

Bacterial Infection in Liver Cirrhosis

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ABSTRACT

Patients with liver cirrhosis frequently have infection which can deteriorate further the already impaired liver function. The most common form of infection in this particular patients are spontaneous bacterial peritonitis, urinary tract infection, and respiratory infection. Causative organism mostly Gram negative micro organism and originate from the gastrointestinal tract. The weaken of immune defense mechanism and also the altered gastrointestinal tract motility can explained most of these infection. This paper will review the bacterial infection in liver cirrhosis with some guidance in the management.

Key words: Liver cirrhosis, spontaneous bacterial peritonitis, systemic antibiotic treatment.

INTRODUCTION

Liver cirrhosis is a diffuse chronic liver disease, characterized by the formation of connective tissue and nodules. It usually begins as inflammation, widespread liver cell necrosis, formation of connective tissue and nodule regeneration. These things cause changes where micro and macro circulation is no longer regular, due to increased connective tissue and the newly formed nodule. In Indonesia, the most common form is post-necrosis liver cirrhosis.^{1,2}

Patients with cirrhosis have a high risk of bacterial infection. This increased risk is correlated to the severity of liver disease and the length of hospitalization. The most frequent infection in cirrhotic patients is spontaneous bacterial peritonitis (7-23%), respiratory tract infection (6-10%), and urinary tract infection (12-29%). However, in 1/3 to 1/2 of cases, the source of infection and type of causative microorganism remains unknown. The incidence of infection in hospitalized patients is very high (30-50%). These bacterial infections cause 25% of deaths in patients with liver cirrhosis.^{5,6}

ETIOLOGY

Escherichia coli is a commonly encountered microbe. Negative-gram bacteria are more common than positive-gram bacteria, as seen in the following table (Table 1 and Table 2).^{7,8}

Table 1. The Microorganism Pattern in Spontaneous Bacterial Peritonitis

Organism	Percentage
E. coli	43
K. pneumoniae	8
Streptococcus pneumoniae	8
Haemolytic streptococcus A	5
Unclassified streptococcus	4
Haemolytic streptococcus B	4
Pseudomonas	2
Staphylococcus aureus	2
Others	16

Table 2. The Microorganism Pattern in Bacteremia in Chronic Liver Disease

Organism	Percentage
Staphylococcus	21
E. coli	16
Streptococcus pneumoniae	16
Streptococcus viridans	5
K. pneumoniae	5
Proteus sp	5
Pseudomonas	-

IMMUNE REACTION DURING INFECTION

Everyone is exposed to various environmental microbes that are ready to attack at any minute, but the body constantly tries to defend itself. The body's reaction towards infection differs according to the type and function of T lymphocytes, B cells that produce antibodies, and the number of memory cells. In addition, immune reactions also depend on the type and character of the attacking microbe. On the other hand, various microbes have different ways to avoid these reactions.³

For most infections, there is a balance between the body's defense system to fight off infection and the ability of the microorganism to avoid the body's defense system. Nevertheless, manifestations of infectious diseases may occur if the host's immune system is unable to ward off infection.^{3,4}

GENERAL IMMUNE RESPONSE AGAINST INFECTION

The Body Surface Defense Mechanism

The body's defense mechanism towards infection can be generally classified into two groups, the non-specific immune response and the specific immune response. Nevertheless, there is no clear cut line between these two defenses systems, since they support each other. The specific immune response can take place with the assistance of components of the non-specific immune system, such as the macrophage, cytokine, and so on. The natural or hereditary non-specific response includes body surface barriers, secretion of certain substances such as lysozyme inside saliva, tears, and nasal secret. Ig A and normal flora are external defense mechanisms, along with phagocytes and complement. The barrier mechanism and the external body defense system are very effective. The skin and the epithelial or mucosal surface are protective systems with a great ability to limit the entrance of pathogenous microorganisms that has effect on body tissues, except if the barrier function is disturbed. On the other hand, pathogenous microorganisms release certain substances on their surface that allow them to adhere to epithelial or mucosal surface. After a microorganism adheres on an epithelial surface, it does not automatically penetrate the cell, even though the microorganism tries to fight the barrier, such as by releasing protease. Even though various cells in the body are capable of phagocytosis, the main cells that play a role in the non-specific defense system are the mononuclear cells (monocytes and macrophages), as well as polymorphonuclear cells or granulocytes. These two kinds of cells are

phagocytes that originate from the granulocyte hemopoietic stem cells that have granules containing hydrolytic enzymes and lactoferrin, which are bactericidal in character. Effective phagocytosis against initial microbial invasion can prevent the development of disease. Phagocytes also interact with complement and the specific immune system. Destruction of microbes occurs in the following levels: chemotaxis, the capture, phagocytosis, the kill, and digestion. Chemotaxis is the phagocytic movement to the site of infection as a response against various factors such as bacterial products and biochemical factors released during complement activation. Destroyed or dead tissue could also release chemotactic factors. Antibodies such as complement (C3b) can increase phagocytosis (opsonization). Phagocytes can more easily recognize antigen bound by antibody to be destroyed.^{1,3,4,8}

Systemic Defense Mechanism

The systemic defense mechanism can generally be classified into the cellular immune response and humoral immune response, also known as the specific immune response in liver cirrhosis.

Evaluation of immune response in patients with liver cirrhosis includes immune response of the gastrointestinal tract mucosa, immune response in the blood, and immune response in ascites fluid.

Immune Response in the Gastrointestinal Tract Mucosa

Most microorganisms are unable to directly penetrate the gastrointestinal tract. Hydrochloride acid in the gaster, proteolytic enzymes and bile in the small intestines are able to create an environment that could prevent infection. Furthermore, lymphoid cells such as the Peyer plaque and the lamina propria, which contain lymphocytes, plasma cells, and macrophages according to their function, stimulate mucosal immune response.^{3,4,5,6}

Abnormalities found in the mucosal immune system in patients with liver cirrhosis may take the form of small intestine dysmotility, bacterial overgrowth, and blood vessel congestion in portal hypertension.

Under normal intestinal peristalsis, gastric acid and mucosal immunity acts to protect the intestines from bacterial overgrowth. Intestinal peristalsis is a significant inhibitor of bacterial colonization and replication in the gastrointestinal tract. However, bacteria growth in the small intestines causes production short-chain fatty acids (SCFA), due to carbohydrate fermentation by the bacteria. SCFA stimulates proliferation of epithelial cells in the small intestines, causing pseudo-obstruction of the bowel, and

is believed to cause bowel dysmotility. When bowel motility and transit is disturbed, bacteria aggregates. Such bowel transit failure has been proven in rats with portal hypertension. In the most recent study on alcoholic liver cirrhosis, patients with bacterial overgrowth in the small intestines develop a higher rate of spontaneous bacterial peritonitis (SBP). This condition was proven from the fact that bacterial growth was higher in patients with liver cirrhosis and SBP than in patients with liver cirrhosis without history of SBP. Bowel dysmotility is more severe in patients with liver cirrhosis and history of SBP. This could be more clearly illustrated from the fact that selective intestinal decontamination with antibiotics could prevent recurrent SBP. Thus, disturbance of intestinal motility causes bacterial overgrowth that could explain the development of recurrent SBP in patients with liver cirrhosis.⁶⁻¹¹

The gastrointestinal mucosa acts as a barrier against bacteria, toxins, and other bacterial products in the lumen. This barrier is important in preventing bacterial translocation from the intestines through the mesenteric lymph nodes and entering the systemic circulation.

Deitch formulated three mechanisms of bacterial translocation, which are as follows: bacterial overgrowth, failure of the body's defense system, and destruction of intestinal mucosa. Bacterial translocation could also occur due to one or more of these mechanisms under portal hypertension or gastroenteropathy congestion, causing failure of acid secretion and reduced mucosal resistance, making it more vulnerable to destruction by alcohol or bile salts, and the mucosa may suffer from ischemia. Ischemic mucosa facilitates bacterial translocation.⁹⁻¹³

Immune Response in the Blood

Patients with liver cirrhosis and bacterial infection suffer from prolonged bacteremia compared to those with liver cirrhosis alone. This could be due to reduced phagocytic activity of the reticuloendothelial system (RES), reduced complement level and reduced leukocyte chemotaxis. Reduced RES activity plays the main role in the development of bacterial infection in patients with liver cirrhosis. The liver RES consists of Kupffer cells and sinusoidal cells. Reduced liver RES activity is compensated by the activity of RES of the spleen and vertebrae. The mechanism of failure of RES phagocytic activity is correlated with intra-hepatic blood flow shunting due to portal hypertension, causing bacteria to elude phagocytosis by liver RES. The number of bacteria in systemic circulation and ascites are thus increased.^{6,7,12,16}

In addition to reduced phagocytic ability, there is also reduced blood complement level. This complement is a normally inactive molecule, which could be activated by certain substances, such as (bacterial) antigen or immune complex. Such activation produces mediators such as C3a, C5a, and C3b, which have active biologic characteristics. C5a helps increase antibody formation and C3b aids the process of opsonization. Complements are synthesized by hepatocytes, and produced by macrophages, gastrointestinal epithelial tissue, and monocytes.^{4,5,9,16}

Immune Response in Ascites Fluid

Ascites is a collection of fluid in the peritoneal cavity. In cases of liver cirrhosis, ascites indicates a poor prognosis. SBP is a serious complication in patients with liver cirrhosis and ascites. SBP is usually associated with several body defense mechanisms, such as reduced phagocytic RES activity, leukocyte dysfunction, reduced serum complement and low bactericidal activity in ascites fluid. Another factor that is believed to influence the immune capability of ascites fluid in eradicating microbes is reduced protein level. If the volume of ascites fluid is large, the protein level is reduced. Reduced protein content in ascites fluid is believed to be able to reduce bactericidal activity, increasing the risk for SBP. The number of bacteria in ascites fluid is only approximately 1-2 bacteria/cc ascites fluid. Thus, if the bactericidal activity in the ascites fluid functions correctly, the bacteria can be eradicated. If there is diuresis, the protein content in the fluid will be increased. It has long been known that malnutrition reduces immune response ability. Such reduced immune response in cases of malnutrition could occur due to reduced albumin level. Serum albumin level influences serum complement level. Several studies also demonstrate that malnutrition is related with bacterial translocation from the intestinal lumen.^{1,2,6,9,14}

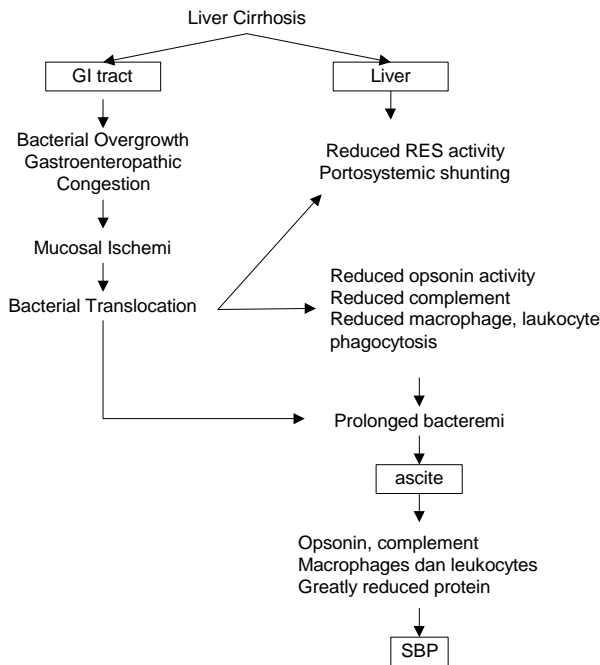


Figure 1. Scheme of Respons in Liver Cirrhosis

Cytokines in Liver Cirrhosis

Cytokine is a peptide mediator that could reduce or increase immune response, inflammation, and the body's response to repair damaged tissue. Cytokines can induce other cytokines or cooperate with other cytokines to stimulate the cell (synergism). On the other hand, cytokines could also prevent the production of other cytokines (antagonism). In general, cytokines can be classified into Interleukin (IL), Interferon (IFN), Tumor Necrosis Factor (TNF), and chemokine (IL-8). Cytokines that have been studied in bacterial infection in patient with liver cirrhosis are IL-1 β , IL-6, IL-8, IFN γ , and TNF α .⁶

Infection results in the release of endogenous mediators that are responsible for inflammatory response, even though such response is aimed towards combating infection, it can also disturb the body's chemo-dynamic and metabolic state. Cytokines, especially TNF α , IL-1 β , and IL-6 are the most important sepsis mediators in patients with liver cirrhosis. In addition, intraperitoneal release of IL-6 is significantly high in patients with cirrhosis and ascites complicated by spontaneous bacterial peritonitis (SBP). The most recent study demonstrated a positive relationship between the circulatory level of TNF α and IL-6 with mortality in alcoholic hepatitis patients.^{6-8,14,18,19}

All data demonstrate that the inflammatory response against infection determined from plasma cytokine

levels and ascites fluid increases in patients with cirrhosis, where cytokine can be an important prognostic factor. Renal insufficiency (RI) in SBP (SBP-RI) is common in patients with cirrhosis accompanied by ascites, and is an important predictor of the patient's survival. The connection between the development of SBP-RI and mortality during hospitalization, and the degree of inflammatory response induced by intraabdominal infection, is through the release of intraperitoneal cytokines into the systemic circulation result in a circulation dysfunction and renal insufficiency, thus leading to death.

Positive culture in 50-85% of SBP cases and cytokine in ascites fluid in SBP may originate from peritoneal macrophages and mesothelial cells. The concentration of IL-6 and TNF α in ascites fluid is far higher than the plasma level. On the other hand, there is a direct relationship between cytokine level in ascites fluid and that in plasma, indicating a cytokine level approximately the same in the blood and intraabdomen. This finding demonstrates a rapid drop of cytokine concentration in ascites fluid and plasma after administration of antibiotics, as seen 48 hours after the administration of cefotaxim, where the cytokine levels in all patients that responded were reduced. Patients with SBP and positive culture containing gram-negative bacteria demonstrated a higher cytokine level in plasma and ascites fluid, as well as increased PMN cell count. This demonstrates that in SBP, intraabdominal inflammatory response can be estimated from PMN concentration and cytokine level in ascites fluid depends on the concentration and type of causative organism. When correlated, SBP-RI demonstrated similarly high concentrations of PMN in ascites fluid and plasma, as well as high cytokine levels in ascites fluid compared to patients without renal insufficiency. Renal insufficiency can occur spontaneously in patients with cirrhosis and ascites. This is believed to be related to arterial vasodilatation. Hepatorenal syndrome is an extreme condition that occurs during this circulatory dysfunction. Nitric oxide is believed to play a role in this abnormality, because cytokine stimulates vascular tissue to produce nitric oxide.^{9,15,19,20,21}

The Effect of Infection on Esophageal Variceal Bleeding

Variceal bleeding is a fatal complication of liver cirrhosis, and bleeding cannot be predicted. Bacterial infection in patients with variceal bleeding may be the main trigger of bleeding. Variceal dilatation and increased pressure of variceal wall causes release of endotoxins

into the systemic circulation during the episode of bacterial infection. Afterwards, portal pressure increases through endothelin induction, producing an end result of cyclo-oxygenase, which causes vasoconstriction. In addition, endotoxin stimulates nitric oxide and prostacyclin. This endothel-produced prostacyclin inhibits platelet aggregation. It could thus be concluded that a combination of these two effects could accelerate variceal bleeding. Varices and variceal bleeding is a direct effect of portal hypertension that occurs in chronic liver disease. Continuous bleeding should receive immediate care, and recurrent bleeding at initial stages could increase the morbidity and mortality rate.^{1,3,4,10,12,16}

Variceal bleeding is a common and severe complication in cirrhotic patients, even with various new therapies such as pharmacotherapy, variceal ligation, and transjugular hepatic portosystemic shunt (TIPS). Nevertheless, the mortality rate remains high due to inability to control bleeding. Sixty percent of cases of bacterial infection that often occurs in cirrhotic patients with gastrointestinal bleeding significantly influences mortality. Research demonstrates that bacterial infection can be prevented by administration of antibiotics. However, we must also be aware that there are differences in the evidence of infection with administration of antibiotics, since bacterial infection in cirrhotic patients cannot be proved microbiologically. Evidence of infection characterized by fever, leukocytosis, or clinical symptoms of pulmonary infection, urinary tract infection, or other infections is a prognostic factor for failure to control bleeding. There is a strong correlation between gastrointestinal bleeding and bacterial infection, which can be caused by diagnostic procedures and invasive therapy, increased bowel bacteria translocation, disturbance of the reticuloendothelial system, complement factor deficiency, which can be a predisposing factor of bacteremia in cirrhotic patients. Vice versa, there are data that supports the role of infection in the development of gastrointestinal bleeding. During bacterial infection, there is a release of endotoxin into the systemic circulation. In cirrhotic patients, the reticuloendothelial system fails to destroy the endotoxin. Thus, inflammatory mediators such as cytokine, nitric oxide, platelet activating factor and leukotriene are activated. These mediators destroy the structure and function of the gastrointestinal tract, characterized by vascular dilatation, bleeding, and necrosis, and several abnormal signs such as platelet dysfunction, reactivation of coagulant and fibrinolytic system, and thus gastrointestinal bleeding is no longer a

rare condition in severe bacterial infection. This hypothesis is supported by the fact that most infection in cirrhotic patients with gastrointestinal bleeding were diagnosed on the first day. Thus, therapeutic or prophylaxis antibiotics should be administered immediately during acute bleeding time, thus reducing the frequency of bacterial infection.^{2,9,11,14,24,26}

The Effect of Endotoxins

Endotoxin is a lipopolysaccharide that makes up the outer wall of the negative-gram bacteria. In vivo, endotoxin stimulates the body defense response mechanism. In this mechanism, endotoxin acts as a trigger, stimulating the production of several mediators. In patients with chronic liver disease, high concentrations of endotoxin in the portal and systemic circulation are found due to increased endotoxin translocation from the bowel to the portal circulation. Disturbed phagocyte function of the reticuloendothelial system as well as portosystemic shunting help endotoxin reach the systemic circulation. Thus, the concentration of endotoxin continuously increases progressively according to the severity of liver dysfunction. During the episode of bacterial infection, the concentration of endotoxin released into the systemic circulation increases. Approximately 35-66% of cirrhotic patients with bacterial infection suffer from variceal bleeding. Most of these infections were diagnosed during the first days of treatment. Spontaneous bacterial peritonitis often occurs prior to variceal bleeding. Secondary endotoxemia from bacterial infection can also induce bleeding. Thus, it can be concluded that endotoxin influences the endotoxin effect through the synthesis of endothelin and nitric oxide. The cascade mechanism activated to produce mediators closely related to endotoxin is the complement system, clotting system, and hemostasis, as well as cytokine pro-inflammatory mediators. Septic shock in bacterial sepsis does not occur solely due to endotoxin, but is a direct effect of the simultaneous interaction between microbes, toxins, and endogenous mediators (cytokine). Liver is the chief target organ that functions to eliminate endotoxin from the circulation (>80%). In the liver, endotoxin will be detoxified by Kupffer cells and parenchyme tissue.^{14,16,17,20,23}

The Effect of Endothelin

Endothelin was first identified in 1988, belonging from the "21-amino acid peptide" family, consisting of 3 structures: endothelin (ET-1), ET-2, and ET-3, with two different pairs of receptors, the endothelin A and endothelin B receptors. Endothelin receptors can be found

in all types of liver cells, the stellate, as well as endothelial cells, Kupffer cells, and hepatocytes, even though examination of liver cells demonstrate a more significant number of endothelin receptor on the stellate. The liver stellate cell is activated during liver destruction until the liver is contracted. Thus, this cell plays an important role in the therapy of intrahepatic portal hypertension in liver cirrhosis. In cirrhotic patients, the concentration of endothelin (especially endothelin-1) is increased in the splanchnic circulation, followed by increased activation of liver stellate cells. What is most important is that endothelin causes contraction of stellate cells, causing increased portal pressure, and medication using the endothelin receptor antagonist Bosentan and TAK-044 can significantly reduce portal pressure. Moller has proved that the release of endothelin-1 by the hepatosplanchnic system has a positive correlation with portal hypertension in patients with liver cirrhosis. In laboratory animals, it has been demonstrated that after exposure to endotoxin, the level of endothelin-1 in liver sinusoid endothelial cells and plasma endothelin concentration increases ten folds. Pannen stated that administration of lipopolysaccharide infusion increases portal flow resistance by inducing endothelin, and this effect is inhibited by administration of bosentan. In addition, Yamamoto found that therapy using bosentan and cyclooxygenase inhibitors such as indomethasin can inhibit increased portal vein pressure. During endotoxemia, cyclooxygenase products such as thromboxane A2 and prostaglandin are vasoconstriction mediators that increase portal pressure. Endothelin also induces variceal bleeding through the endothelin effect, where platelet aggregation is inhibited by prostacyclin, a strong platelet aggregation inhibitor. Prostacyclin increases in cirrhotic patients during endotoxemia, by direct action of endotoxin. In addition to inducing endothelin and cyclooxygenase, endotoxin also induces nitric oxides, which inhibit platelet aggregation. A combination of these factors accelerate variceal bleeding.^{4,6,20,23}

MANAGEMENT

Prevention

In patients with liver cirrhosis who suffer from gastrointestinal bleeding, prophylactic antibiotics can reduce the incidence of infection, but does not demonstrate increased survival rate.

Success in selective intestinal decontamination with norfloxacin for prevention of bacterial infection in liver cirrhosis with gastrointestinal bleeding has been

demonstrated in several studies. Administration of 400 mg of norfloxacin twice daily for 7 days significantly reduces the incidence of bacterial infection such as SBP and urinary tract infection.

Aerobic gram-negative bacteria are the most common cause of such bacterial infection, and culture performed on patients with infection for the first 10 days of hospitalization. Initial studies demonstrate bacterial infection in 22% of patients in the first 48 hours after hospitalization. For 7 to 14 days after the initial time of bleeding, the incidence of bacterial infection reaches 35-66%. In addition, infection is closely related to the prognosis of cirrhotic patients suffering from bleeding. A study demonstrated that bacterial infection is the main causative factor of recurrent bleeding in 7 days. Enteric bacteria are the most common cause of infection in patients with liver cirrhosis. Administration of non-absorbable antibiotics reduces the incidence of infection in patients with liver cirrhosis suffering from bleeding. Several studies demonstrate that administration of prophylactic antibiotics can reduce the incidence of infection.

Quinolone, amoxicillin plus clavulanic acid, and non-absorbable antibiotics are possible antibiotics for prophylaxis. Even though therapy seems to differ, their capability in preventing infection has been clearly demonstrated. These medications may be administered for 5 to 10 days.

However, a study by Pauwel demonstrated that administration of prophylactic antibiotics should only be considered in patients with a high risk for infection, Child-pugh's class-C or that with bleeding.

Norfloxacin is a quinolone that produces Selective Intestinal Decontamination (SID) that can inhibit gram-negative aerobic bowel flora, but can maintain anaerobic flora and resistance to colonization in the gastrointestinal tract. Norfloxacin reduces the incidence of infection due to negative gram-bacteria in patients with granulocytopenia, and is useful to prevent recurrent SBP in patients with liver cirrhosis hospitalized with ascites. Rimola found reduced incidence of enteric bacterial infection for the initial 10 days of hospitalization in patients who received non-absorbable oral antibiotics.

The ability of norfloxacin in preventing bacterial infection in patients with liver cirrhosis and gastrointestinal bleeding can be administered orally or via NGT with a dose of 400 mg 2 times/daily for 7 days, and should be administered as soon as possible. It is also said that prophylactic treatment with norfloxacin may

be administered for over 6 months without side effects and without causing bacterial resistance. Because almost 25% of deaths in patients with liver cirrhosis are directly caused by infection, reduction of the incidence of infection should reduce mortality.

Even though gram-negative bacteria are commonly found, Rimola found a high incidence of infection caused by other types of bacteria, especially negative gram cocci. This could occur due to invasive procedures performed on these patients, since infection related to invasive procedures are often caused by gram-positive cocci.^{1,2,8,10,24,25}

Even though usage of prophylactic antibiotics is recommended, long-term administration could increase the incidence of resistance of gram-negative bacilli towards Quinolone. Increased bacterial resistance against prophylactic antibiotics can cause more severe infection than that in patients who have never received prophylactic treatment. Resistance to β lactam has also been observed, since it has been commonly used for the treatment of infection. This makes the treatment of infection in liver cirrhosis more difficult. It must be noted that infection due to norfloxacin-resistant E-coli can occur only after several days of prophylactic treatment. Development of multi-resistant bacteria (resistance to antibiotics other than norfloxacin) should caution the use of prophylactic antibiotics. Analysis of norfloxacin-resistant E. coli demonstrated cross-resistance against quinolone and other quinolones such as ciprofloxacin and ofloxacin. This is related to mutation that influences the target quinolone DNA-gyrase and/or topoisomerase that is the most important mechanism in the development of quinolone resistance.

Increased infection has been observed due to norfloxacin-resistant E-coli in cirrhotic patients who have received other prophylactic antibiotics, trimethoprim/sulfamethoxazole.^{6,10,13,17,26}

Therapy with Systemic Antibiotics

Acute infection, especially bacteremia and infection of ascites fluid, is the most common complication in patients with liver cirrhosis, most commonly caused by microorganism in the gastrointestinal tract. High risks of infection during gastrointestinal bleeding is caused by endoscopic and resuscitation procedures as well as translocation of bowel bacteria. Risks of bacterial infection are associated with the severity of liver disease. The frequency of bacteremia during endoscopic sclerotherapy can reach 50% with the incidence of bleeding. Endoscopic hematemesis of the upper gastrointestinal tract or insertion of the nasogastric tube

could also induce pneumonia.

Short-term mortality in infected patients associated with liver failure is quite high.

There have been study reports that administration of oral antibiotics in patients with liver cirrhosis during gastrointestinal bleeding demonstrates reduced incidence of bacterial infection due to enterobacteria. The latest studies even demonstrate the efficacy of oral norfloxacin in preventing infection by enterobacteria without causing resistance. However, certain therapy cannot be administered during bleeding, and cannot prevent extra-digestive infection.

Systemic antibiotic treatment (SAT) can prevent infection and even reduce mortality. In addition, SAT has the ability to eradicate positive-gram and anaerobic bacteria found from endoscopy during active bleeding. Associated reduction of infection with positive-gram bacteria, especially streptococcus and haemophilus influenzae is found from studies using amoxicillin-clavulanic acid (ACA) and ofloxacin (OFL). Thus, it can be concluded that SAT using ofloxacin and ACA bolus prior to endoscopic procedure can prevent infection in cirrhotic patients with gastrointestinal bleeding, where administration of systemic antibiotics is very simple during gastrointestinal bleeding compared to in oral decontamination.^{8,12,27}

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