

## Roles of albumin in patients with chronic liver disease: Evidence-based medicine

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*This article details the roles of albumin in patients with chronic liver disease especially cirrhosis according to evidence-based information. In addition, this review includes the summary of several guidelines for albumin use in patients with chronic liver disease including those who are undergoing large volume paracentesis (more than 5 litre), those with spontaneous bacterial peritonitis (SBP), and those with hepatorenal syndrome (HRS), which occurred mainly in decompensated cirrhotic patients and acute liver failure. The physiologic functions of albumin and the other potential indications of albumin in cirrhotic patients are also mentioned.*

**Keywords:** Albumin, liver disease, cirrhotic patients.

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บทความนี้เป็นการทบทวนหลักฐานทางการแพทย์เกี่ยวกับการใช้แอลูมิเนียมในผู้ป่วยโรคตับเรื้อรังโดยเฉพาะผู้ป่วยตับแข็ง โดยรวบรวมคำแนะนำการใช้สารแอลูมิเนียมในผู้ป่วย สามกลุ่มหลัก คือ ผู้ป่วยที่มีโรคตับแข็งที่ต้องรับการเจาะน้ำในท้องออกปริมาณมาก (มากกว่า 5 ลิตร), การใช้สารแอลูมิเนียมในผู้ป่วยตับแข็งที่มีการติดเชื้อแบคทีเรียของน้ำในช่องท้อง และผู้ป่วยที่มีไตวายจากตับแข็ง ซึ่งมักพบในผู้ป่วยตับแข็งระยะสุดท้ายหรือผู้ป่วยตับแข็งเฉียบพลัน นอกจากนี้ยังรวบรวมข้อมูลพยาธิสรีรวิทยาของสารแอลูมิเนียม และข้อบ่งชี้อื่น ๆ ที่มีใช้ในผู้ป่วยโรคตับ

**คำสำคัญ :** แอลูมิเนียม, โรคตับ, ผู้ป่วยตับแข็ง.

This article details the roles of albumin in patients with chronic liver disease according to evidence-based information. In addition, this review includes the summary of several guidelines for albumin use in patients with chronic liver disease including those who are undergoing large volume paracentesis, those with spontaneous bacterial peritonitis (SBP), and those with hepatorenal syndrome (HRS), which occurred mainly in decompensated cirrhotic patients and acute liver failure. The physiologic functions of albumin and the other potential indications of albumin in cirrhotic patients are also mentioned. These guidelines comprise American Association for the Study of Liver Diseases or AASLD, European Association for the Study of the Liver or EASL and International ascites club recommendation. AASLD guideline requires a Class (reflecting benefit versus risk) and Level (assessing strength or certainty) of Evidence to be assigned and reported with each recommendation (Table 1).<sup>(1)</sup> EASL guideline has been graded

according to the GRADE system (Grading of Recommendations Assessment Development and Evaluation). The strength of evidence has been classified into three levels: A, high; B, moderate; and C, low-quality evidence, while that of the recommendation into two: strong and weak to be assigned and reported with each recommendation (Table 2).<sup>(2)</sup>

Albumin has been used for a long time for medical treatment since early 1800s. Albumin was used for fluid resuscitation in severely burned sailors at Pearl Harbor. First report of albumin use was prescribed in six cirrhotic patients treated with 25 grams of albumin per day, and then it was used for many years in cirrhotic patients with ascites.<sup>(3)</sup> Albumin is known as a multifunctional protein with oncotic and non-oncotic properties (immunomodulatory, antioxidant and detoxification). This review aims to emphasize the role of albumin in patients with liver disease.

**Table 1.** AASLD Grading System for recommendations.

| <b>Classification</b>    | <b>Description</b>   |
|--------------------------|--|
| Class I                  | Conditions for which there is evidence and/or general agreement that a given diagnostic evaluation, procedure or treatment is beneficial, useful, and effective.           |
| Class II                 | Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a diagnostic evaluation, procedure or treatment.        |
| Class IIa                | Weight of evidence/opinion is in favour of usefulness/efficacy.  |
| Class IIb                | Usefulness/efficacy is less well established by evidence/opinion.  |
| Class III                | Conditions for which there is evidence and/or general agreement that a diagnostic evaluation/procedure/treatment is not useful/effective and in some cases may be harmful. |
| <b>Level of Evidence</b> | <b>Description</b>   |
| Level A                  | Data derived from multiple randomized clinical trials or meta-analyses.  |
| Level B                  | Data derived from a single randomized trial, or nonrandomized studies.   |
| Level C                  | Only consensus opinion of experts, case studies, or standard-of-care.  |

**Table 2.** EASL Grading evidence and recommendations.

|                                     | Notes   | Symbol |
|-------------------------------------|---|--------|
| Grading of evidence                 |   |        |
| High quality evidence               | Further research is very unlikely to change our confidence in the estimate of effect  | A      |
| Moderate quality evidence           | Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate  | B      |
| Low or very low quality of evidence | Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Any estimate of effect is uncertain             | C      |
| Grading recommendation              |   |        |
| Strong recommendation warranted     | Factors influencing the strength of the recommendation included the quality of evidence, presumed patient-important outcomes, and cost  | 1      |
| Weaker recommendation               | Variability in preferences and values, or more uncertainty: more likely a weak recommendation is warranted<br>Recommendation is made with less certainty: higher cost or resource consumption | 2      |

### Albumin homeostasis

Albumin is synthesized in the liver at a rate of 10 - 15 g/day from 20 - 30% of hepatocyte synthetic function. One-third of albumin distributes in the plasma compartment and then circulates to interstitial tissues through the capillaries and returns to the intravascular compartment via the lymphatic system. The normal serum albumin concentration is approximately 3 - 5 g/L. Albumin homeostasis is maintained by degradation pathway in the muscle, liver, kidney and gastrointestinal tract. Its half-life is 12 - 19 days with mean half-life of 14.8 days in healthy young adult males.<sup>(4)</sup>

### Structure

Albumin contains a molecular mass of 66.5 kDa and comprises 609 amino acids with globular heart-shaped tertiary structure and high  $\alpha$  helical content as well as three repeated homologue domain (site I, II, III). An albumin molecule comprises Cys-34 and Trp-214 that confer an antioxidant function.<sup>(5)</sup>

### Physiologic functions of albumin

#### 1. Colloid oncotic pressure

Albumin is the most abundant plasma protein and accounts for 50% of intravascular protein pool in healthy persons. It is responsible for 75% of plasma oncotic pressure. One-third of the oncotic property is derived from negative charges surrounding albumin

at pH 7 that can attract sodium ions followed by water retention. The remaining two-thirds of the oncotic property is derived from direct osmotic effect; - therefore, albumin is an effective plasma volume expander.<sup>(4)</sup>

### 2. Vascular stabilization and permeability

Albumin confers both direct and indirect impacts on vascular integrity.<sup>(6)</sup> The direct effect is the binding to extracellular matrix and sub-endothelium, while the indirect effect is derived from scavenging reactive oxygen and nitrogen species. Therefore, hypoalbuminemia results in edema.

### 3. Antioxidant

Albumin confers antioxidant potential. It contains free cysteine residues, which their thiol groups act as potent scavengers of reactive oxygen and reactive nitrogen species. In vitro, albumin shows antioxidant effects against carbon tetrachloride and uremic toxins. In addition, albumin removes neutrophil-derived reactive oxygen species, regulates cell signaling moieties in the inflammatory reaction, interferes with neutrophil adhesion to capillary endothelium and binds free copper from accelerated

free radicals, leading to reduced inflammation.

### 4. Transportation

The molecule of albumin is flexible. It can bind to and transport several substances, for example, fatty acids, bilirubin, amino acids, thyroxin, drugs, metal ions and nitric oxide (Table 3).<sup>(7)</sup>

### 5. Immunomodulation

*In vitro*, albumin has endotoxin binding capacity resulting in decreased endotoxin levels. In addition, albumin modulates cellular glutathione levels to protect cells against oxidant substances, regulates NF-kappaB activation, selectively inhibits TNF alpha and induces VCAM-1 expression as well as monocyte adhesion resulting in intracellular protection.<sup>(8)</sup>

### 6. Hemostatic effect

Albumin can bind to nitric oxide at Cys-34 site to form nitroso-albumin, which induces vasodilator and inhibits platelet aggregation. However, there was a study indicating that hypoalbuminemia increased platelet aggregating activity. This inverse correlation implies that these relationships may be secondary to other factors such as inflammation.<sup>(9)</sup>

**Table 3.** Albumin as a transport vehicle.

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|   |
|---|
| Amino acids (tryptophan, cysteine)  |
| Bilirubin   |
| Cationic metal ions(Ag, Ca, Cd, Co, Cu, Hg, Mg, Mn, Ni, Zn)                                       |
| Chloride  |
| Drugs (warfarin, digitalis, ibuprofen, diazepam, lidocaine, furosemide, valproic acid, phenytoin) |
| Fatty acids   |
| Bile acid (lithocholate, chenodeoxycholate)   |
| Steroid hormones(cortisone, estradiol, progesterone, aldosterone)                                 |
| Thyroxine   |
| Toxins (aflatoxin,digitoxin,organic anion)  |

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## Role of albumin in patients with chronic liver disease

Albumin has been used for a long time in medical treatment. The current evidence-based indications of albumin used in liver disease are : 1) large volume paracentesis to prevent circulatory dysfunction; 2) improving survival renal function and circulatory function in cirrhotic patients with spontaneous bacterial peritonitis (SBP), and; 3) improving renal function in cirrhotic patients with hepatorenal syndrome.<sup>(10 - 12)</sup>

### A. Large volume paracentesis

Large volume paracentesis has been used for cirrhotic patients with tense or refractory ascites. Therapeutic paracentesis is a treatment option to shorten hospital stay and reduce the cost compare to diuretic therapy.<sup>(13)</sup> Paracentesis-induced circulatory dysfunction (PICD) is a condition occurring in a large volume paracentesis (more than 5 L); and PICD is associated with impaired renal function and decreased survival. The underlying pathophysiology is related to the exacerbation of arteriolar vasodilatation, effective intravascular volume depletion and the reaccumulation of ascites. PICD increases the risk of hepatorenal syndrome and mortality.<sup>(11, 12, 14)</sup>

PICD is able to be attenuated by albumin infusion. The incidence of PICD is significantly decreased in patients receiving paracentesis with albumin infusion group compared to those receiving paracentesis alone (16% versus 30%).<sup>(11)</sup> The other study that compared albumin and isotonic saline administration during large volume paracentesis showed significantly higher in the incidence of

PICD in saline group (33% versus 11%,  $P = 0.03$ ).<sup>(15)</sup> Comparative studies between albumin and other colloid fluid, such as dextran-70 and polygeline, were also performed and demonstrated that albumin remained the most effective treatment.<sup>(10)</sup> In a recent meta-analysis, albumin was able to reduce morbidity and mortality among patients with tense ascites undergoing large-volume paracentesis compared to alternative treatments such as artificial colloids and vasoconstrictors.<sup>(16)</sup> A recent study that compared midodrine and albumin in the prevention of PICD suggested that midodrine was not as effective as intravenous albumin in preventing PICD after large-volume paracentesis.<sup>(17, 18)</sup> Moreover, a combination of midodrine and octreotide is not superior to albumin alone in recurrence of ascites in patients with cirrhosis. There was a study that compared the dose of albumin between the standard dose of 8 g and the half dose of 4 g per liter of removal ascites demonstrated the similar incidence of PICD between two groups.<sup>(16)</sup> However, the sample size was too small to demonstrate the equivalence of these two treatment strategies.

### International ascites club recommendation 2006<sup>(19)</sup>

: Dose 6 - 8 g of intravenous albumin should be infused per litre of ascitic fluid removed for large volume paracentesis greater than 5 - 6L, while up to 5L ascitic fluid can be tapped without any need of albumin infusion.

### EASL guideline recommendation 2010<sup>(2)</sup>

: Repeated large-volume paracentesis plus albumin (8g/L of ascitic fluid removed) is the first line of treatment for refractory ascites (level A1).

### **AASLD guideline recommendation 2013**<sup>(1)</sup>

: Post-paracentesis albumin infusion may not be necessary for a single paracentesis of less than 4 - 5 L (Class I, Level C).

: For large-volume paracentesis, an albumin infusion of 6 - 8 g per litre of fluid removed appears to improve survival and is recommended (Class IIa, level A).

### **B. Spontaneous bacterial peritonitis**

Spontaneous bacterial peritonitis (SBP) is acute bacterial infection of ascitic fluid, which is an ominous complication of patients with cirrhosis.<sup>(20)</sup> It is defined by an ascitic PMN count higher than  $0.25 \times 10^9/L$  (250cells/ mm<sup>3</sup>) in the absence of recognizable causes of peritonitis.<sup>(1)</sup> SBP is believed to occur via direct transmural migration of bacteria from the intestine or hollow viscous organs due to delayed intestinal transit and increased permeability of intestinal wall, a phenomenon called bacterial translocation. Another proposed mechanism for bacterial inoculation of ascites is hematogenous transmission in combination with an impaired immune system.<sup>(21)</sup> SBP is usually accompanied by systemic inflammatory response (SIR) that deteriorates hepatic, renal and hemodynamic functions and results in renal failure, which is the most important factor of reducing survival in patients with SBP. The RCT study of the effect of albumin infusion on renal function and mortality in patient with SBP was done to compare cefotaxime alone or cefotaxime plus albumin infusion with the rate of 1.5 g/kg in first 6 hours followed by 1 g/kg on the third day. The results showed that patients who received albumin infusion did not have any increase in plasma renin activity, while decreasing

the incidence of renal failure as well as hospital mortality rate compared to those receiving cefotaxime alone (10% versus 29%,  $P < 0.01$ ).<sup>(22,23)</sup> Another study using albumin infusion in patients with SBP showed improvement of cardiac function, renal function and survival benefit but only in high-risk patients (BUN >30mg/dL and/or bilirubin > 4mg/dL).<sup>(24)</sup> A trial of regular dose albumin (1.5 g/kg in first 6 hours followed by 1 g/kg on day 3) and reduced albumin dose (1g/kg and 0.5g/kg, respectively) showed similar efficacy between the two groups.<sup>(25)</sup> However, the small sample size of this trial was noted; therefore, the type 2 error might have occurred.<sup>(1)</sup>

### **International ascites club recommendation 2006**<sup>(19)</sup>

: Patients with SBP and signs of developing renal impairment, albumin should be given at 1.5g /kg in the first 6 hours followed by 1g/kg on day 3 (level of evidence:IIb; recommendation: B).

### **EASL guideline recommendation 2010**<sup>(2)</sup>

: Hepatorenal syndrome (HRS) occurs in approximately 30% of patients with SBP treated with antibiotics alone, and is associated with poor survival. The administration of albumin (1.5 g/kg at diagnosis followed by 1g/kg on day 3) decreases the frequency of HRS and improves survival (level A1).

: It is unclear whether albumin is useful in the subgroup of patients with baseline serum bilirubin < 4 mg/dl and creatinine <1 mmol/L (level B2).

: Until more information is available, we recommend that all patients who develop SBP should be treated with broad-spectrum antibiotics and intravenous albumin (level A2).

**AASLD guideline recommendation 2013**<sup>(1)</sup>

: Patients with ascitic fluid PMN counts greater than or equal to 250 cells/mm<sup>3</sup> (0.25 x10<sup>9</sup> /L) and clinical suspicion of SBP, who also have a serum creatinine >1 mg/dl, blood urea nitrogen >30 mg/dl, or total bilirubin >4 mg/dl should receive 1.5g albumin/kg within 6 hours of detection followed by 1 g/kg on day 3 (Class IIa, level B).

**C. Hepatorenal syndrome (HRS)**

HRS, the serious complication of end stage liver disease, occurs mainly in decompensated cirrhotic patients and acute liver failure. Diagnostic criteria and classification for HRS are defined as follows:<sup>(26 - 29)</sup>

**Diagnosis criteria**

- Cirrhosis with ascites
- Serum creatinine > 1.5mg/dl (133 μmol/L)
- Absence of shock
- Absence of hypovolemia as defined by no sustained improvement of renal function (creatinine decreasing to <1.5 mg/dl) following at least 2 days of diuretic withdrawal (if on diuretics) and volume expansion with albumin at 1g/kg/day up to a maximum of 100g/day
- No current or recent treatment with nephrotoxic drugs
- Absence of parenchymal renal disease as defined by proteinuria <0.5 g/day, no microhematuria (<50 red cells/high powered field) and normal renal ultrasonography

**Classification**

- Type 1 HRS: a rapid progressive renal failure as defined by doubling of initial serum creatinine concentration to a level greater than 2.5 mg/dl in

less than 2 weeks. It often appears after a precipitating event, most frequently spontaneous bacterial peritonitis.

- Type 2 HRS: a moderate renal failure (serum creatinine from 1.5 to 2.5 mg/dl), with a steady or slowly progressive course. It appears spontaneously and typically associated with refractory ascites.

The pathophysiology of HRS involves splanchnic arterial vasodilatation leading to central blood volume depletion. Consequently, vasopressor systems are activated for compensation that results in marked vasoconstriction of renal artery and cirrhotic cardiomyopathy (consisted of systolic incompetence under condition of stress and diastolic dysfunction related to altered diastolic relaxation). These compensated mechanisms lead to renal hypoperfusion followed by acute renal failure.<sup>(26-29)</sup>

When cirrhotic patients are suspected to develop HRS, a diuretic should be removed, and albumin infusion should be given with albumin of 1g/kg up to 100g/day for at least 2 days to exclude hypovolemic renal failure. The management of type 1 HRS is the combination of vasoconstrictor, usually terlipressin, and plasma volume expansion.<sup>(30, 31)</sup>

The RCT studies demonstrated that terlipressin administration improved renal function, especially when combined with the infusion of albumin 1 g/kg followed by 20 - 40 g/day.<sup>(28,31,32)</sup> However, only a few studies in the management of type 2 HRS as uncontrolled trials supported the use of vasoconstrictors in combination with albumin for improving renal function.<sup>(31)</sup> The recent study comparing between two vasoconstrictors, terlipressin *versus* noradrenaline in type 2 HRS, revealed that both terlipressin and noradrenaline were safe and



effective in treatment of HRS, but noradrenaline is less expensive.<sup>(33)</sup> Baseline serum creatinine, urine output and urinary sodium were good predictors of response.<sup>(33, 34)</sup>

### **EASL guideline recommendation 2010**<sup>(2)</sup>

: Management of type 1 hepatorenal syndrome (HRS)

Drug therapy of type 1 HRS; Terlipressin (1 mg/4 - 6 h intravenous bolus) in combination with albumin should be considered the first line therapeutic agent for type 1 HRS. (level A1).

: Management of type 2 hepatorenal syndrome

Terlipressin plus albumin is effective in 60 - 70% of patients with type 2 HRS. There are insufficient data on the impact of this treatment on clinical outcomes (level B1).

### **AASLD guideline recommendation 2013**<sup>(1)</sup>

: Albumin infusion plus administration of vasoactive drugs such as octreotide and midodrine should be considered in the treatment of type I HRS. (Class IIa, level B)

: Albumin infusion plus administration of norepinephrine should also be considered in the treatment of type I HRS, when the patient is in the intensive care unit. (Class IIa, level A)

### **Other potential indications of albumin in cirrhosis**

#### **Bacterial infections other than SBP**

Infections in cirrhotic patients are associated with renal dysfunction. A randomized controlled study of 110 cirrhotic patients with non-SBP bacterial infections, mainly pneumonia or urinary-tract infection,

were randomized to receive antibiotics plus albumin (1.5 g albumin/kg at diagnosis and 1 g/kg at day 3) or antibiotics alone.<sup>(22)</sup> The result showed that serum creatinine levels decreased in the albumin group, while increasing in the control group, but it did not show statistical significance. Although a three month survival rate did not achieve in the intention to treat analysis, but it showed a potential benefit in high risk cirrhotic patients. Further studies are needed to confirm these findings and explore the cost-effectiveness of this approach.

### **Long-term treatment of ascites**

Clinical benefit of albumin infusion in long-term therapy of ascites is controversial because albumin is a high cost treatment, and there is little evidence that supports its use in long-term therapy. There are only two controlled trials of long-term albumin infusion. In the first study, patients were randomized into two groups. The first group received diuretics and albumin of 12.5 g/day during hospitalization and 25 g/week after discharge, whereas the second group received diuretics alone in the follow up duration of 3 years. The results showed that the patients in the diuretics plus albumin group had significantly lower cumulative probability of developing ascites (19% *versus* 30% at 12 months, 56% *versus* 79% at 24 months, and 69% *versus* 82% at 36 months, respectively). All the results showed significantly decreased probability of readmission (15% *versus* 27% at 12 months, 56% *versus* 74% at 24 months, 69% *versus* 79% at 36months).<sup>(35-37)</sup> The subsequent study randomized patients into two groups to receive diuretics plus albumin 25 g/week in the first year and 25 g every two weeks, while the other

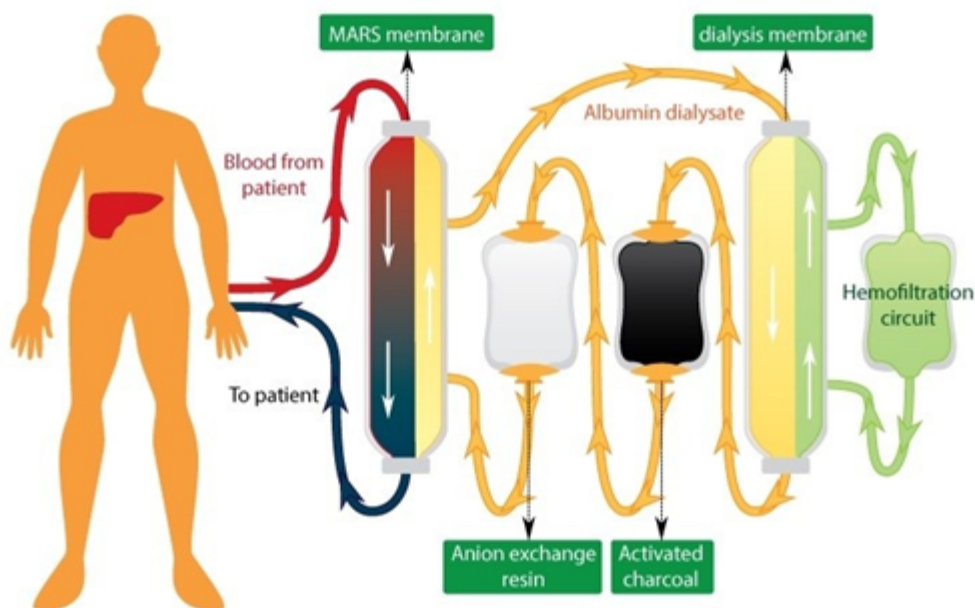
group received diuretics alone. The median time of follow-up was 84 months. Albumin plus diuretics group had greater cumulative survival and lower probability of ascites recurrence (51% versus 94%,  $P < 0.0001$ ).<sup>(37)</sup> The two studies showed the benefit of albumin in cirrhotic patients with ascites, but the cost-effectiveness of this treatment strategy remains unclear due to the small sample sizes.

### Artificial liver support device

Acute liver failure or acute on chronic liver failure with high MELD score are associated with high 90-day mortality rate, and liver transplantation is the treatment of choice. However, it may take time to receive donated liver. Thus, the bridging therapy

before liver transplantation has been developed.<sup>(38, 39)</sup> The artificial liver support devices such as molecular adsorbent recirculating system (MARS) (Fig.1) are developed to remove albumin-bound toxins and water-soluble toxins from the patients with acute or acute on chronic liver failure (so-called albumin dialysis).<sup>(40)</sup> MARS has been shown to be effective in improvement of hepatic encephalopathy, lowering of intracranial pressure, reduction of portal hypertension, improvement of jaundice and attenuation of the hyperdynamic circulation. Despite many studies showing the beneficial effects, data from multicenter controlled trials show no benefit in transplant-free survival in patients with fulminant or sub-fulminant liver failure.<sup>(41 - 44)</sup>

### Molecular adsorbent recirculating system (MARS) uses albumin as dialyzer to remove albumin-bound and water-soluble toxin

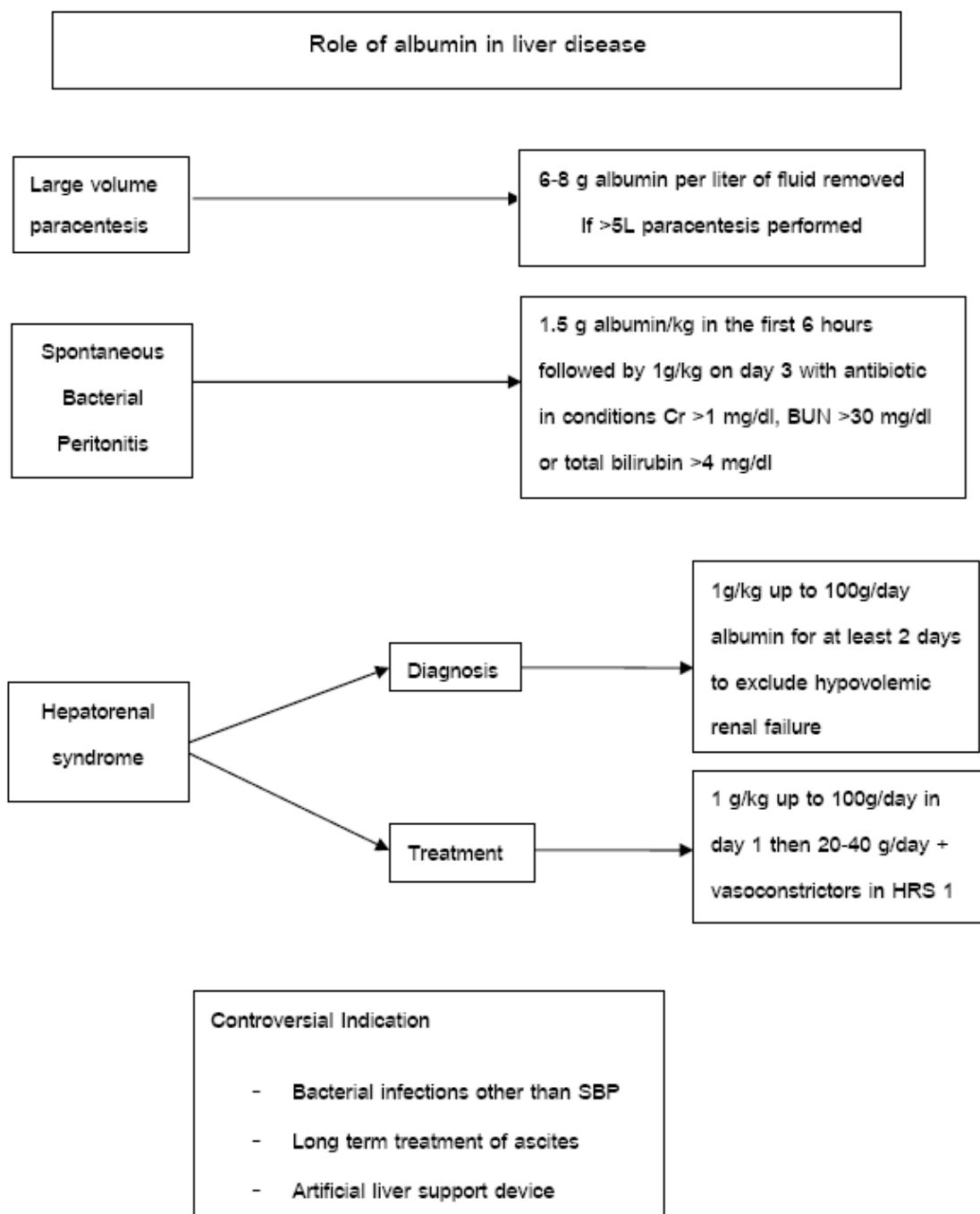


**Figure 1.** Molecular adsorbent absorbent recirculating system (MARS) uses albumin as dialyzer to remove albumin-bound and water-soluble toxins (modified from Sen S, *et al.* Am J Gastroenterol 2005)<sup>(45)</sup>

**Conclusion**

Albumin has been used for a long time in several indications. Currently, the recommendation in several practice guidelines of albumin use in patients with liver disease are for the prevention of paracentesis-induced circulatory dysfunction, improvement of the survival and beneficial effects on renal and circulatory functions in patients with

spontaneous bacterial peritonitis (SBP) and improvement of the renal function in cirrhotic patients with hepatorenal syndrome as shown in Fig 2. Other conditions, such as bacterial infections other than SBP, long-term treatment of ascites and artificial liver support device are required further large studies before recommendation in practice guidelines.



**Figure 2.** Summary indications of albumin infusion in liver disease.

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