ABSTRACT

Background: Spontaneous bacterial peritonitis (SBP) is a common and severe complication in patients with cirrhosis and ascites. It is accompanied by severe inflammatory and hemodynamic alterations that predispose to complications such as renal failure. Albumin as a plasma expander might have a role in maintaining effective blood volume in cirrhosis patients with SBP.

Method: In order to know the effectiveness and efficacy of albumin infusion for our cirrhosis patient with SBP, five steps of evidence based medicine is conducted; that is (1) Formulate the clinical question; (2) Search the evidence, (3) Appraise the study, (4) Apply the answer, and (5) Assess the outcome. The search was using terms: "(((spontaneous bacterial peritonitis) AND albumin infusion) AND renal impairment)".

Result: 41 articles were gathered, 36 of which were excluded because were not RCT or meta-analysis and were not written in English. We limit our search only on published articles and articles which are not focusing on answering clinical question were later excluded. We appraised 1 meta-analysis study which analyzed the use of albumin infusion in cirrhosis patients with SBP.

Conclusion: Albumin infusion can prevent renal impairment and reduce mortality among cirrhosis patients with SBP.

INTRODUCTION

Spontaneous bacterial peritonitis (SBP) is one of the complications seen in cirrhosis patients. Spontaneous bacterial peritonitis defined as an ascitic fluid infection without an evident intra-abdominal, surgically-treatable source.[1] All patients with cirrhosis and ascites are at risk of SBP. The prevalence of SBP in outpatients is 1.5-3.5% and about 10% in hospitalized patients.[2] Diagnosis of SBP is established by a positive ascitic fluid bacterial culture and an ascitic fluid absolute polymorphonuclear (PMN) leukocyte count $\geq$ 250 cells/mm3.[3]

The pathogenesis of SBP is based on the combination of factors inherent in cirrhosis and ascites, such as prolonged bacteremia secondary to compromised host defenses, intrahepatic shunting of colonized blood, and defective bactericidal activity within the ascitic fluid. Cirrhosis patients have low complement and malfunctioning of the neutrophils and reticuloendothelial systems.[4,5] The important risk factors that contribute to the occurrence of SBP are high serum bilirubin level (above 2.5 mg/dl) and a low ascitic fluid protein concentration (less than 1 g/dl).[6]

The clinical manifestations of SBP are abdominal pain, abdominal tenderness, vomiting, diarrhea, ileus, fever, altered white blood cell count, and worsening of liver function.[7,8] Since the diagnosis of SBP based on PMN count and culture, the most important thing to do in all cirrhosis patients with ascites is ascitic fluid cell analysis and culture. The most common pathogens in SBP are *Escherichia coli* and Gram-positive cocci (Streptococcus and enterococcus).[2]

Cirrhosis patients who develop SBP have been reported to develop renal impairment and mortality. Renal dysfunction is related to altered systemic hemodynamics that lead to decrease arterial blood volume. Renal impairment develops in 30-40% of patients with SBP, even after the infection is controlled.[9,10] Albumin, as a plasma expander, is believed to decrease the recurrence of renal impairment in patients who develop SBP. Albumin is the most abundant protein in the human circulatory system. The functions of albumin are to maintain the osmotic pressure, bind and transport of various ligands, and serve as antioxidant and anti-inflammatory effects.[11] The mechanisms of renal failure in SBP patients are based on the effect of inflammatory cytokines and nitric oxide production in

cirrhosis patients. All of the mechanisms lead to worsened arterial vasodilatation and perfusion to the kidneys.[12] The aim of this case report is to determine the use of albumin infusion in preventing the occurrence of renal dysfunction in cirrhosis patients with SBP.

CASE ILLUSTRATION

A 51-year-old male patient was brought to the Emergency Room Cipto Mangunkusumo Hospital by his wife because of worsened epigastric pain since 10 days before admission.

Two months before admission he felt epigastric pain with no radicular pain. He felt no nausea but he did feel loss of appetite. There was weight reduction approximately 7 kg in 2 months. There were no significant changes in his stool or urine. Patient was brought to Tarakan Hospital and underwent abdomen ultrasonography. From the USG, the doctor found there was mass in the liver. He was referred to Ciptomangunkusumo Hospital to get further treatment. Patient was planned to do TACE based on the staging of the mass. The schedule of TACE is in 2015.

About 10 days before admission, the patient felt worsened abdominal pain and the mass became bigger. There was no fever and shortness of breath. The patient was not able to do routine activities because of the pain. The patient was brought to the emergency room by the family.

There was no history of diabetes, hypertension, or dyslipidemia in patient. There was no history of hepatitis but the patient has history of gastric ulcer in 1983. Patient had history of smoking but there was no history of intravenous drugs, tattoo, or herbal consumption. Patient had history of unsafe sex and alcohol consumption.

From the physical examination when the patient came, we found stable vital sign, with ECOG 3 and VAS 6. His sclerae was icteric with pale conjunctivae. The abdomen was enlarged with positive shifting dullness and enlargement of the liver (8 cm below arcus costae and 10 cm below proceccus xyphoideus). Flapping tremor and palmar erythema were positive. Laboratory findings showed that he was in anemic condition (Hb 9.2 g/dl) with elevated level

of white blood cell (18.840/uL), and elevated liver function tests (AST and ALT were 251 mg/dl and 57 mg/dl) and bilirubin level (total and direct were 4.49 mg/dl and 2.71 mg/dl). He also had low albumin level (2.86 mg/dl). His renal function was normal (ureum 34 mg/dl and creatinine 1.38 mg/dl). His serology marker was positive for hepatitis C infection.

From the abdominal ultrasound, we found that there were multiple nodules at the liver with slightly splenomegaly. From multi-phase abdominal CT, we found that there was liver mass at segment 1,2,3,4, and 5 with portal vein thrombus. From the clinical manifestation of the patient and abdominal CT scan, we could not do the TACE procedure to the patient.

Ascitic fluid analysis was yellow with positive rivalta and cell 330, PMN 270, MN 60, LDH ratio 0.36, protein ratio 0.45, and SAAG 1.8. From the analysis, we found that the ascitic fluid was transudate.

The diagnosis of the patient were spontaneous bacterial peritonitis, hepatocellular carcinoma with cancer pain, liver cirrhosis CTP B with ascites, hepatic encephalopathy, and hypoalbuminemia, chronic hepatitis C, hyponatremia, and anemia. The patient got partial parenteral and laculax 3x15 ml, sucralfate 3x15 ml, cefoperazone 2x1 g, omeprazole 1x40 mg, furosemide 1x40 mg, LOLA, and aldactone 1x100 mg.

In order to reduce the possibility of renal dysfunction in cirrhosis patients with SBP, we conducted five steps of EBCR; that is (1) Formulate the clinical question; (2) Search the evidence, (3) Appraise the study, (4) Apply the answer, and (5) Assess the outcome, to evaluate the efficacy of albumin infusion in cirrhosis patients with SBP.

CLINICAL QUESTION

In cirrhosis patients who develop SBP, does albumin infusion compared to placebo can prevent the occurrence of renal impairment?

SEARCH THE EVIDENCE

To answer the clinical question above, we searched the journals by using several search engines, such as Pubmed database and Cochrane library. We used terms:

by using terms: "(((spontaneous bacterial peritonitis) AND albumin infusion) AND renal impairment)". All terms were searched by using title, abstract, and keywords. From the searching, 41 articles were gathered and only 2 articles were discussed about this topic. (Figure 1.)

The scheme of steps in searching the evidence is illustrated in the figure (**Figure 1**).

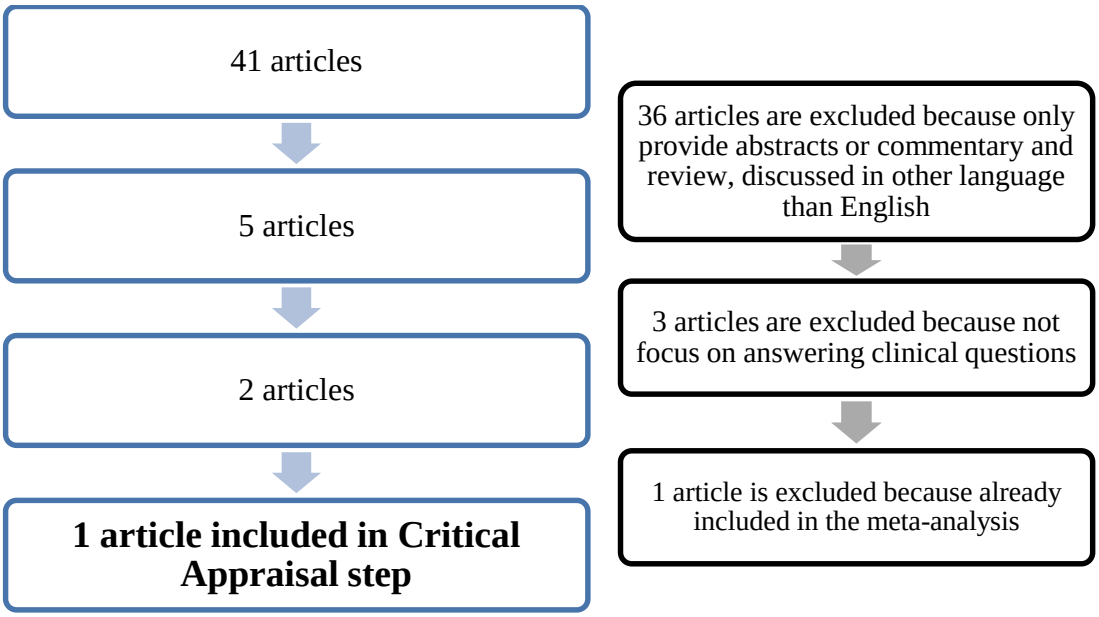

Figure 1. Scheme of steps in searching the evidence

APPRAISE THE STUDY

The first thing to do before appraising the study, we had to find the studies in order to make a decision. Clinical foreground question is the most important thing to be considered which has four elements, consist of Patient, Intervention, Comparison, and Outcome. In appraising the meta-analysis of the therapeutic research, we use the guidance from PRISMA (Table 1.).

Table 1. PRISMA checklist of the metanalysis

TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	123
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration	123

		number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	123-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	124 (I and O)
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	124
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	124
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	124
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	124
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	124
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	N/A
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	124
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	124
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	124
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	124
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	124
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	124-6
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	125
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	125-6
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	125-6
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	125-6
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	126
DISCUSSION			

Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	127
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	127-8
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	127-8
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	N/A

Table 2. Critical Appraisal Skills Programme of the Meta-analysis

Number	Question	Answer
1	Did the review address a clearly focused question?	Yes
2	Did the authors look for the appropriate sort of papers?	Yes
3	Do you think the important, relevant studies were included?	Yes
4	Did the review's authors do enough to assess the quality of the included studies?	Yes
5	If the results of the review have been combined, was it reasonable to do so?	Yes
6	What are the overall results of the reviews?	Detailed in page 126-7 the odds ratio of the study for both outcomes
7	How precise are the results?	The study use formal statistical analysis and there was confidence interval for both outcomes
8	Can the results be applied to the local population?	Yes
9	Were all important outcomes considered?	Yes
10	Are the benefits worth the harms and costs?	Yes

APPLY THE ANSWER

In accordance with current consideration that albumin infusion decreases the incidence of renal failure and mortality among patients with SBP, we appraise this journal to evaluate the efficacy of albumin infusion.

Renal failure is prevalent and particularly severe in patients with SBP. Renal impairment develops in 30-40% of patients with SBP even after the infection is controlled.[9,13] Renal dysfunction in SBP is the most powerful independent predictor of mortality, which is 67% in the presence of renal dysfunction vs 11% in its absence.[14] The mechanisms of renal impairment is by splanchnic vasodilation which results in reduced effective arterial blood volume and leads to compensatory activation of renin-angiotensin-aldosterone system and symphathetic nervous system in nonsplanchnic vascular beds, including kidneys.[13]

There are 4 trials that were included to this meta-analysis. Study by Fernandez, et al. (2005) showed comparison between albumin and HES as plasma volume expansion. The oncotic capacity of 1 g albumin is identical to that of 1 g HES 200/0.5. However, the pharmacokinetics and pharmacodynamics of both substances as well as the characteristics of the solution are markedly different.[15,16] The major difference between HES and albumin is the half-life of the solution. In healthy subjects, the half-life of albumin is 19 days and decreases to 9 days in patients with sepsis and even more in patients with SBP. In contrast, the half-life of HES ranges from 6 hours to 3 days in healthy subjects.[15,17] From this study, Fernandez, et al. showed that the administration of albumin improves circulatory function in patients with SBP which were not observed after the administration of the synthetic plasma expander HES 200/0.5. Both plasma expanders were given at the same dose (1.5 g/kg body weight after baseline measurement and 1 g/kg body weight on day 3). The limitation of this study is the sample was too little and we cannot establish a cause-effect relationship from this study because the lack of control group.[15]

Study from Sort, et al. (1999) (n=126 patients) showed that the infection resolved in 59 patients in the cefotaxime group (94%) and 62 patients in the

cefotaxime-plus-albumin group (98%), p=0.36. The mortality was higher in the cefotaxime group compared to the cefotaxime-plus-albumin group (p=0.01). Sort, et al. concluded that treatment with intravenous albumin in addition to antibiotic reduces the incidence of renal impairment and death.[16]

Same results were shown from study by Xue, et al. (2002). Trial that was conducted by Xue, et al. showed that cirrhosis patients who were given albumin had decreased incidence of renal failure (9% versus 34%, p=0.002) and decreased mortality rate (9% versus 35%, p=0.01). Both study from Sort, et al. and Xue, et al. had many participants so that both trials give bigger value for this meta-analysis. Some limitations were met in Xue's trial, such as there was no data about randomization process and the statistical analysis was not sufficiently detailed.[17]

From this meta-analysis, we can see the odds ratio (OR) for 2 outcomes, renal failure and mortality. Across 4 trials, 12 of 144 albumin recipients (8.3%) develop renal impairment, compared with 44 of 144 control group patients (30.6%). The odds ratio ranging from 0.19-0.30 with the pooled OR was 0.21. There was no evidence of significant heterogeneity (p=0.99) and publication bias (p=0.11) with respect to the renal impairment end point (Figure 2.).[18]

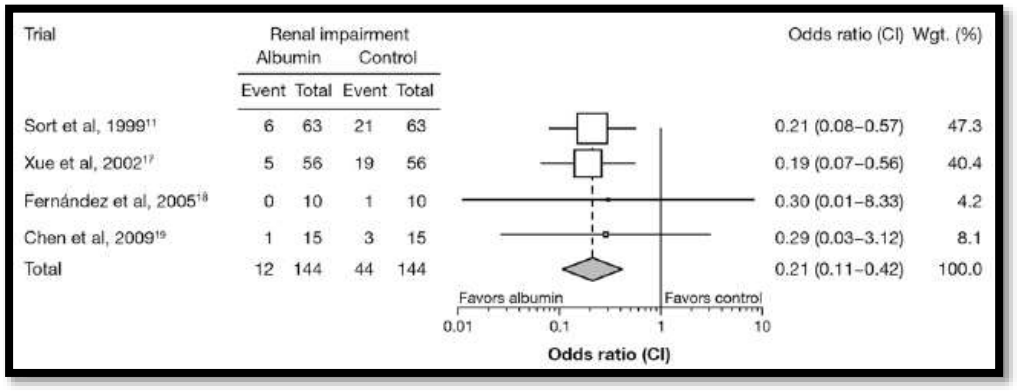

Figure 2. Odds ratio for renal impairment after albumin infusion[18]

Mortality was seen in 23 of 144 patients who received albumin treatment (16%) and 51 of 144 patients to the control group (35.4%). The odds ratio for mortality quite similar, ranging from 0.16-0.55 with the pooled OR was 0.34. There was also no significant heterogeneity (p=0.72) or publication bias (p=0.69) with respect to mortality (Figure 3.).[18]

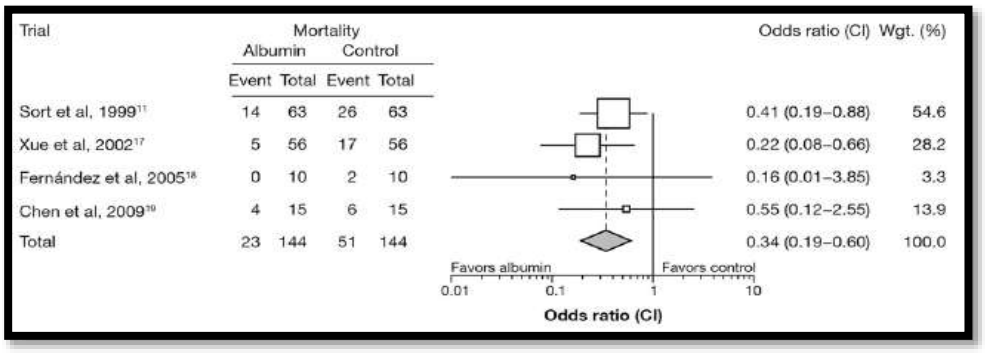

Figure 3. Odds ratio for mortality after albumin infusion[18]

Furthermore, there were some trials assessing the use of albumin infusion in high-risk patients versus low-risk patients based on its mortality rate. Study from Poca, et al. (2012) showed that renal failure before SBP resolution was less frequent after low-risk episodes than high-risk episodes (47% versus 25.6%, p=0.001), in-hospital mortality was lower (3.1% versus 38.2%, p<0.001); and the 3-month probability of survival was higher (93% versus 53%, p<0.001). For the high-risk group, patients who received albumin had lower in-hospital mortality than those not treated with albumin (28.8% versus 46.8%, p=0.02), and a greater 3-month probability of survival (62% versus 45%, p=0.01).[19] Based on previous study, patients were considered at low risk of mortality when urea was < 11 mmol/L (BUN 30 mg/dl) and bilirubin <68 µmol/L (4 mg/dl) and at high risk of mortality when urea was ≥ 11 mmol/L and/or bilirubin ≥ 68 µmol/L.[19] Both variables were found to be independent predictive factors of mortality in the study by Sort, et al. in 1999.[16]

ASSESS THE OUTCOME

Several studies about the use of albumin infusion to prevent renal impairment in cirrhosis patients with SBP showed good outcome. There were no reports of significant side effects of albumin infusion but the trial was relatively small to detect side effects. The dose-response relationship between infused albumin and outcome of SBP needs to be further delineated. Three out of 4 trials in this meta-analysis used albumin dosages of 0.5-1.5 g/kg for at least 3 days.

Unfortunately, in our patient, he had complication because of the SBP, such as sepsis and renal impairment even after the patient got albumin infusion and antibiotics for the infection.

CONCLUSION

Spontaneous bacterial peritonitis is one of the complications of liver cirrhosis with ascites. The occurrence probability based on the severity if the disease that can be seen from child pugh score of the patients. The morbidity and mortality of cirrhosis patients who develop SBP are high. One of the common complications of SBP is renal impairment and type I-hepatorenal syndrome.

Albumin can become the basic treatment to maintain the effective blood volume to keep enough blood flow to many organs, including kidneys. Early diagnosis and adequate treatment of SBP by using antibiotics and albumin are really important to reduce the morbidity and mortality in liver cirrhosis patients.

Conflict of interest

We hereby declare that there was no conflict of interest in this evidence based case report.

REFERENCES

1. Such J, Runyon BA. Spontaneous bacterial peritonitis. Clin Infect Dis 1998; 27: 669.
2. EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. Journal of Hepatology 2010; 53: 397-417.
3. Runyon BA. AASLD. Introduction to the revised American Association for the Study of Liver Diseases Practice Guideline management of adult patients with ascites due to cirrhosis 2012. Hepatology 2013; 57: 1651.
4. Tandon P, Garcia-Tsao G. Bacterial infections, sepsis and multiorgan failure in cirrhosis. Semin Liver Dis 2008; 28: 26–42.
5. Alaniz C, PharmD, Regal RE. Spontaneous bacterial peritonitis: A review of treatment options. Continuing Education Credit 2009; 34(4): 204-10.
6. Gines P, Arroyo V, Rodes J. Therapy of ascites and spontaneous bacterial peritonitis. In: Cohen S, Davis GL, Gianella RA, et al., eds. Therapy of Digestive Disorders: A Companion to Sleisenger and Fortran's Gastrointestinal and Liver Disease. Philadelphia: WB Saunders, 2000:373–384.
7. Møller S, Henriksen JH. The systemic circulation in cirrhosis. In: Ginès P, Arroyo V, Rodés J, Schrier RW, editors. Ascites and renal dysfunction in liver disease. Malden: Blackwell; 2005. p. 139–155.
8. Guevara M, Cárdenas A, Uriz J, Ginès P. Prognosis in patients with cirrhosis and ascites. In: Ginès P, Arroyo V, Rodés J, Schrier RW, editors. Ascites and renal dysfunction in liver disease: pathogenesis, diagnosis and treatment. Malden: Blackwell; 2005. p. 260–270.
9. Follo A, Llovet JM, Navasa M, et al. Renal impairment after spontaneous bacterial peritonitis in cirrhosis: incidence, clinical course, predictive factors and prognosis. Hepatology 1994;20:1495–1501.
10. Ruiz-del-Arbol L, Urman J, Fernández J, et al. Systemic, renal, and hepatic hemodynamic derangement in cirrhotic patients with spontaneous bacterial peritonitis. Hepatology 2003;38:1210–1218.
11. Peters T Jr. Serum albumin. Adv Protein Chem 1997;45:153-203.
12. Navasa M, Follo A, Filella X, et al. Tumor necrosis factor and interleukin-6 in spontaneous bacterial peritonitis in cirrhosis: Relationship with the development of renal impairment and mortality. Hepatology 1998;27:1227-32.
13. Ginès P, Schrier RW. Renal failure in cirrhosis. N Engl J Med 2009;361:1279–1290.
14. Tandon P, Garcia-Tsao G. Renal dysfunction is the most important independent predictor of mortality in cirrhotic patients with spontaneous bacterial peritonitis. Clin Gastroenterol Hepatol 2011;9: 260–265.
15. Fernández J, Monteagudo J, Bargallo X, et al. A randomized unblinded pilot study comparing albumin versus hydroxyethyl starch in spontaneous bacterial peritonitis. Hepatology 2005;42: 627–634.
16. Sort P, Navasa M, Arroyo V, et al. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. N Engl J Med 1999;341:403–409.
17. Xue HP, Lin B, Zhong J, et al. Effect of albumin infusion on preventing the deterioration of renal function in patients with spontaneous bacterial peritonitis. Chin J Dig Dis 2002;3:32–34.

18. Salerno F, Navickis RJ, Wilkes MM. Albumin infusion improves outcomes of patients with spontaneous bacterial peritonitis: A meta-analysis of randomized trials. Clinical Gastroenterology and Hepatology 2013; 11: 123-30.
19. Poca M, Concepcion M, Casas M, et al. Role of albumin treatment in patients with spontaneous bacterial peritonitis. Clinical Gastroenterology and hepatology 2012; 10: 309-15.