Antimicrobial therapy in patients with acute variceal hemorrhage

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BACKGROUND: Acute variceal hemorrhage is a serious complication of liver disease and hospital outcome is closely related to infection. Patients with cirrhosis are at greater risk for developing bacterial infection, which is associated with failure to control bleeding and higher rates of hospital mortality. Many clinical practice guidelines endorse antimicrobial prophylaxis as standard of care for cirrhotic patients.

OBJECTIVE: The present study was performed to characterize the use of antimicrobial therapy for patients hospitalized with acute variceal hemorrhage.

METHODS: Medical records of 98 patients hospitalized with suspected variceal hemorrhage were retrospectively reviewed.

RESULTS: One-half of the patients received antimicrobials at any time during their hospital admission, and in very few (24%) could prescribed therapy be considered prophylactic. Seventy-seven per cent of patients undergoing endoscopy did not receive an antimicrobial within 24 h of the procedure. Those who received antimicrobial therapy had more severe liver disease (model for end-stage liver disease scores of 19.5±10 versus 12.9±8, P<0.05; Child-Pugh class C 78% versus 65%, not significant) and worse in-hospital outcome (length of stay 17 versus 6.5 days, P<0.05; mortality 15 versus two, P<0.05). Cephalosporins were the most widely prescribed agents (45%), followed by fluoroquinolone (40%). Regimens ranged in length from single-dose administration to two weeks.

CONCLUSIONS: Patients with liver disease admitted with variceal hemorrhage were often not prescribed antimicrobial therapy to reduce the risk of bacterial infection. These results imply that published practice guidelines are not being consistently observed. A large, well-designed study with mortality outcome may be required for clinical guidelines to be successfully implemented in practice.

Key Words: *Antimicrobials; Liver disease; Variceal hemorrhage*

Une thérapie antimicrobienne chez des patients souffrant d'une hémorragie variqueuse aiguë

HISTORIQUE : Une hémorragie variqueuse aiguë est une grave complication de l'atteinte hépatique, et son issue hospitalière est étroitement liée à l'infection. Les patients cirrhotiques sont plus vulnérables à l'infection bactérienne, laquelle est reliée à l'incapacité de contrôler le saignement et à des taux plus élevés de mortalité en milieu hospitalier. De nombreux guides de pratique clinique font de la prophylaxie antimicrobienne une norme des soins aux patients cirrhotiques.

OBJECTIF : La présente étude a été menée en vue de caractériser l'utilisation de la thérapie antimicrobienne pour les patients hospitalisés à cause d'une hémorragie variqueuse aiguë.

MÉTHODOLOGIE : Les dossiers médicaux de 98 patients hospitalisés en raison d'une hémorragie variqueuse présumée ont fait l'objet d'une analyse rétrospective.

RÉSULTATS : La moitié des patients ont reçu des antimicrobiens à un moment ou un autre de leur hospitalisation, et chez quelques-uns d'entre eux (24 %), le traitement prescrit pouvait être considéré comme prophylactique. Soixante-dix-sept pour cent des patients subissant une endoscopie n'avaient pas reçu d'antimicrobiens dans les 24 heures de l'intervention. Ceux qui en avaient reçu présentaient plus d'indices de maladie hépatique grave (modèle d'insuffisance hépatique terminale de 19,5±10 par rapport à 12,9±8, P<0,05; 78 % de stade C de la classification de Child-Pugh par rapport à 65 %, non significatif) et une issue plus négative en milieu hospitalier (durée de l'hospitalisation de 17 jours par rapport à 6,5; P<0,05; 15 mortalités par rapport à 2, P<0,05). Les céphalosporines étaient les agents les plus prescrits (45 %), suivies de la fluoroquinolone (40 %). Le schéma posologique variait entre l'administration d'une seule dose et un traitement de deux semaines.

CONCLUSIONS : Souvent, aucun traitement antimicrobien n'était prescrit aux patients ayant une atteinte hépatique hospitalisés en raison d'une hémorragie variqueuse, afin de réduire le risque d'infection bactérienne. Selon ces résultats, les guides de pratique clinique ne sont pas observés de manière constante. Une grande étude bien conçue précisant l'incidence de mortalité pourrait être nécessaire pour que les directives cliniques soient bel et bien adoptées en pratique.

Gastrointestinal (GI) hemorrhage is a common cause of hospitalization and is associated with significant morbidity and mortality (1). Patients with liver disease and evidence of varices represent 10% to 30% of patients admitted with upper GI bleed, and are at particular risk of poor outcome (2). Approximately 20% of cirrhotic patients will develop bacterial infections within 48 h of admission for GI bleed, and the incidence can reach as high as 35% to 66% within two weeks of hospitalization (3-5). Prognosis in terms of failure to control bleeding and survival are closely related to infection (6-8). Patients with cirrhosis and GI bleed who develop bacterial infection have a five- to sixfold increase in hospital mortality compared with a general hospital population (9).

Urinary tract infections (12% to 29%) and spontaneous bacterial peritonitis (SBP) (7% to 23%) are the most frequently observed infections in hospitalized cirrhosis patients, followed by respiratory tract infections (6% to 10%) and primary bacteremia (4% to 11%) (4,10,11). Gram-negative bacilli (*Escherichia coli* and *Klebsiella* species) are the principally isolated organisms. Impaired white blood cell (WBC)

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TABLE 1
Patient admission characteristics

Variables	n=98
Age (years)*	55.9±12.1
Sex (male)	54 (55.1)
Source of liver disease	
Alcohol	46 (46.9)
Hepatitis	42 (42.8)
Child-Pugh score A/B/C†	2/23/71
MELD score*†	17±10
Admission bleed (n=98)	
Varices	73 (74.4)
Ulcer	8 (8.2)
Other	9 (9.2)
Unknown	8 (8.2)
Variceal hemorrhage management (n=73)	
Octreotide	21 (28.7)
Band ligation	6 (8.2)
Octreotide + band ligation	31 (42.5)
Octreotide + sclerotherapy	3 (4.1)
Intravenous proton pump inhibitor	7 (9.6)
Other	5 (6.8)
Past medical history	
Prior variceal hemorrhage	40 (40.8)
Spontaneous bacterial peritonitis	5 (5.1)
Ascites	59 (60.2)
Encephalopathy	16 (16.3)
Diuretic therapy	
Spironolactone alone	13 (13.3)
Spironolactone + furosemide	31 (31.6)
Possible infection at admission	14 (14.3)
Antimicrobial therapy during hospitalization	55 (56.1)
Antimicrobial therapy within 24 h of admission	25 (25.5)
Length of stay (days)*	12.4±9.7
In-hospital mortality	17 (17.3)

*Results are n (%) unless otherwise specified. *Results expressed as mean ± SD; †Two patients did not have all data available necessary to calculate Child-Pugh class and model for end-stage liver disease (MELD) scores*

function, portosystemic shunting, and enteric flora alterations associated with cirrhosis may contribute to increased risk of infections in these patients with GI bleed (5-7). This is particularly true of those patients undergoing invasive diagnostic or therapeutic procedures, such as endoscopy (12).

A number of studies have evaluated the role of antimicrobials for the prevention of bacterial infections in patients with liver disease and GI bleed. Meta-analyses of these data demonstrate that single-dose or short-course antibiotic therapy decreases infections and reduces 19-day mortality (13,14). No specific regimen appears more efficacious when the limited number of comparison trials are evaluated, although the fluoroquinolones are the most studied.

Based on these data, a number of professional bodies now endorse routine use of antimicrobial prophylaxis in cirrhosis patients with GI bleed (15,16). However, it is recognized that clinical guidelines have inconsistent influence on physician practice (17).

The objective of the present study was to characterize antimicrobial use in a population of patients with liver disease who were hospitalized for suspected variceal hemorrhage.

METHODS

A retrospective chart review was conducted at a major tertiary care centre in Canada. Patients admitted to hospital with suspected variceal hemorrhage during a 33-month period between January 2001 and September 2003 were evaluated for inclusion. The study received university and hospital ethics approval before initiation.

Patients with liver disease were included if they had evidence of bleeding varices by upper endoscopy performed at hospital admission. Cirrhosis patients admitted and found to have bleeding from other GI sources were also reviewed. Data were collected pertaining to the etiology of liver disease, history or current physical findings of ascites, hepatic encephalopathy and SBP, as well as admission vital signs and laboratory values, including blood pressure (BP), heart rate (HR), temperature, hemoglobin, WBC, platelets, urea, serum creatinine, albumin, international normalized ratio, total and direct bilirubin, aspartate aminotransferase and alanine aminotransferase. Management strategies for the presenting hemorrhage and length of stay were recorded. The Child-Pugh and model for end-stage liver disease (MELD) scores were also calculated (18,19).

Information pertaining to possible infection was collected for all patients, including culture and susceptibility studies of any blood, urine, ascitic fluid or sputum samples performed and types of organisms isolated. Those patients who received antibiotic therapy during hospitalization were identified; time-to-medication initiation was recorded, specifically, in those prescribed antimicrobial therapy within 24 h of admission and subsequent endoscopy. Selection of specific agents was documented.

The χ^2 test was used for comparisons between qualitative variables, and Student's *t* test was used for comparisons between quantitative variables expressed as mean ± SD. Multivariate analysis techniques (SPSS 11.0 for Windows, SPSS Inc, USA) were performed to determine if any factors were associated with antimicrobial use.

RESULTS

Of the 205 patients screened, 98 were included in the present analysis. Ninety-two patients initially identified as having suspected variceal hemorrhage (*International Classification of Diseases*, 10th edition [20] code) did not in fact have diagnosed liver disease or varices on examination of their medical records. Eight patients experienced variceal hemorrhage more than 72 h following admission for a separate complaint. Seven other patients had been readmitted during the study period; only their first hospitalization was used for the purpose of the present analysis. Patient characteristics are summarized in Table 1. The mean age was 56 years and slightly over one-half were men. Most had identifiable causes of liver disease, notably alcoholic cirrhosis (47%) and viral hepatitis (43%). Nearly two-thirds had a history of ascites which was managed by a spironolactone-based diuretic therapy before admission (45%), but a few presented with a history of encephalopathy (16%) or prior SBP (5%). Twenty-four patients were awaiting liver transplantation.

Of the 96 patients with evaluable data for scoring, most were classified as Child-Pugh class C (74%). The mean MELD score was 17±10.

TABLE 2
Antimicrobial therapy prescribed

Antimicrobial	Prescribed any time during hospitalization n=55	Prescribed within 24 h of admission n=25
Cephalosporins, n (%)	25 (45)	12 (48)
Ceftriaxone, n	13	11
Cefuroxime, n	5	0
Cefazolin, n	7	1
Ciprofloxacin, n (%)	22 (40)	10 (40)
Penicillins, n (%)	15 (27)	4 (16)
Ampicillin, n	8	3
Piperacillin, n	3	0
Cloxacillin, n	4	1
Imipenem, n (%)	6 (11)	1 (4)
Vancomycin, n (%)	17 (31)	3 (12)
Anaerobic coverage, n (%)	12 (22)	3 (12)
Clindamycin, n	9	2
Metronidazole, n	3	1
Cotrimoxazole, n (%)	3 (5)	1 (4)

The source of hemorrhage on admission was primarily variceal bleed (74.5%) and largely managed by band ligation and octreotide (42.5%) or octreotide alone (29%). The majority underwent endoscopy for diagnosis and management (91%). Many had physical findings of ascites (76.5%) and nearly one-half at some point during admission developed symptoms consistent with encephalopathy. The average length of hospitalization was almost two weeks. Seventeen patients did not survive to discharge.

At admission, 14 patients had vital signs and/or laboratory findings consistent with possible infection. Culture and susceptibility testing for infection was ultimately performed in 66 patients: urine (n=52); blood (n=46); sputum (n=25); and ascitic fluid (n=19). Organisms were isolated most often from urine (48%), sputum (44%), blood (30%) and, rarely, ascitic fluid (10.5%). Most positive urinary cultures grew *Enterococcus* species or *E coli* (15% grew both).

Fifty-five (56%) patients received antibiotics at any time during their hospital stay. Of those prescribed antimicrobial therapy, antibiotics were initiated in 25 (45.4%) within 24 h of admission and subsequent endoscopy. Cephalosporins were the most widely prescribed antibiotic class (45%), followed by fluoroquinolones (40%) (Table 2). Many patients also received treatment with vancomycin (31%). The majority of patients who were prescribed an antimicrobial within 24 h of admission and subsequent endoscopy received monotherapy. However, nine patients were prescribed a combination of agents, generally ciprofloxacin or ceftriaxone plus an antibiotic with extended Gram-positive coverage (eg, ampicillin or vancomycin). Length of therapy ranged from single-dose administration to 14 days.

Antimicrobial therapy is characterized in Table 3. Patients who received an antimicrobial had more severe liver disease (MELD score 19.5±10 versus 12.9±8, P<0.05 and Child-Pugh C score 78% versus 65%, not significant) compared with those patients who did not receive therapy. These patients also experienced worse in-hospital outcome; length of stay was prolonged (mean 17 versus 6.4 days, P<0.05) and fewer survived to discharge (73% versus 95%, P<0.05). Patients prescribed

TABLE 3
Characteristics of patients who did or did not receive antimicrobial therapy

Characteristic	No antimicrobial prescribed n=43	Antimicrobial prescribed n=55	P
Age (years)*	57.6±12	54.7±12	NS
Sex (male)	24 (55.8)	30 (54.5)	NS
Child-Pugh class C	28 (65.1)	43 (78.2)	NS
MELD score*	13±8	20±10	<0.05
Platelets*	160±141	145±94	NS
Albumin (g/L)*	27±6	24±6	<0.05
Infection at admission	5 (11.6)	9 (16.4)	NS
Endoscopy performed	41 (95.3)	48 (87.3)	NS
Hemorrhage			
Variceal	37 (86)	36 (65.4)	<0.05
Ulcer	3 (7.0)	5 (9.1)	NS
History of SBP	1 (2.3)	4 (7.3)	NS
Ascites	34 (79.1)	46 (83.6)	NS
Patients with positive cultures	8 (18.6)	13 (24)	NS
Length of stay (days)*	6.4±3.7	17±17	<0.05
Mortality	2 (4.7)	15 (27.3)	<0.05

*Results are n (%) unless otherwise specified. *Results expressed as mean ± SD. MELD Model for end-stage liver disease; NS Not significant; SBP Spontaneous bacterial peritonitis*

antimicrobials tended to have more clinical or laboratory findings consistent with possible infection at the time of admission (16% versus 12%, not significant) and more documented positive cultures during their hospitalization (24% versus 18%, not significant). A greater proportion of patients undergoing endoscopy did not receive antimicrobial therapy (95% versus 87%, not significant). Seventy-seven per cent of patients undergoing endoscopy did not receive antimicrobial therapy within 24 h before the procedure. No difference was found between groups with respect to history of prior SBP or GI hemorrhage (variceal or ulcer). Based on univariate analysis results, no variables were suitable to conduct multivariate analysis.

DISCUSSION

GI bleeding is a common and serious complication of portal hypertension, and varices are the most common source of hemorrhage in cirrhosis. While advances in acute management have improved outcomes following variceal hemorrhage, mortality is still unacceptably high, especially in patients with severe liver disease (21-23). Cirrhotic patients with GI bleeding are at a greater risk for developing bacterial infection, which in turn is associated with failure to control bleeding and higher in-hospital mortality (5,9). The clinical application of antibiotic therapy following admission for suspected variceal hemorrhage and within 24 h of endoscopy in our population was low. Those patients who received antibiotics were more ill, as reflected by MELD scores and Child-Pugh class, and had prolonged admission and greater in-hospital mortality.

Fourteen per cent of all hospitalized patients had findings consistent with potential infection at the time of admission, reflecting rates found elsewhere in the literature (4-8). A variety of organisms were isolated from urine, sputum, blood and ascites fluid samples tested. Identification of *E coli* and *Enterococcus* species was anticipated based on data and clinical

experience reported in the literature, but bacteremia with Gram-positive organisms was not. These findings may be explained by the prolonged hospitalization in our patient group and acquisition of nosocomial *Staphylococcus* infection. Empirical use of third-generation cephalosporins and quinolone as probable prophylaxis and treatment was compatible with other published reports and guidelines.

In addition to GI bleeding and severity of liver disease, risks for infection in hospitalized cirrhotic patients include low protein ascitic fluid, low serum albumin level, thrombocytopenia and therapeutic endoscopy (5,24). Most clinical guidelines recommending antimicrobial prophylaxis suggest that all patients with cirrhosis and GI hemorrhage receive therapy, regardless of other risks for infection (8,12,14,16). No clinically relevant difference in albumin or platelet values was found between patients treated with antibiotics or not; however, relatively fewer patients undergoing endoscopy received antibiotic therapy.

According to present clinical practice guidelines, gaps in antimicrobial therapy were observed in our patient population at risk of infection following variceal hemorrhage. Because many of the patients reviewed were hospitalized before most of the recommendations were published and widely disseminated, our results may not actually be an example of how clinical practice guidelines often have limited effect on changing physician behaviour (17). While it appears that adherence to guidelines may be greater when they are endorsed by a professional organization, the country of origin may have an impact on adherence (25,26). Canadian practice guidelines regarding antimicrobial prophylaxis pertain only to minimizing risk of endocarditis in high-risk patients undergoing endoscopy and who do not necessarily have cirrhosis (27). Successful integration of clinical guidelines into practice may also rely on how credible and compelling are the studies on which they are based (28). Clinical data demonstrate antibiotic prophylaxis decreases mortality in liver disease patients following GI bleeding. However, the strength of this evidence may still be in question by clinicians. A total of 864 patients were evaluated in the eight studies of antimicrobial prophylaxis in cirrhotic patients with GI bleeding. Methodology differed with respect to selection of intervention, timing and length of therapy. These variations make a specific antimicrobial recommendation and associated outcome difficult to identify.

The limitations of our study hinge primarily on the retrospective design, and warrant further discussion. It is not possible to accurately ascertain clinical findings of infection in a medical record review due to incomplete or undocumented data. Microbiological and laboratory findings were employed to ascertain whether patients had developed site-specific infection, but we have no important information on patient symptoms (eg, urinary frequency, cough or abdominal pain); therefore, our values may actually underestimate the occurrence of clinically relevant infection. Unfortunately, we were also unable to consistently collect relevant investigative information (eg, urinalysis, chest radiograph or ascitic fluid). Because data were not collected prospectively, it cannot be determined with full certainty whether antimicrobial therapy was prescribed as prophylaxis against infection or treatment of infection suspected on admission; one-half of cirrhotic patients who received antibiotics did so within 24 h of admission or endoscopy before microbiological findings of infection were available. Length of antimicrobial therapy was not easily determined, because many patients received more than one agent to complete one course of therapy and some patients received repeat treatment during long hospital stays. Tolerability and adverse effects of administered antibiotics were not evaluated, but have not previously been demonstrated to be appreciable when used as prophylaxis (10). Finally, while different bleeding etiologies were identified in our initial search for cirrhotic patients hospitalized specifically with variceal hemorrhage, a review of antimicrobial therapy for cirrhotic patients with any source of GI bleeding would be valuable. Despite the methodological limitations, the overall proportion of patients prescribed antimicrobials in our population was consistent with low rates of antibiotic administration following acute variceal hemorrhage observed in other studies (21).

CONCLUSION

Patients with liver disease admitted with variceal hemorrhage were often not prescribed antimicrobial therapy to reduce the risk of bacterial infection. Our results imply that published practice guidelines are not being consistently observed. A large-scale, well-designed study with mortality outcome may be required to support the recommendations made in clinical guidelines and their successful implementation in practice.

The authors have no conflict of interest to declare. A poster of this research report was presented at the American College of Clinical Pharmacy Annual Meeting in October 2004. This was an unfunded study conducted at Vancouver General Hospital and undertaken in fulfillment of the requirements for directed studies project credit, Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, British Columbia.

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