Review Article

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Infections in Acute Variceal Bleeding and Role of Antibiotics

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Epidemiology

Due to several defective in bacterial defense mechanisms, cirrhotic patients are susceptible to bacterial infections. The most common infections are spontaneous bacterial peritonitis (23-32%), urinary tract infection (10-41%), pneumonia (17-21%) and bacteremia (13-21%)[1-4]. Majority of infections involved in a single site[3], gram negative bacteria especially *Escherichia coli* being the most common pathogen detected[3]. Apart from impairment of the reticuloendothelial system, small bowel dysmotility, bacterial overgrowth in the small intestine, and increased intestinal permeability in cirrhotsis[5], variceal bleeding has been reported as an independent factor for bacterial infection[1,2,6]. Husová, *et al* reported a higher rate of bacterial infection among patients with acute portal hypertensive related bleeding (25 of 35 patients, 71%) than among patients with liver cirrhosis and portal hypertension without acute bleeding (14 of 35 patients, 40%, $p < 0.01$). Various tubes insertion (NG, CVP, endotracheal and Senstagen-Blakemore) causing infections has been concerned as another important factor. Gastric content refluxation as an endogenous source for bacterial colonization of ventilator tubing systems was demonstrated from a surveillance study in patients who admitted in the intensive care unit[7]. One of the well known infections related to Senstaken-Blakemore tube insertion is the development of aspiration pneumonia after prolonged tube insertion[8]. To date, there has been no direct study comparing the risk from these tubes causing infection in variceal bleeders.

Prophylactic antibiotics and risk of infection, mortality and rebleeding

The routine investigation to detect early infection nowadays in patients who present with variceal bleeding includes a complete blood count, urine analysis. A chest X-ray, abdominal paracentesis, throat culture, and hemoculture are indicated in selected patients. In a prospective surveillance study, Lata et al demonstrated a higher rate of positive blood and throat cultures in bleeders than controls[9].

Since anaerobic bacteria has been known to maintain gut resistance against intestinal colonization, overgrowth, and extra-intestinal spread of pathogens[10], then selective intestinal decontamination by eradicating gram negative bacteria and preserving anaerobic flora has been suggested as a method of preventing bacterial infections in these patients. A meta-analysis from 19 randomized controlled trials, without heterogeneity, showed the beneficial effect of prophylactic antibiotics in reducing mortality (RR: 0.70; 95% CI: 0.56, 0.89) and prevention of bacterial infection (RR: 0.39; 95% CI: 0.32, 0.48) for cirrhotic. Patients who admitted in the hospital[11]. When focusing in the group with gastrointestinal bleeding, prophylactic antibiotics play important roles in reducing mortality (RR 0.73, 95% CI 0.55 to 0.95) and the incidence of bacterial infections (RR 0.40, 95% CI 0.32 to 0.51) significantly[12]. The same meta-analysis[12] also reported no significant efficacy of the individual antibiotic regimens versus placebo/no intervention on the survival rate (quinolones: RR 0.73, 95% CI 0.46 to 1.15;

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quinolones + amoxycillin/clavulonic acid: RR 0.74, 95% CI 0.42 to 1.31; other antibiotic regimens: RR 0.72, 95% CI 0.48, 1.08). Moreover, all regimens provided significant results over the placebo/no intervention regarding the incidence of bacterial infections (quinolones: RR 0.30, 95% CI 0.20 to 0.46; quinolones + amoxycillin/clavulonic acid: RR 0.38, 95% CI 0.23 to 0.62; other antibiotic regimens: RR 0.53, 95% CI 0.38, 0.75). Comparing to on demand antibiotic treatment, a study from Taiwan[13] has shown that antibiotic prophylaxis can prevent infection and rebleeding as well as decrease the amount of blood transfused for acute variceal bleeding. In addition, early rebleeding within 7 days reduced significantly (4/12 vs. 21/27, $p = 0.0221$). The relative hazard of rebleeding within 7 days was 5.078 (95% CI: 1.854-13.908, $p < 0.0001$). Likewise in a study with the use of an intravenous cefotaxime, June *et al* reported that the actuarial rebleeding rate in patients who received prophylactic antibiotic was significantly lower than that in the on-demand group (33.9% vs 62.1%, $p = 0.004$)[14]. Currently, there is no consensus on the choice of antibiotic for this situation, oral quinolones and intravenous cephalosporins as a single agent or in a combination have been used in many trials[15-18]. However, in the era of high incidence of infections caused by quinolone-resistant organism, a recently study from Barcelona demonstrated that 7 days intravenous ceftriaxone was better than oral norfloxacin for prevention of possible infections, proved infections, and spontaneous bacteremia or spontaneous bacterial peritonitis (11% vs 33%, $p = 0.003$; 11% vs 26%, $p = 0.03$; and 2% vs 12%, $p = 0.03$, respectively)[19]. In Asian-Pacific countries where quinolones have been used widely, the possibility of quinolones failure to prevent infection, rebleeding rate and decreasing mortality has to be kept in mind.

Risk of infection in elective endoscopy for esophageal and gastric varices

Although, elective sclerotherapy and band ligation for esophageal varices (EV) have been reported to be associated with transient bacteremia in 2-12% of cirrhotic patients[20-24], the reported risk of clinical infection was insignificant. Gram-positive oral flora were mostly identified from blood cultures, In contrast, patients who developed clinical significant peritonitis, gram negative bacilli were identified and these were not correspondent to the results of blood cultures[24]. Elective injection of gastric varices (GV) with cyanoacrylate has been accepted as a common practice worldwide to further obliterate GV. The risk of bacteremia from cyanoacrylate injection for GV was only found during the emergency endoscopy[25]. By contrast, in an elective setting, the risk of bacteremia was reported as zero[26]. It is speculate that the bacteremia develops from ruptured variceal membrane. In addition, gastric acidity and pepsin possibly reduce the number of organism in the stomach of patient undergoing elective GV injection[27]. Moreover, a significant protective effect of bacterial invasion by cyanoacrylate has been shown in vitro studies[28,29].

Consensus statements

1) Acute variceal bleeding contains a significant risk for bacterial infections (1b, A), and prophylactic antibiotic is recommended (1a, A).

2) Antibiotics have been proven to prevent bacterial infection (1a, A), to reduce mortality (1a, A) and rebleeding rates in cirrhotics with acute bleeding (1b, A).

3) Intravenous cephalosporin is preferred over oral quinolone for prophylaxis against infection, bacteremia and spontaneous bacterial peritonitis (1b, A).

4) Risk of significant infection in elective sclerotherapy and variceal ligation for esophageal and gastric varices is low, therefore prophylactic antibiotic may not be necessary (1b, A).

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