Role of prophylactic antibiotics in cirrhotic patients with variceal bleeding

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Abstract

Bacterial infections are common in cirrhotic patients with acute variceal bleeding, occurring in 20% within 48 h. Outcomes including early rebleeding and failure to control bleeding are strongly associated with bacterial infection. However, mortality from variceal bleeding is largely determined by the severity of liver disease. Besides a higher Child-Pugh score, patients with hepatocellular carcinoma are particularly susceptible to infections. Despite several hypotheses that include increased use of instruments, greater risk of aspiration pneumonia and higher bacterial translocation, it remains debatable whether variceal bleeding results in infection or vice versa but studies suggest that antibiotic prophylaxis prior to endoscopy and up to 8 h is useful in reducing bacteremia and spontaneous bacterial peritonitis. Aerobic gram negative bacilli of enteric origin are most commonly isolated from cultures, but more recently, gram positives and quinolone-resistant organisms are increasingly seen, even though their clinical significance is unclear. Fluoroquinolones (including ciprofloxacin and norfloxacin) used for short term (7 d) have the most robust evidence and are recommended in most expert guidelines. Short term intravenous cephalosporin (especially ceftriaxone), given in a hospital setting with prevalent quinolone-resistant organisms, has been shown in studies to be beneficial, particularly in high risk patients with advanced cirrhosis.

Core tip: Bacterial infections are common in cirrhotics with variceal bleeding and can influence its outcomes that include early rebleeding, failure to control bleeding and mortality. It remains unsure whether infection or bleeding is the initiating event but prophylactic antibiotics have been proven useful. Short term fluoroquinolones and cephalosporins are the most studied antibiotics, and they are recommended by guidelines in clinical situations that depend on the severity of liver disease and resistance profile.

INTRODUCTION

Upper gastrointestinal (GI) variceal bleeding is associated with significant mortality in cirrhosis. The prevalence of variceal bleed is known to occur in 20%-50% of patients with cirrhosis, with rebleeding as a significant cause of death[1,2]. For the past 30 years, the mortality has improved markedly from intensive use of endoscopic

therapies, vasoactive drugs and antibiotics[3,4]. However, rebleeding and failure to control bleeding remain a significant problem and factors that affect rebleeding are not well-established. Guidelines of major GI societies adopt the use of antibiotics in acute variceal bleeding due to its efficacy in the reduction of bacteremia and spontaneous bacterial peritonitis. The recommendations on the choice of antibiotics are however based on a limited number of studies and mostly with small sample sizes. Furthermore, the clinical effectiveness of antibiotics in preventing rebleeding and/or mortality is not firmly established[5]. There are also issues with antibiotic resistance and emergence of hospital-acquired infections.

The current review aims to revisit issues surrounding infection and antibiotic usage in cirrhotics with variceal bleeding. PubMed/Medline was searched for English language scientific publications for human studies from 1980 to the present. MeSH terms including "antibiotic(s)", "infection(s)", "variceal", "cirrhotic", "hemorrhage or haemorrhage", "bleeding" were searched with operators "AND" and "OR". A total of 72 articles were returned from the search and these were further filtered and classified for the current review with additional articles taken from references in the above papers, if deemed necessary. Guidelines of societies including American Association of Study of Liver Diseases (AASLD), American College of Gastroenterology (ACG), World Gastroenterology Organisation (WGO), British Society of Gastroenterology (BSG) and the Baveno V consensus conference were also reviewed.

ROLE OF BACTERIAL INFECTIONS IN REBLEEDING AND MORTALITY

Bacterial infections are frequent in cirrhotic patients with liver failure. The reported in-hospital incidence is approximately 40% with mortality being related to a higher Child-Pugh score[6]. Likewise, infections are common in cirrhotic patients with variceal bleeding, with the risk of death higher in those with infection diagnosed within 48 h. Bleichner *et al*[7], retrospectively found 22% of bacterial infection occurring within 48 h of admission which was similar to a prospective study by Bernard *et al*[8]. In the same study by Bernard *et al*[8], early rebleeding, defined as recurrence of bleeding within 7 d after admission, was present in 43.5% of patients with bacterial infection compared to 9.8% in those without infection. Using stricter criteria including initial failure to control bleeding and early rebleeding or death within 5 d from admission, Goulis *et al*[9] reported 47% of failures in the control of cirrhotic bleeding. Besides bacterial infections or prior antibiotic use, active bleeding during endoscopy and a higher Child-Pugh score were associated with failure to control bleeding in the multivariable analysis performed in the Goulis's study[9]. These studies suggest that bacterial infection is responsible for early rebleeding (within 7 d) and is associated with failure to control bleeding but its role in mortality is not clear because of small sample

sizes of reported studies and there is an influence of severity of liver disease on death.

Which group of cirrhotic patients is at a higher risk for infection during bleeding? Patients with hepatocellular carcinoma (HCC) and variceal bleeding tend to have a greater rebleeding rate[10] and a study from Taiwan suggests that this was due to a higher infection rate in these subjects[11]. However, studies from the West, with patients mostly having alcoholic cirrhosis as the etiology, indicate that the severity of liver disease is a predictor of infection[8,9].

BLEEDING FIRST OR INFECTION FIRST?

It remains debatable whether variceal bleeding results in bacterial infections or vice versa. The invasive nature of endoscopic procedures[12] or other instrumentations that include urethral catheters and transjugular intrahepatic portosystemic shunts (TIPS) may cause a breakdown in natural defenses. Moreover, there is an increased risk for aspiration pneumonia as a result of hematemesis, during endoscopy and placement of balloon tamponade[12]. The increased bacterial translocation[13] and deficiency of complements[14] in bleeding cirrhotics and hypovolemia may also predispose to infection. On the other hand, bacterial infections, through the release of endotoxins and the failure of cirrhotics to remove them, can result in a generalized intravascular activation of mediators (endothelins) that damage the vessels, increase the portal pressure as well as hematologic or hemostatic impairment[15,16].

If infection is the cause of bleeding, then antibiotic administration as soon as possible is a logical approach, and those who are cirrhotics already on antibiotic prophylaxis may have a reduced chance for bleeding. If bleeding is the cause of infection, then likewise, antibiotics should be administered as soon as possible, even prior to endoscopic therapy. Retrospective studies have shown that infection occurred in 13% of patients within 24 h and increasing to 22% within 48 h, reiterating the importance of starting antibiotics early[7]. Indeed, experts and guidelines recommend administration of antibiotics prior to endoscopy but again evidence are lacking on whether this approach does reduce rebleeding and improves mortality. There is a window of opportunity of 8 h for administering antibiotics following endoscopy if this is initially missed[17]. A retrospective study suggested that antibiotics administered up to 8 h following endoscopy were associated with improved survival at 28 d and a trend in reducing 28-d rebleeding rate[17].

WHICH ORGANISMS ARE INVOLVED IN CIRRHOTIC BLEEDING?

The most commonly isolated organisms during bleeding are aerobic gram negative bacilli of enteric origin which can include *Escherichia coli*, *Klebsiella* spp, *Enterococcus* and *Pseudomonas* spp[11,18]. Bacteremia, spontaneous bacterial

peritonitis (SBP) and urinary tract infections were clinical infections most commonly reported in association with the above mentioned organisms. There are a number of case reports of less common organisms being isolated and which can be associated with more severe bleeding complications. These organisms include Oerskovia xanthineolytica[19], methicillin-resistant Staphylococcus aureus[19] and vibrio vulnificus[20]. Infections can also be introduced during endoscopic ligation therapy, which is occasionally severe, as in a reported case of pyogenic meningitis[21]. Bacteremia is also more common following cyanoacrylate therapy for bleeding gastric varices but not elective cyanoacrylate injection for non-bleeding gastric varices[22]. Organisms identified from blood cultures and needle-tip cultures performed in the former group were from the oral and GI tract[22].

Helicobacter pylori (*H. pylori*) infection is also thought to have a role in cirrhotic GI bleeding. A recent study from Japan suggests a protective role for *H. pylori* in variceal bleeding through the induction of gastric mucosal atrophy and concomitant hypoacidity[23]. The use of broad spectrum antibiotics and for long duration in cirrhotics may result in the emergence of health-care associated infections especially *Clostridium difficile* (*C. difficile*), which was recently shown to result in a higher mortality in this group of patients[24]. Although the study by Brown *et al*[17] did not find any significant difference in the incidence of *C. difficile* infection, the prevalent use of metronidazole in this retrospective study casted doubt on the validity of their result[25].

CHOICE OF ANTIBIOTICS: WHAT IS THE EVIDENCE?

The use of antibiotics in cirrhotic bleeding arises from its success in the prevention of SBP and spontaneous bacteremia. This was first shown in a study by Rimola and colleagues in 1985[26]. In this study, 140 cirrhotic patients were randomized into 2 groups - one with oral, non-absorbable antibiotics (gentamicin + vancomycin + nystatin or neomycin + colistin + nystatin) for 48 h and the other without antibiotics. The incidence of infection was observed to be significantly lower in the group receiving antibiotics compared to the group without (16.1% *vs* 34.7%)[26].

Fluroquinolones, namely norfloxacin and ciprofloxacin, seem to be obvious choices for prophylaxis since this group of antibiotics is active against the majority of enterobacteria and aerobic gram negative bacilli. Norfloxacin, given orally or through a nasogastric tube, 400 mg twice daily for 7 d immediately after emergency endoscopy, was shown to reduce infection, with a rate of only 10% in 60 patients compared to 37.2% in 59 controls[27]. Ciprofloxacin has the advantage of being well-tolerated, has low hepatic toxicity and also less bacterial resistance even after 6 mo of treatment. In a case-control study from Taiwan, 120 cirrhotic patients with upper GI bleeding who had received ciprofloxacin 500 mg twice daily after endoscopy for 7 d were found to have a lower incidence of proven bacterial infection, but not mortality, compared to 60 patients who had placebo (10% *vs* 45%)[18]. Patients with Child-Pugh Class C and those with hepatocellular carcinoma are particularly prone to infection and ciprofloxacin in these patients were found to be especially useful. In a study by Pauwels *et al*[28], 30 patients with advanced cirrhosis were found to have a higher rate of infection compared to 55 patients with Child-Pugh Class A-B (52.9% *vs* 18.2%). In the same study, a selected group of high risk patients were administered amoxicillin-clavulanic 1 g/200 mg *iv* q8h followed by ciprofloxacin 200 mg *po* q12h for 3 d after cessation of bleeding, and a significant reduction in infection was observed, compared to those who did not receive this regime (13.3% *vs* 52.9%)[28].

In addition to reducing the incidence of infection, prophylactic quinolones given during cirrhotic bleeding have been shown to reduce early rebleeding and requirements for blood transfusion. This was shown in another study from Taiwan that randomized cirrhotic patients with bleeding into two groups - one group with 59 patients given prophylactic antibiotics (ofloxacin 200 mg *iv* q12h for 2 d followed by oral ofloxacin 200 mg q12h for 5 d) and the other group with 61 patients that only received antibiotics when infection became evident (on-demand group)[11]. Again, survival was not shown to be different between the two groups despite the beneficial effect of prophylaxis on rebleeding rate.

Several earlier studies explored the administration of intravenous antibiotics prior and immediately after endoscopic sclerotherapy, but no efficacy could be demonstrated. Rolando *et al*[29] commenced imipenem-cilastatin 500 mg *iv* at sedation and a further 500 mg 6 h after endoscopic sclerotherapy in 107 sessions and this was compared to dextrose-saline in 88 sessions. There was no significant difference in the infection rate (1.1% *vs* 5.6%), and the authors concluded that a short antibiotic regime does not affect the risk of early bacteremia following endoscopic sclerotherapy. Likewise, Selby *et al*[30] could not demonstrate the clinical efficacy of prophylactic antibiotics (cefotaxime 1 g *iv*) given in 19 patients before sclerotherapy, as clinical infection attributable to sclerotherapy did not develop despite a reduction in bacteremia.

The choice of oral quinolones as the best antibiotic for preventing infection in cirrhotic bleeding has been questioned in recent studies. There are increasing reports of quinolone-resistant flora[31] especially *Escherichia coli*[32] and other infections which were gram-positive possibly related to invasive procedures[33] performed in these patients. This led to a study from Barcelona that randomized 124 patients with advanced cirrhosis into 2 groups - one group with 63 patients given oral norfloxacin 400 mg q12h for 7 d and the other group given *iv* ceftriaxone 1 g once daily for 7 d)[34]. Ceftriaxone was chosen by the investigators for 2 reasons; one being that most quinolone-resistant bacteria are susceptible to third-generation cephalosporins and the other fact that the *iv* route is

more accessible during active GI bleeding. This study demonstrated that norfloxacin was associated with a higher probability of SBP and spontaneous bacteremia as compared to ceftriaxone, but hospital mortality was not different between the two groups. The changing microbiology of infection (susceptibility to both gram negative and positive organisms) and the delay in onset of action from an oral route of norfloxacin, might explain the failure of oral quinolones. Most importantly, *iv* ceftriaxone is more efficacious in the setting of severe liver failure since non-enterococcal streptococci and quinolone-resistant gram negative organisms were more common in this group of patients. A study from Poland, however, did not find any difference in early or late survival rate whether antibiotics were administered orally (norfloxacin) or *iv* (ampicillin/sulbactam), but this study suffered from a small sample size[35].

Other cephalosporins that have been recently studied include *iv* cefotaxime (third generation) and *iv* cefazolin (first generation). In a prospective randomized trial from South Korea, *iv* cefotaxime 2 g q8h for 7 d was administered to 62 cirrhotics with GI bleeding and this was compared to 58 patients given on-demand quinolones[36]. The prophylactic group was shown to have a lower infection and early rebleeding rate within 6 wk. However, it was not known whether *iv* cefotaxime was similarly effective as *iv* ceftriaxone in cirrhotics with more severe liver disease. A study from Taiwan recently studied *iv* cefazolin, a first generation cephalosporin, which has been shown to be effective in reducing infection in bleeding cirrhotics and is also cheaper than *iv* ceftriaxone[37]. The study found that *iv* cefazolin is as similarly effective as *iv* ceftriaxone for patients with Child-Pugh Class A (group A; 51 patients) but not Class B and C (group B; 51 patients)[38]. However, the small sample size and retrospective design did not allow a firm conclusion on the role of *iv* cefazolin.

Similar to esophageal varices, bleeding gastric varices is associated with bacteremia and antibiotic prophylaxis is recommended. In a study from Taiwan, 32% of patients with gastric varices developed bacteremia, and the risk was higher in emergency gastric varices obliteration[39]. More patients injected with cyanoacrylate had positive blood cultures than the control group (15/47 *vs* 1/47). Most episodes of bacteremia were found to be transient and organisms cultured were identical to those cultured from endoscope accessory channel. In another study from the same group in Taiwan, routine antibiotic prophylaxis was given to all 20 subjects who received simultaneous injection of gastric varices and banding of esophageal varices[40]. Even though the infection rate did not increase, the rebleeding rate did not differ either. In a long-term follow-up of four years of 31 patients receiving cyanoacrylate for gastric variceal bleeding, only two subjects developed pyrexia within 24 h of injection that settled with prophylactic antibiotic and had a low rebleeding rate of 16%[41]. These studies indicate that while bacteremia is common after cyanoacrylate therapy for bleeding gastric varices, it is transient and easily treated with prophylactic antibiotic.

Aside from their anti-microbial actions, prokinetic effects of antibiotics such as erythromycin have also been found to be beneficial in cirrhotic bleeding by improving visibility during endoscopy. In a randomized double-blind placebo-controlled study involving 102 patients, *iv* erythromycin lactobionate significantly improved visualization of the stomach and shortened the duration of endoscopy following a cirrhotic GI bleed[42].

WHAT THE GUIDELINES SAY?

All practice guidelines and consensus statements agree that antibiotic prophylaxis is an integral part of medical therapy in cirrhotics with acute GI bleeding. The British Society of Gastroenterology (BSG) guideline in 2000 suggested that the choice of antibiotic and its dose should be decided by the unit where patients were being treated. However, it recognized that fluoroquinolones (ciprofloxacin) had the best evidence at that time[43]. AASLD and ACG practice guideline in 2007 recommended the use of short term prophylactic antibiotics in cirrhotics and GI bleeding with or without ascites[44,45]. Oral Norfloxacin 400 mg q12h for 7 d was the suggested schedule, with oral or *iv* ciprofloxacin the alternative. Although *iv* ceftriaxone was mentioned as being more effective than norfloxacin in advanced cirrhosis, the AASLD/ACG practice committee felt that the prevalence of quinolone-resistant organisms in individual studies would have affected the results. WGO practice guideline in 2008 gave similar recommendations but with *iv* ceftriaxone being recommended in advanced cirrhosis[46]. The Baveno V consensus workshop in 2010 recommended oral quinolones for most patients and *iv* ceftriaxone in advanced cirrhotics only in hospital settings with a high prevalence of quinolone-resistant bacterial infections and in patients on previous quinolone prophylaxis[47].

EFFICACY OF COMBINATION THERAPY THAT INCLUDES ANTIBIOTIC IN ACUTE VARICEAL BLEEDING

While the evidence suggests an integral role of antibiotics, it is not used in isolation. Antibiotics in combination with somatostatin and endoscopic ligation were shown in a study from Barcelona to be effective in reducing mortality in all stages of cirrhosis, even in the high risk groups (Child-Pugh Class B with active bleeding and Child-Pugh Class C)[48]. Patients with Child-Pugh Class C and a baseline creatinine of $\geq$ 1.0 mg/dL are at an especially high risk, and an early use of covered TIPS in such patients may be beneficial[49]. In a study from Italy, the 5-d mortality rate was related to Child-Pugh Class C, white cell count > 10×10^9/L and the presence of portal vein thrombosis[4]. In this Italian study with a 28.1% hepatocellular carcinoma rate, treatment with a combination of vasoactive drugs, band ligation and antibiotics was found

Table 1 Summary of studies on antibiotics used in cirrhotics with acute variceal bleeding

Ref.	Year	Sample size, with antibiotics *vs* control group (total)	Type of antibiotic (s) *vs* control group	Infection rate in those with antibiotics *vs* control group
Rimola *et al*[26]	1985	68 *vs* 72 (140)	Gentamicin + vancomycin + nystatin Or neomycin + colistin + nystatin *vs* without antibiotic	16.2% *vs* 34.7%
Soriano *et al*[27]	1992	60 *vs* 59 (119)	Norfloxacin 400 mg *po* q12h *vs* no antibiotic	10% *vs* 37.2%
Rolando *et al*[29]	1993	107 *vs* 88 sessions	Imipenem-cilastatin 500 mg *iv* at sedation, further 500 mg 6 h after sclerotherapy *vs* dextrose-saline	1.1% *vs* 5.61%
Selby *et al*[30]	1994	19 *vs* 20 (39)	Cefotaxime 1 g *iv* before sclerotherapy *vs* no antibiotic	5.3% *vs* 31.6%
Pauwels *et al*[28]	1996	34 *vs* 30 (64)	Amoxicillin-clavulanic 1 g/200 mg *iv* q8h followed by ciprofloxacin 200 mg *po* q12h for 3 d after cessation of bleeding *vs* no antibiotics (high risk group)	13.3% *vs* 52.9%
Hsieh *et al*[18]	1998	120 *vs* 60 (180)	Ciprofloxacin 500 mg *iv* q12h *vs* without antibiotic	10% *vs* 45%
Hou *et al*[11]	2004	59 *vs* 61 (120)	Ofloxacin 200 mg *iv* q12h 2 d followed by ofloxacin 200 mg *po* q12h 5 d *vs* without antibiotic	3.4% *vs* 26.2%
Fernández *et al*[34]	2006	61 *vs* 63 (124)	Ceftriaxone 1 g *iv* od 7 d *vs* norfloxacin 400 mg *po* q12h 7 d	2% *vs* 12%
Jun *et al*[36]	2006	62 *vs* 58 (120)	Cefotaxime 2 g *iv* q8h 7 d *vs* on-demand quinolone	3.2% *vs* 15.5%
Wu *et al*[38]	2013	Child-Pugh A: 51; Child-Pugh B + C: 51 (102)	Cefazolin 1 g *iv* q8h 2-7 d *vs* ceftriaxone 1 g q12h 2-7 d	6.9% *vs* 9.11% (Child-Pugh A) 22.2% *vs* 12.5% (Child-Pugh B + C)

[1]*P* value not significant (> 0.05).

to be effective in controlling bleeding.

CONCLUSION

Bacterial infection is frequent in cirrhotic patients who present with upper GI bleeding. It is associated with early rebleeding and possibly mortality, especially in those patients with severe liver disease and HCC. To date, it is uncertain whether infection or bleeding is the primary event. Antibiotics given in combination with other standard therapy (including vasoactive agents and endoscopic therapy) and initiated for short term (7 d) before endoscopy and possibly up to 8 h following endoscopy are associated with a reduction in infection rate and a lower early rebleeding rate, but not improvement in survival. A summary of reported studies on antibiotic use in cirrhotics with acute variceal bleeding is given in Table 1. Oral quinolones, given for a short term (7 d) are useful in mild liver disease and in settings where quinolone-resistance is less of a problem. Intravenous ceftriaxone (or other third-generation cephalosporin) is likely useful in the setting of advanced liver disease and where quinolone-resistance is a concern.

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