Detection Of Helicobacter Pylori Infection With Stool Antigen: Comparison With Other Techniques

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ABSTRACT

Helicobacter pylori has been known as a cause of chronic gastritis, a predisposition to gastric and duocenal ulcers, and a class I gastric carcinogen. Throughout the world, H. pylori infection is very common, reaching 40% -50% of the population in developed nations and 80% – 90% of the population in developing nations.

Several techniques have been used to detect H. pylori infection, such as the urea breath test, rapid urease test, serological test, as well as biopsies of gastric or duodenal tissues for culture and histopathology. In this review article, we will discuss a relatively new method to detect H. pylori antigen in stools with enzyme immunoassay, and comparisons with other standard techniques. However, the H. pylori stool antigen test is not yet commercially available in Indonesia.

Key words: *Helicobacter pylori - stool antigen - enzyme immunoassay*

INTRODUCTION

Helicobacter pylori is a bacteria that infects over 50% of the human population.[1] H. pylori infection particularly occurs during childhood, and resides in the gastric mucosa for long periods of time, or even eternally, if no erradication measures with specific a ntibiotics are taken. In South and Central America, Asia and Africa, approximately 80% of all children are infected by H. pylori at the age of 10 years. Worldwide, H. pylori is very common, reaching 40- 50% of all populations in developed nations and 80-90% of all population in developing nations. In Indonesia, seroepidemiologic studiens at several centers found a prevalence rate of 36-64,3%, with the youngest age of infection at 5 months.[2]

Warren and Marshall were the first to report H. pylori bacteria and its histological correlation with gastritis. This bacteria is associated with acute and active chronic gastritis, peptic ulcer, and atrophic gastritis.[1,3] H. pylori is considered as a class I gastric carcinogen, since its involvement is suspected in gastric adenocarcinoma and mucosa-associated lymphoid tissue (MALT) lymphoma.[4,5,6,7,8] H. pylori erradication in patients with low-grade lymphoma produces a remission rate in approximately 80% of all patients.[9]

Presently, several invasive as well as non-invasive methods are available to detect H. pylori infection, such as the urea breath test, the rapid urease test, serologic testing, and gastric or duodenal tissue biopsy by endoscopy for culture and histopathological evaluation. Nonetheless, for the patient's comfort, diagnostic acuracy, and evaluation of erradication treatment, various new methods have been developed in the hope to find a better diagnostic test. Recently, the non-invasive enzyme immunoassay (EIA) technique to detect H. pylori antigen in the patient's stool (H. pylori stool antigen (HpSA) has been developed. This method has been used in various countries to diagnose H. pylori infection, and even as a follow-up/evaluation of erradication treatment.

CHARACTERISTICS OF HELICOBACTER PYLORI

H. pylori is a negative-Gram bacteria, shaped as spiral, the letter S or curved, is micro-aerophillic, 0.5 x 3 mm in size, and has 4 to 7 coated flagels at one end. When dormant, the bacteria is shaped like a cocoid, and thus can survive in difficult environments. Its natural habitat is the human gaster. However, H. pylori can also

be found in primates and cats.[10]

H. pylori can produce a number of important virulence factors to be able to colonize the gaster and survive in unfriendly environments. The factors include:[1]

1. Urease, which plays an important role in neutralizing gastric acid secretion.
2. Flagel, to assist H. pylori in swimming in the mucous layer.
3. Superoxide dysmutase.
4. Several molecules involved in the specific adhesion to gastric superficial epithelial cells.
5. Cytotoxin-associated gene (CagA) and vacuolating cytotoxin (VacA) proteins, only produced by certain types of H. pylori.

To detect the presence of a microorganism, it is also important for us to know the mechanism for its transmission, to be able to determine the best method of evaluation for certain specimens.

H. Pylori transmission can occur through the following three (3) pathways:

1. Fecal-oral; H. pylori has been isolated in feces.[11]
2. Oral-oral; H. pylori has been isolated from the mouth cavity.
3. Iatrogenic; transmission from instruments for endoscopy, biospy forceps, or pH electrode contaminated with H. pylori.

TESTS TO DETECT H. PYLORI

The Urea Breath Test

The urea breath test (UBT), which uses the isotop ^{13}C or ^{4}C is an easy to perform non-invasive examination. Unlike the serological test, a positive result on the UBT signifies current H. pylori infection with a high sensitivity and specificity rate.[12] The goal of the UBT is to evaluate H. pylori urease activity. The UBT is able to prevent errors due to incorrect endoscopic biopsy sampling in cases of patchy gastritis. The UBT can be used to evaluate H. pylori 4 weeks after the administration of antibiotics, when serologic testing still produces a positive result.[2,13] False negatives occur if H. pylori has been suppressed by treatment with antibiotics or proton pump inhibitors.[12] UBT has a sensitivity rate of 95-99% and a specificity of 94-99%, while for the evaluation of post-H. pylori erradication treatment, it has a sensitivity rate of 94% and a specificity rate of 95%.[9] Cutler et al (1995) in his study compared the sensitivity and specificity of several diagnostic procedures for H. pylori and found the non-invasive UBT procedure as acurate as the campylobacter like organism test (CLO test) and Warthin-Starry staining to determine the H. pylori status in patients that have not undergone treatment.[14] However, the cost to perform this test and the complecity of the instruments cause this test to be rarely used.

Serological Testing

The objective of serological testing is to detect IgG anti-Hp antibodies. This test is non-invasive and is not too expensive compared to the UBT. However, since it requires blood sampling, it sometimes becomes a problem, particularly in children. After treatment for H. pylori, the serological titer for anti-Hp antibodies is slowly reduced within several months to several years, but does not always become negative. In addition, within 6 weeks after treatment for the erradication of H. pylori, the level of H. pylori antibodies only falls to 50-60% from the level before treatment, thus making it more difficult to evaluate the success of treatment.[15] A positive serological test result does not always determine cuurent infection with life bacteria. Serological testing is recommended for epidemiological surveys.[2,13] It has a sensitivity and specificity rate of only 82% and 81%, respectively.[9] A meta-analysis study on 11 commercial enzyme-linked immunoadsorbent assay (ELISA) kit and 1 latex agglutination kit found a sensitivity rate of 85% and a specificity rate of 79%.[16]

Polymerase Chain Reaction

Detection of H. pylori using the polymerase chain reaction (PCR) method was first introduced in early 1990. Because of its sensitivity, PCR is the method of choice to evaluate treatment response, if treatment has been able to reduce the number of bacteria. PCR can be performed from samples from saliva, dental plaques, gastric aspiration, and feces. PCR evaluation from gastric aspiration fluid has a sensitivity and specificity rate of 96% and 96% respectively compared to culture and histological evaluation from antrum biopsy specimens.[17] For H. pylori detection from fecal samples, the PCR has a specificity and sensitivity rate of 93,7% and 100% respectively.[3] Up to now, the PCR has not been frequently used for daily clinical purposes, and is instead more commonly used for research purposes.

Culture

H. pylori can be cultured from gastric biopsy, but the process is slow and requires a specific culture media, thus causing this method to be rarely used.[12] The sensitivity rate can reach over 95%, but other methods to diagnose H. pylori are relatively easier and produces more rapid results. The advantage of performing a culture is the

ability to determine antibiotic resistance. In the case of patchy H. pylori infection, it is difficult to obtain a representative sample for this method of evaluation.[14]

Histopathology

The gold standard for the diagnosis of H. pylori is to detect the organism from gastric biospy that has been processed with histological staining. The sensitivity rate for biopsy reaches 100% for biopsy of the angulus, 96-97% for antrum biopsy and 91-94% for corpus biopsy. If biopsy is taken from the antrum and corpus, the sensitivity rate can reach 100%. Specimen staining methods can influence the acuracy of H. pylori detection.[14] If examined by an experienced pathologist, routine staining with hematoxyllin and eosine can demonstrate the presence of H. pylori. The presence of polymorphonuclear leukocytes in the inflammed gastric mucosa supports H. pylori gastritis due to other causes (such as alcohol and non-steroid anti-inflammatory agents), and does not produce significant PMN infiltration.[12] Other staining include Giemsa, Warthin-Starry and Genta.

Rapid Urease Test

The rapid urease test, also known as the CLO test, was developed by Marshall and specifically designed to detect H. pylori. It has a sensitivity rate of approximately 90%, but varies from one study to the next, even within each institution. Its specificity reaches 95-100%. Gastric biopsy is placed in a media containing urea and phenophtaline. With the presence of H. pylori urease, urea is conversed into ammonium hydroxide, which changes the color of the indicator from yellow to red. A positive CLO test in patients with peptic ulcer is a strong proof of H. pylori infection. If the CLO test proves negative, further histological evaluation is required. As in the UBT, the CLO test and result in a false negative in patients whose infection is suppressed by antibiotics or proton-pump inhibitors.[12] Due to its high cost, the CLO test has become more difficult to obtain in Indonesia.

Enzyme Immunoassay Test for HpSA

It has been proven that patients infected with H. pylori can excrete H. pylori bacteria in their feces, thus allowing the bacteria to be detected in fecal specimen using PCR or culture.[3,11] However, culture of H. pylori from the feces is very difficult, since it is few in number, and PCR is costly. Thus, these two methods cannot be used as routine diagnostic procedures. Thus, a new method using the EIA, which is able to detect H. pylori antigen in human feces was developed (HpSA).

The method of evaluation is roughly as follows. The fecal sample is mixed with 200ml of the sample solvent. The fecal sample is then dissolved with peroxidase conjugated polyclonal antibody and inserted into the micro-well, to then be incubated for 1 hour in room temperature. After the discs are washed to eliminate materials that are not bound, add 2 drops of substrate liquid and incubate for 10 minutes in room temperature. The reaction is terminated by dropping 1 drop of terminating agent. The result is then read using a spectrophotometer.[18]

Makristathis *et al.* (1998) in his prospective study, found that EIA has a sensitivity of 88,9% and a specificity of 94,6% to detect HpSA prior to eradication treatment. Thus, we could conclude that EIA is a satisfactory method to detect H. pylori infection in the feces, since it is just as sensitive as PCR, histology, and gastric biopsy culture.[3]

Fanti *et al.* (1999) in his study to evaluate EIA for HpSA found that this method has a sensitivity of 98,2%, with a negative prediction value of 96,4% and a specificity rate of 93,1% with a positive prediction value of 96,4%. Fanti *et al* concluded that this test has a high and specific sensitivity for the detection of H. pylori infection. Nevertheless, the acuracy of EIA in detecting antigen after erradication treatment requires further evaluation. The most recent reports demonstrate conflicting results, even though most studies report a satisfactory sensitivity and specificity even for HpSA testing after erradication treatment. Likewise, the precise point for the monitoring of H. pylori erradication treatment needs further evaluation.[15]

Vaira *et al.* (1999), in a multi-center prospective study, found a sensitivity rate of 94,1% and a specificity rate of 91,8% for HpSA testing. The HpSA test and the UBT conducted 4 weeks after erradication treatment also found a sensitivity and specificity rates of 90% and 95,3% respectively for HpSA testing, and 90% and 98,9% respectively for the UBT. Thus, unlike serologic testing that requires several months to achieve significant reduction in antibody titer, the HpSA and UBT with ^{13}C can be used not long after treatment (4 weeks).[4]

Formé *et al.* (2000) compared HpSA testing with histological methods, , UBT ewith ^{13}C and the rapid urease test for the diagnosis of H. pylori infection and to evaluate the use to determine H. pylori state after treatment. To diagnose H. pylori infection, the HpSA test has a sensitivity and specificity rates of 89,5% and 77,8% respectively. The specificity is lower than that of UBT, histological evaluation and rapid urease test. Within 24 hours after treatment, the sensitivity test for HpSA is 0%. Within 6 weeks after treatment, the sensitivity falls to 70,4% and 81,6%.

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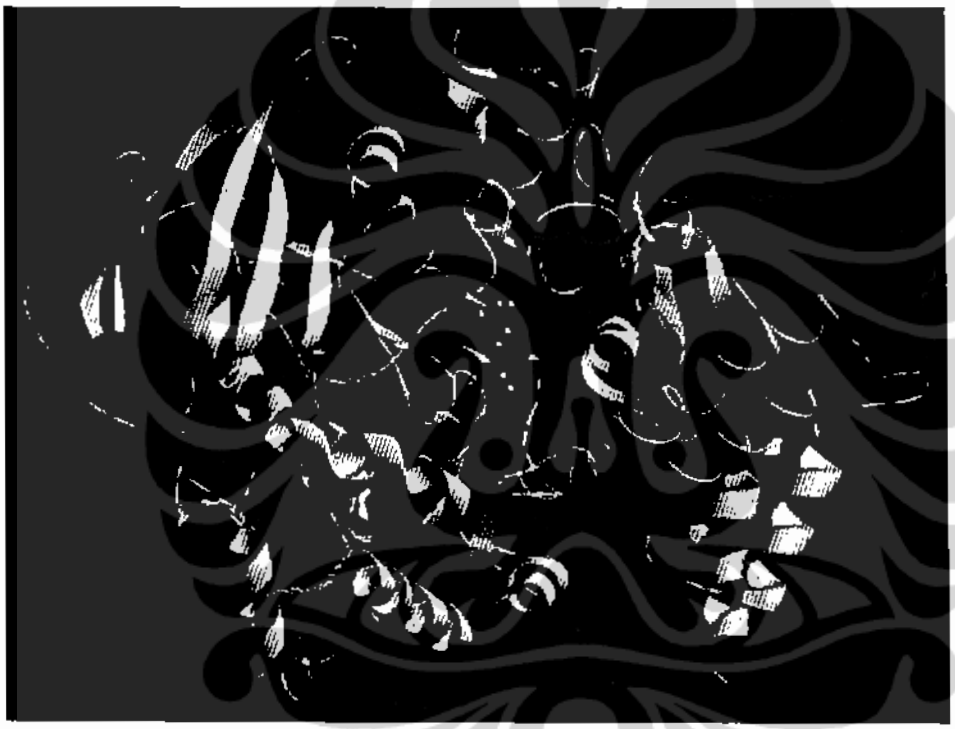

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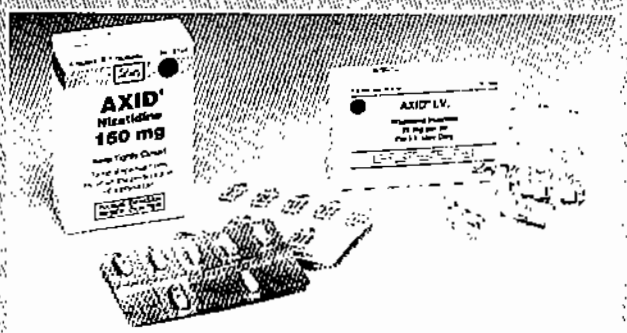

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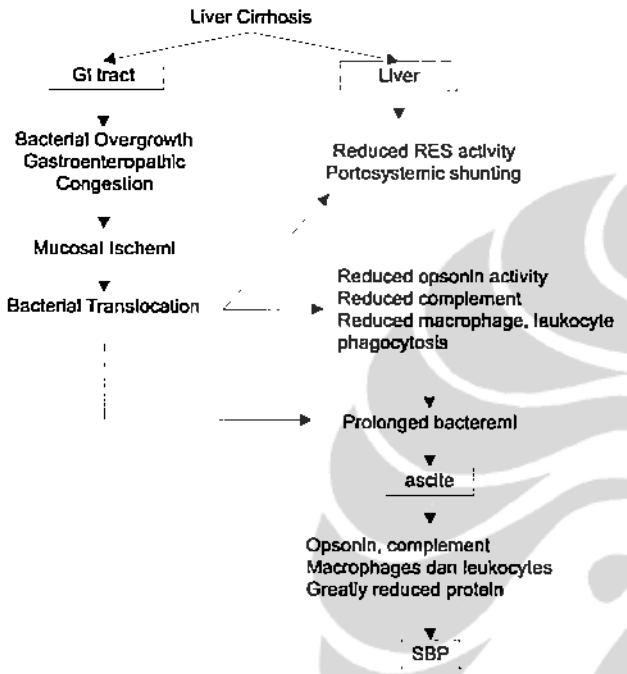

Figure 1. Scheme of Respons in Liver Cirrhosis

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 stimulated 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 splancnic 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 hepatosplancnic 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, amoxycillin 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 theses 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 ciprofloxacine and ofloxacine. 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, trimethropin/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 amoxycillin-clavulanic acid (ACA) and ofloxacine (OFL). Thus, it can be concluded that SAT using ofloxacine 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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