or procedures, some of these patients would have been missed on the PHIS database. Besides, it was impossible to obtain data on specific laboratory results, or clinical symptoms or signs at the time of presentation, which might have influenced the clinical decision for antibiotic use. It was unclear whether antibiotics were given for prophylaxis before an endoscopic procedure versus treatment of infection (i.e., treatment for cholangitis in patients with biliary atresia), versus suspected infection pending sepsis work-up, etc. Moreover, children with hepatorenal syndrome and hepatic encephalopathy might present with a more severe disease on admission,

which might have influenced providers to use antibiotics. Furthermore, since the PHIS database includes data from children's hospitals in the United States, findings from the present study might not be generalizable to patients presenting to other general hospitals.

In conclusion, this is the first pediatric study on antibiotic use in cirrhotic children with acute UGIB before an endoscopic procedure to control bleeding. The present study suggested that antibiotic use within 48 hours of admission in cirrhotic children with acute UGIB might have a positive impact on the percentage of children free of bacteremia and the readmission rate. Given the clear benefits of antibiotic prophylaxis demonstrated in adult cirrhotic patients with acute UGIB, a larger scale, multicenter, prospective pediatric study is warranted to further investigate the association between the use of prophylactic antibiotics and outcomes of infectious complications, hospitalization characteristics, cost-effectiveness, and short-term mortality in cirrhotic children presenting with acute UGIB. A prospective study should also investigate whether prophylactic antibiotics should be targeted only to a subgroup of cirrhotic children with acute UGIB who are particularly at high risk for bacterial infection, taking into account routine use of antibiotics may increase the risk of developing multidrug-resistant bacteria and/or other antibiotics-associated side effects.

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