

## Evidence-based Guidelines for the Use of Albumin Products

### Japan Society of Transfusion Medicine and Cell Therapy

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Therapeutic plasma exchange

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## 1. Introduction

### 1) Purpose of the Development of the Guidelines

Albumin was introduced into clinical use in 1941 and has been widely used worldwide for about 70 years because of its efficacy and safety in patients with hypovolemic shock or those with marked edema. "Guidelines for use of blood products" were developed in 1999 by the Ministry of Health, Labour and Welfare and have been amended and revised, but have not provided any evidence-based recommendation levels. Meanwhile, in recent years, studies on albumin and its use in critically ill patients have been increasingly published and provided important insights into clinical use of albumin for the treatment of different pathological conditions. The purpose of these guidelines is to provide healthcare professionals with support in making an appropriate decision on the use of albumin to promote the appropriate use of albumin and to ensure better treatment. Although these guidelines are evidence-based, they merely provide evidence of results of clinical studies and do not guarantee the universal use of albumin. In clinical practice, albumin should be used based on an overall judgment by healthcare professionals and these guidelines do not restrict the use of albumin. In addition, healthcare professions or these guidelines are not legally held, regardless of whether or not the use of albumin included in these clinical practice guidelines is followed.

### 2) Background of the Development of the Guidelines

This project was initiated as the Literature Search Project for the Development of Guidelines for the Appropriate Use of Albumin Products, a research project funded by the Health and Labour Sciences Research Grants, in March 2012 and has been, since 2013, taken over to the Taskforce for the Development of Guidelines for Administration of Albumin Products, a subcommittee of the Guidelines Committee of the Japan Society of Transfusion Medicine and Cell Therapy, and Research on the Development of Evidence-based Guidelines for Blood Transfusion, a research project funded by the Health and Labour Scientific Research Grants. Members of the Taskforce for the Development of Guidelines for Administration of Albumin Products were elected in meetings of the board of directors in May 2013 in consideration of their specialty.

Guidelines committee members

● Research project funded by the Health and Labour Sciences Research Grants

"Literature Search Project for the Development of Guidelines for the Appropriate Use of Albumin Products"

Principal Investigator: Shigeyoshi Makino, Toranomon Hospital

● Research project funded by the Health and Labour Sciences Research Grants

"Research on the Development of Evidence-based Guidelines for Blood Transfusion etc."

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### 3) Method of the Development of the Guidelines

Clinical questions (CQs) were formulated regarding a total of 17 pathological conditions, including indications and inappropriate uses specified in Chapter 5 "Appropriate use of albumin products," "Guidelines for Administration of Blood Products," and a search was conducted based on a total of 3,059 domestic and overseas papers on albumin published in 1972 to 2014, of which 310 papers were included in the primary selection, as shown in the

table below. Other important published papers or papers necessary for formulating statements were added as hand-searched papers and levels of evidence and grades of recommendation were determined for each CQ according to the *Minds Handbook for Clinical Practice Guideline Development 2014*. For these guidelines, a guidelines committee member was assigned to each CQ and the chairperson was responsible for overall supervision.

● Status of the collection of published papers

Source	Year of Starting Search	Hit Counts of Papers on Search	Number of Papers Included in the Primary Selection
MEDLINE	1972	1,979	245
Cochrane	1992	881	26
JAMAS	1983	199	39

Important papers that were searched for each CQ were included. Draft guidelines were reviewed and modified by the Taskforce. Subsequently, public comments were invited on the society's web site and any necessary modifications were made for the finalization of the guidelines.

Evidence levels and grades of recommendation were determined according to the *Minds Handbook for Clinical Practice Guideline Development 2014*<sup>1)</sup>. The strength of recommendations was presented in two ways: "1": strongly recommended and "2": weakly recommended (suggested). The overall strength of evidence across outcomes (A, B, C, D) was put down with the above strength of recommendations.

A (strong): strongly confident of the estimate of effect

B (moderate): moderately confident of the estimate of effect

C (weak): limited confidence of the estimate of effect

D (very weak): very little confident of the estimate of effect

#### 4) Publication and Revision

These guidelines are publicly available on the *Journal of the Japan Society of Transfusion Medicine and Cell Therapy* and the society's website. They will be revised with accumulating evidence.

#### 5) Funding and Conflict of Interest

The development of these guidelines was funded by the Health and Labour Sciences Research Grants Literature Search Project for the Development of Guidelines for the Appropriate Use of Albumin Products and Research on the Development of Evidence-based Guidelines for Blood Transfusion. The content of these guidelines have no interest in specific profit and nonprofit organizations, drug manufacturers, medical device manufacturers, etc., the guidelines committee members declared the status of conflict of interest to the Japan Society of Transfusion Medicine and Cell Therapy, and the COI committee confirmed there was no conflict of interest.

## 2. Types of Albumin Products and Assessment of Administration

Albumin products are available in an isotonic 5% solution and a hypertonic 20% to 25% solution. A heat-treated human plasma protein fraction (PPF), which has an albumin concentration of  $\geq 4.4\%$  and in which albumin accounts for  $\geq 80\%$  of the total protein, is also osmotically equivalent to normal plasma. Isotonic albumin products are used for the replacement of circulating plasma volume in hemorrhagic shock, severe burns, etc., while heat-treated human PPF is, in principle, contraindicated in patients undergoing therapeutic plasma exchange not requiring the replacement of coagulation factors or those undergoing cardiopulmonary bypass because it can cause decreased blood pressure in rare cases. In addition, it is administered at a rate of  $\leq 5$  to 8 ml/minute.

In contrast, hypertonic albumin products, which have a colloid osmotic pressure 4 to 5 times higher than that of plasma, are suitable for the treatment of ascites or pulmonary edema secondary to hypoproteinemia.

Both each 250 ml of a 5% product and each 50 ml of a 25% product contain 12.5 g of albumin, which is equivalent to the amount of albumin produced daily in adults.

Because albumin administered intravenously is evenly dispersed in the vascular compartment within 10 to 15 minutes and evenly distributed in the extravascular pool within 4 to 7 days, the transfer of albumin to the extravascular compartment accounted for 60% of the intravenous dose. When 50 ml (12.5 g) of a 25% product is administered to an adult male weighing 65 kg, the expected increase in albumin level (g/dl) can be calculated using the

following equations, on the assumption that the intravascular recovery of albumin is 40%:

$$\begin{aligned}
 & \text{Expected increase in albumin level (g/dl)} \\
 & = \{\text{dose of albumin administered (g)/circulating plasma volume (dl)}\} \times 0.4 \\
 & \quad (\text{intravascular recovery of albumin administered of 40\%}) \\
 & = \{\text{dose of albumin administered (g)/body weight (kg)} \times 0.4 \text{ dl}\} \times 0.4 \\
 & \quad (\text{circulating plasma volume} \doteq \text{body weight (kg)} \times 0.4 \text{ dl}) \\
 & = \{\text{dose of albumin administered (g)/body weight (kg)}\} \\
 & = \{12.5 \text{ (g)}/65 \text{ (kg)}\} \doteq 0.2 \text{ (g/dl)}
 \end{aligned}$$

However, because extravasation of albumin is increased in many pathological conditions, such as major surgery, trauma, burns, sepsis, and shock, resulting in a further increase in the extravascular pool, the expected value is not often obtained. The response to administration is assessed and based on measurements of albumin levels and symptomatic improvement. There are reports demonstrating that albumin is effective as measured by the assessment of organ functions using sequential organ failure assessment (SOFA) scores or oxygenation in patients with acute lung injury<sup>2)3)</sup>.

### 3. Hypoalbuminemia and Indications of Albumin

Causes of hypoalbuminemia include hemorrhage, increased capillary permeability, loss due to excessive renal excretion etc., increased metabolism, decreased hepatic synthesis, and dilution with intraoperative fluid therapy. In nephritic syndrome or protein-losing gastrointestinal disorders, loss of albumin can lead to hypoproteinemia. In highly invasive surgery, sepsis, trauma, hepatic disease, and malignancy, decreased synthesis and leakage of albumin can trigger hypoalbuminemia. Although serum albumin levels are a measure of nutritional status or prognosis, improvement of pathological conditions with the treatment of underlying diseases is given first priority because hypoalbuminemia itself is not adverse. Albumin products are used for temporary improvement of pathological conditions due to acute hypoproteinemia or pathological conditions due to chronic hypoproteinemia that are difficult to manage with other treatment approaches.

Although there are many clinical studies in which albumin was administered in the acute phase with a target serum albumin level of 2.5 to 3.0 g/dl, no superiority of albumin has not been demonstrated<sup>4)~6)</sup>. It at least appears that serum albumin levels of  $\geq 2.5$  g/dl do not have to be maintained. In addition, although some guidelines set the target albumin level at 2.0 to 2.5 g/dl for hypoalbuminemia in various pathological conditions<sup>7)</sup>, there are no thresholds that has reached scientific consensus.

Therefore, there are no clear thresholds for albumin administration and the use of albumin products is not indicated for hypoalbuminemia alone. A decision to use albumin products should be made after consideration of disease and patient conditions.

### 4. Effects of Different Assays on Serum Albumin Levels

In discussion differences among assays, the following three aspects have to be considered: i) the magnitude of differences in observed values among assays, ii) the accuracy of observed values with each assay, and iii) which assay controlled trials with a high evidence level use. For the i) above, the BCG (bromocresol green) method has limited accuracy because of cross-reaction with globulin and provides higher values than the modified BCP (bromocresol purple) method. The proposal of the Japanese Society of Laboratory Medicine states that "It is extremely difficult to specify conversion formulas for both methods by pathological condition and, if an albumin value of  $\leq 3.5$  g/dl is obtained with the modified BCP method, the obtained value plus 0.3 g/dl should be approximated as the estimate with the BCG method."<sup>8)</sup> For the ii) above, according to the report on the results of quality control by the Japan Medical Association and Japanese Association of Medical Technologists, the coefficient of variation of values obtained using reagents that were adopted by multiple facilities was generally less than 2%, suggesting that the accuracy was within the acceptable range<sup>9)</sup>. In contrast, in overseas countries, it has been noted that the degree of inaccuracy of measured albumin levels was unacceptable and has to be improved<sup>10)</sup>. For the iii) above, the reports of large controlled trials after 2000 (e.g., SAFE study, ALBIOS study)<sup>4)5)</sup> do not include

the method of measurement and therefore the methods of measurement used are unknown. Based on the above, it has to be considered difficult to develop the guidelines of albumin use by assay at this time. Instead, considering that there are no clear threshold levels for pathological conditions that are eligible for albumin products, the necessity of albumin products should be considered, bearing in mind that values obtained the BCG method have limited accuracy.

## 5. Benefits and Recommendations for Albumin Use by Pathological Condition

### i) Hemorrhagic shock

#### ● Statement

CQ1. Do patients with hemorrhagic shock benefit from albumin?	Grade	Evidence Level		Reference
		Overseas	Japan	
1. In patients with decreased intravascular volume secondary to trauma, surgery, etc. in whom fluid therapy is considered to be required to maintain or expand the intravascular volume, the use of albumin is not associated with improvement in survival compared with the use of crystalloids.	1	A	None*	4, 11-14
2. When albumin is used for the replacement for hypovolemia secondary to trauma, surgery, etc., it can potentially improve morbidity.	2	C	None*	15

\*No clinical study was available.

#### ● Commentaries

For the treatment of hypovolemia induced by hemorrhage, crystalloids, such as normal saline and lactated Ringer's solution, and colloids capable of maintaining plasma oncotic pressure, such as human albumin solution, dextran solution, and hydroxyethyl starch (HES) solution, are used.

In 1998, the Cochrane Injury Group Albumin Reviewers conducted a meta-analysis of randomized controlled trials comparing albumin versus other fluid therapies in critically ill patients with hypovolemia due to hemorrhage from trauma or surgery<sup>11)</sup>. They found that albumin administration was associated with a trend for higher mortality (relative risk, 1.46; 95% confidence interval, 0.97 to 2.22). When patients with burn and those with hypoalbuminemia, who were also analyzed, were included, it was found that albumin administration was associated with higher mortality (relative risk, 1.68; 95% confidence interval, 1.07 to 2.67).

In 2001, another meta-analysis of randomized controlled trials comparing albumin administration versus other fluid therapies was conducted<sup>12)</sup>. The relative risk for mortality in the group treated with albumin for trauma or surgery was 2.13 (95% confidence interval, 0.81 to 5.64). When all the indications, such as burns, hypoalbuminemia, high-risk neonate, and ascites, were pooled, the relative risk for mortality with albumin administration was 1.11 (95% confidence interval, 0.95 to 1.28), which failed to demonstrate evidence that albumin administration increased mortality.

In 2004, results were reported from a prospective, randomized, controlled trial in which 6,997 ICU patients requiring intravascular blood volume replacement received 4% albumin solution or normal saline (SAFE Study)<sup>4)</sup>. The primary endpoint of this study is mortality at 28 days and the secondary endpoints include the number of days of ICU stay, the number of days of hospital stay, the number of days of mechanical ventilation, and the number of days of renal-replacement therapy. For mortality at 28 days, the relative risk in the albumin group was 0.99 (95% confidence interval, 0.91 to 1.09), thus providing no evidence that 4% albumin solution is superior to normal saline in ICU patients requiring intravascular blood volume replacement (i.e., normal saline and 4% albumin solution are equivalent when mortality is used as an endpoint). In addition, there were no differences between the normal saline and 4% albumin groups in the number of days of ICU stay, number of days of hospital stay, number of days of mechanical ventilation, or number of days of renal-replacement therapy. A subsequent analysis of data from the SAFE study investigated mortality in patients with 4% albumin solution or normal saline, stratified by baseline albumin level ( $\leq 2.5$  g/dl or  $> 2.5$  g/dl) and found no differences in mortality at 28 days regardless of baseline albumin level (odds ratio, 0.87; 95% confidence interval, 0.73 to 1.05 for patients with a baseline albumin level

$\leq 2.5$  g/dl; odds ratio, 1.09; 95% confidence interval, 0.92 to 1.28 for patients with a baseline albumin level  $>2.5$  g/dl)<sup>13)</sup>.

The most recent meta-analysis including the SAFE study concluded that for critically ill patients with hypovolemia, there was no evidence that albumin reduced mortality when compared with cheaper fluids (odds ratio, 1.02; 95% confidence interval, 0.92 to 1.13)<sup>14)</sup>. For critically ill patients with burns or hypoalbuminemia, there was a suggestion that albumin administration may increase mortality.

When critically ill patients with hypovolemia due to hemorrhage from trauma or surgery received albumin or other fluid therapies, morbidity was lower in the albumin group (relative risk, 0.58; 95% confidence interval, 0.40 to 0.85)<sup>15)</sup>.

#### ● Recommendation

1. In patients with decreased intravascular volume secondary to trauma, surgery, etc. in whom fluid therapy is considered to be required to maintain or expand the intravascular volume, the use of albumin is not associated with improvement in mortality compared with the use of crystalloids (strong recommendation against use, 1A).

2. When albumin is used for the replacement for hypovolemia secondary to trauma, surgery, etc., it can potentially improve morbidity (2C).

#### ii) Severe sepsis

##### ● Statement

CQ2. Do patients with severe sepsis benefit from albumin?	Grade	Evidence Level		Reference
		Overseas	Japan	
1. In patients with severe sepsis or septic shock, the use of albumin is not associated with improvement in mortality compared with the use of crystalloids.	1	B	None*	4, 5, 16-18
2. In the initial treatment in patients with severe sepsis, albumin administration stabilizes hemodynamics.	2	C	None*	4, 5, 16-18

\*No clinical study was available.

##### ● Commentaries

In the International Guidelines for Management of Severe Sepsis and Septic Shock published in 2012, the following recommendations regarding fluid therapy in patients with severe sepsis are included<sup>16)</sup>: 1) We recommend crystalloids be used as the initial fluid of choice for the resuscitation in patients with severe sepsis and septic shock (Grade of Recommendation 1, Evidence Level B); 2) We recommend against the use of hydroxyethyl starches (HES) for fluid resuscitation of severe sepsis and septic shock (Grade of Recommendation 1, Evidence Level B); and 3) We suggest the use of albumin in the fluid resuscitation of severe sepsis and septic shock when patients require substantial amounts of crystalloids (Grade of Recommendation 2, Evidence Level C).

In a subgroup analysis of patients with sepsis in the SAFE study, mortality at 28 days tended to be lower among patients treated with 4% albumin than among patients treated with normal saline (relative risk, 0.87; 95% confidence interval, 0.74 to 1.02;  $p=0.09$ )<sup>4)</sup>. Organ functions etc. were further characterized in this subgroup<sup>17)</sup>. Compared with the normal saline group, the albumin group had a significantly lower heart rate up to 3 days of treatment and a significantly higher central venous pressure, but there were no significant differences between the groups in the duration of renal-replacement therapy or sequential organ failure assessment (SOFA) score. However, when baseline characteristics were also included, mortality at 28 days was significantly lower in the albumin group than in the normal saline group, suggesting that albumin administration might reduce the risk of death in patients with sepsis.

In 2014, results were reported from a randomized, controlled trial, involving 1,818 patients, which investigated the benefit of albumin in patients with severe sepsis and septic shock<sup>5)</sup>. During the first 7 days, the albumin group had a higher mean blood pressure and lower net fluid balance. However, mortalities at 28 and 90 days did not differ between the groups, indicating that albumin did not improve the rate of survival in patients with severe sepsis. Based on a network meta-analysis, which can evaluate the effect of 3 or more treatment interventions simultaneously, albumin has been considered to contribute to survival to an equal or greater extent than crystalloids<sup>18)</sup>.

● Recommendation

1. In patients with severe sepsis or septic shock, the use of albumin is not associated with improvement in mortality compared with the use of crystalloids (strong recommendation against use, 1B).

2. In the initial treatment in patients with severe sepsis, albumin administration stabilizes hemodynamics (2C).

**iii) Ascites secondary to liver cirrhosis**

● Statement

CQ3. Is the use of albumin effective in ascites secondary to liver cirrhosis?	Grade	Evidence Level		Reference
		Overseas	Japan	
1. In patients with ascites secondary to liver cirrhosis who are on diuretics, albumin increases the rate of disappearance of ascites, prevents the recurrence of ascites, and improves the rate of survival.	1	B	None*	19, 20
2. Albumin is superior to other plasma expanders in preventing circulatory failure and reducing mortality after large volume paracentesis.	1	A	None*	21-24
3. In patients with spontaneous bacterial peritonitis, albumin improves systemic hemodynamics and prevents the development of hepatorenal syndrome.	1	A	None*	25-28
4. Albumin in combination with inotropic agents is an effective treatment regimen for hepatorenal syndrome. Improvement in renal function is observed in 65% of patients with type 1 hepatorenal syndrome. Albumin administered for the treatment of hepatorenal syndrome before liver transplantation is associated with improved prognosis.	1	A	None*	29-31

\*No clinical study was available.

● Commentaries

In patients with liver cirrhosis, the half-life of albumin is prolonged and its catabolism rate is also reduced, but excessive administration of albumin induces isoleucine deficiency and causes impaired protein synthesis or increased albumin degradation. In addition, from a standpoint of appropriate use, it has been believed that chronic administration of albumin should be avoided in patients with chronic liver disease. However, the use of high doses of albumin that are well above the level covered by insurance in Japan is recommended in Western countries, depending on the condition of decompensated cirrhosis.

1. Position of albumin for the treatment of ascites

Cases of marked edema, ascites, or pleural effusion in decompensated cirrhosis are first managed with sodium and fluid restriction plus aldosterone antagonists and loop diuretics, but cases of treatment-resistant, so-called refractory, ascites are treated for a short time with hypertonic albumin products. In particular, marked hypoalbuminemia (albumin level  $\leq 2.5$  g/dl) commonly does not respond to an increase in the dose of diuretics and thus is usually treated in combination with hypertonic albumin products that have a low sodium content. Albumin, which is beneficial in maintaining plasma osmotic pressure and enhancing the effect of diuretics, increases the rate of disappearance of ascites, prevents the recurrence of ascites<sup>19)</sup>, and improves the rate of survival in patients with ascites secondary to liver cirrhosis when administered on an outpatient basis for a long time<sup>20)</sup>. Cases of refractory ascites that failed to respond to drugs are eligible for cell-free and concentrated ascites reinfusion therapy, peritoneo-venous shunt, or transjugular intrahepatic portosystemic shunt.

2. Use of albumin during paracentesis

Refractory ascites with breathing difficulty or marked abdominal distension is eligible for paracentesis. Large volume ( $\geq 4$  l) paracentesis causes adverse effects secondary to decreased circulating plasma volume, such as renal impairment and hyponatremia, in approximately 30% of cases. Paracentesis-induced circulatory dysfunction (PICD) is accompanied by marked renal impairment and is associated with death. Albumin has been shown to help prevent these adverse effects. A comparison of the group administered albumin at a dose of 40 g per 4 to 6 l of ascitic fluid removed and the group undergoing paracentesis alone found that patients experiencing hyponatremia or renal impairment after the first paracentesis had a poor prognosis, indicating that albumin administration was

important to prevent renal impairment or electrolyte abnormality following large volume paracentesis<sup>21</sup>. Albumin has been compared with other colloid solutions for the reason of its expensive nature and PICD occurred significantly less frequently in patients treated with albumin (18.5%) than in those receiving dextran 70 (34.4%) or polygeline (37.8%)<sup>22</sup>. Although there was no difference in the incidence of PICD between patients receiving normal saline and albumin when 4 to 5 l of ascetic fluid with each paracentesis is removed<sup>23</sup>, albumin at a dose of 8 to 10 g per l of ascetic fluid is effective if larger volume is removed<sup>24</sup>.

### 3. Use of albumin in spontaneous bacterial peritonitis (SBP)

Spontaneous bacterial peritonitis secondary to decompensated cirrhosis is also a condition with a poor prognosis. It is predominantly caused by aerobic Gram-negative bacteria, such as *E. coli* and *Klebsiella*, and treated with 3rd-generation cephem antibiotics or penicillin. However, a clinical study comparing the treatment with cefotaxime alone and in combination with albumin showed that coadministration with albumin reduced the development of hepatorenal syndrome (33% for cefotaxime alone vs. 10% for cefotaxime plus albumin,  $p=0.002$ ) and mortality (29% for cefotaxime alone vs. 10% for cefotaxime plus albumin,  $p=0.01$ )<sup>25</sup>. In this study, albumin was given at a dose of 1.5 g per kilogram of body weight within 6 hours after diagnosis, followed by 1 g per kilogram of body weight on day 3 of illness. Albumin is beneficial, especially for patients with impaired renal function<sup>26)27</sup>, and its benefits observed by a meta-analysis were appreciated<sup>28</sup>.

### 4. Use of albumin in hepatorenal syndrome (HRS)

Hepatorenal syndrome is referred to as acute renal failure in patients with end-stage liver cirrhosis or hepatic insufficiency, such as fulminant hepatitis, but represents functional pre-renal failure without any organic or pathological changes in renal tissues. Hepatorenal syndrome is classified into 2 types: type 1 showing rapidly progressive symptoms of renal failure and type 2 showing slowly progressive renal failure. Patients with hepatorenal syndrome has a low glomerular filtration rate (serum Cr >1.5 mg/dl or 24-hour CCr <40 ml/min), resulting in oliguria. In many cases, hepatorenal syndrome progresses in an irreversible manner, is associated with a mortality rate of  $\geq 90\%$ , and is one of the causes of death in end-stage liver cirrhosis. The use of terlipressin and albumin is recommended for the treatment of type-1 hepatorenal syndrome<sup>29)30</sup>. Improvement of renal impairment is also noted in 83% of patients with coadministration of norepinephrine and albumin, which represents a beneficial treatment regimen while waiting for a liver transplant<sup>31</sup>.

#### ● Recommendation

1. In patients with ascites secondary to liver cirrhosis who are on diuretics, albumin increases the rate of disappearance of ascites, prevents the recurrence of ascites, and improves the rate of survival after a long-term administration (1B).

2. When  $\leq 4$  to 5 l of ascetic fluid with each paracentesis is removed, albumin is not necessary because paracentesis-induced circulatory dysfunction can be managed with electrolyte replacement. When a larger volume of ascetic fluid is removed, a hypertonic albumin solution at a dose of 8 to 10 g per l of ascetic fluid is effective (1A).

3. Spontaneous bacterial peritonitis with renal impairment benefits from the treatment with a hypertonic albumin solution at a 1.5 g/kg body weight within 6 hours after diagnosis, following by 1 g/kg body weight on day 3 of illness (1A).

4. Treatment with a hypertonic albumin solution and a vasoconstrictor is effective in improving type-1 hepatorenal syndrome. Albumin should be administered at a dose of 1 g/kg body weight on day 1 and 20 to 40 g/body weight on subsequent days, in combination with terlipressin and other drugs (1A).



**iv) Nephritic syndrome with refractory edema or pulmonary edema**

## ● Statement

CQ4. Is albumin therapy effective in nephritic syndrome with refractory edema or pulmonary edema?	Grade	Evidence Level		Reference
		Overseas	Japan	
Although albumin is used as an act of necessity in combination with a diuretic, its efficacy is transient.	2	D	D	32-35

## ● Commentaries

Use of albumin in nephritic syndrome

Because albumin is rapidly excreted in urine after dosing in patients with nephritic syndrome, its efficacy in improving refractory edema is minimal and transient<sup>(32)(33)</sup>. Instead, albumin has reported to worsen renal impairment<sup>(34)</sup> and is thus not used for improving edema<sup>(35)</sup>. In patients with nephritic syndrome who have decreased blood pressure due to decreased colloid osmotic pressure or massive pleural effusion or ascites resulting in breathing difficulty and who have been difficult to treat with other approaches, albumin is used as an act of necessity in combination with a diuretic, but its efficacy is transient, with limited reports indicating its benefits.

## ● Recommendation

In nephritic syndrome with refractory edema or pulmonary edema, hypertonic albumin is expected to show only transient efficacy and is not recommended with the exception of use as an act of necessity (2D).

**v) Extracorporeal circulation with unstable hemodynamics**

## ● Statement

CQ5. Is the use of albumin effective during extracorporeal circulation, such as hemodialysis, in cases with unstable hemodynamics (e.g., in patients with diabetes)?	Grade	Evidence Level		Reference
		Overseas	Japan	
Although albumin is effective, normal saline is the first choice. Dose adjustment of antihypertensive drugs, use of vasopressors, or continuous dialysis is available as an alternative.	2	C	None*	36-38

\*No clinical study was available.

## ● Commentaries

Use of albumin during extracorporeal circulation, such as hemodialysis, in cases with unstable hemodynamics (e.g., in patients with diabetes)

Dialysis-induced hypotension is a common complication of dialysis that is due to decreased blood volume. It presents with symptoms, such as nausea, sweating, convulsion, and dizziness; is characterized by an abrupt drop in blood pressure; and has been treated with the administration of normal saline, albumin, isotonic colloids, etc<sup>(36)</sup>. Knoll et al. conducted a double-blind, randomized, cross-over trial designed to evaluate the superiority of albumin to normal saline in 45 patients with a history of dialysis-induced hypotension and found no evidence of efficacy of albumin with the exception that the albumin group was administered a smaller volume of normal saline<sup>(37)</sup>.

There are no other trials comparing the efficacy of albumin with other fluid therapies<sup>(38)</sup> and therefore normal saline is the first choice for hypotension during dialysis. In addition, dose adjustment of antihypertensive drugs, use of vasopressors, or continuous dialysis is available as an alternative to albumin in dialysis patients with unstable hemodynamics, including hypotension.

## ● Recommendation

In principle, the use of isotonic albumin is not recommended during extracorporeal circulation, such as hemodialysis, in cases with unstable hemodynamics (e.g., in patients with diabetes) (weak recommendation against use, 2C).

**vi) Therapeutic plasma exchange not requiring the replacement of coagulation factors**

## ● Statement

CQ6. Is the use of albumin effective during therapeutic plasma exchange not requiring the replacement of coagulation factors (e.g., in autoimmune neurological disorders)?	Grade	Evidence Level		Reference
		Overseas	Japan	
1. Therapeutic plasma exchange using albumin as a replacement fluid is an effective treatment for neurological disorders.	1	A	None*	39-45
2. Therapeutic plasma exchange is beneficial in removing anti-A or anti-B antibodies for ABO-incompatible transplantation when used in combination with immunosuppressant agents.	1	B	None*	46
3. In other diseases, therapeutic plasma exchange is less effective than causal therapy and shows only transient benefits.	2	C	None*	47, 48

\*No clinical study was available.

## ● Commentaries

Therapeutic plasma exchange not requiring the replacement of coagulation factors

Plasma exchange (PE) is a therapeutic procedure in which a plasma fractionator is used to separate the patient's blood into plasma and blood cellular components and replace the plasma containing pathogenic substances with a replacement fluid in order to remove the pathogenic substances and has been shown to be beneficial in many diseases<sup>39)</sup>. In therapeutic PE not requiring replacement of plasma components, a diluted albumin replacement fluid is recommended rather than fresh frozen plasma (FFP) from a viewpoint of the prevention of infections and simple plasma exchange and double-filtration plasmapheresis (DFPP) have been performed<sup>40)</sup>. Heat-treated human plasma protein fraction is, in principle, not used because it may cause anaphylactic reactions to contaminating proteins, such as hypotension.

A high evidence level is available regarding the efficacy of therapeutic PE in chronic inflammatory demyelinating polyneuropathy (CIDP), Guillain-Barre syndrome (GBS), and acute myasthenia gravis<sup>41)</sup>. Although PE, steroid therapy, or high-dose gamma-globulin therapy is available for the treatment of CIDP, there are no differences in effect among these treatments and treatment is selected depending on pathological conditions<sup>42)</sup>. A meta-analysis of RCTs has shown that PE provides short-term symptomatic improvement in approximately 70% of patients with CIDP<sup>43)</sup>. PE is also effective in GBS<sup>44)</sup> and a trial comparing plasma with albumin as a replacement fluid has indicated that there are no differences in treatment effect between them and that albumin replacement has a lower frequency of complications<sup>45)</sup>.

PE and DFPP are performed for removing anti-A or anti-B antibodies in ABO-incompatible transplantation and have been shown to be beneficial when used in combination with immunosuppressants<sup>46)</sup>.

Therapeutic PE is effective in acute exacerbation of steroid-refractory multiple sclerosis<sup>47)</sup>. In addition, PE was used for immunoglobulin removal in multiple myeloma or macroglobulinemia and produced improvements in renal function and survival rate<sup>48)</sup>. However, PE has shown only transient efficacy in these diseases.

## ● Recommendation

1. PE using an isotonic or diluted hypertonic albumin solution as a replacement fluid (1- to 1.5-fold plasma volume per session) is recommended for the treatment of neurological disorders, such as CIDP and GBS (1A).

2. PE using an isotonic or diluted hypertonic albumin solution as a replacement fluid is recommended for removing anti-A or anti-B antibodies in ABO-incompatible transplantation when used in combination with immunosuppressant agents (1B).

3. In principle, drug therapy is used in multiple sclerosis or hematological disorders (e.g., multiple myeloma or macroglobulinemia) and therapeutic PE is restricted (2C).

**vii) Severe burns**

## ● Statement

CQ7. Is the use of albumin beneficial for severe burns?	Grade	Evidence Level		Reference
		Overseas	Japan	
Albumin products are indicated in burns involving $\geq 50\%$ of the total body surface area.	2	C	None*	49
Although such burns within 18 hours of injury are usually managed with extracellular fluid, albumin products are used even within 18 hours of injury if an albumin level is $< 1.5$ g/dl.	2	B	None*	50-53
The efficacy of albumin on severe burns, length of stay, and mortality has not been proven.	1	B	None*	49, 54-58

\*No clinical study was available.

## ● Commentaries

1. Use of albumin in burns involving  $\geq 50\%$  of the total body surface area

Regarding  $\geq 50\%$  TBSA (% of the total body surface area) burns in children, there is only studies that were published long ago, there are a limited number of cases, and almost all cases led to death, with no survival benefit of albumin demonstrated. A possible reason is that *Pseudomonas aeruginosa* infection after burns was difficult to treat<sup>49)</sup>. In Reference 55, approximately half of patients in both the albumin group and the control group had possibly a  $\geq 50\%$  TBSA and albumin showed no benefits in cardiopulmonary function or survival.

## 2. Extracellular fluid is usually used within 18 hours of injury

In principle, albumin administration is recommended to be started within 24 hours of injury. Plasma proteins other than albumin have been reported to cause shock or reduced blood pressure when administered by bolus<sup>50)</sup>. Albumin is considered to extravasate within 6 to 18 hours of injury<sup>51)52)</sup>.

3. Albumin is indicated even within 18 hours of injury if an albumin level is  $< 1.5$  g/dl

Based on a paper on a burned Jehovah's witness<sup>53)</sup> who could endure albumin levels down to 1.2 g/dl without administration of blood products, an albumin level of 1.5 g/dl was considered appropriate.

## 4. Benefits of albumin

Although a paper reported that albumin improved morbidities<sup>58)</sup>, the study included only a limited number of patients, with 7 patients both in the albumin and control groups. Based on other papers including meta-analyses<sup>54)~57)</sup>, there were no statistical differences in morbidity. In addition, the length of stay<sup>56)</sup> or mortality was not improved<sup>54)~58)</sup>.

## ● Recommendation

No paper provides evidence of the efficacy of albumin in severe burns and its benefits to length of stay and mortality (strong recommendation against use, 1B). The use of isotonic albumin should be limited to cases of a serum albumin level of  $< 2.0$  g/dl after 18 hours of injury (2B).

**viii) Pulmonary edema or marked edema due to hypoproteinemia**

## ● Statement

CQ8. Is the use of albumin effective in pulmonary edema or marked edema due to hypoproteinemia?	Grade	Evidence Level		Reference
		Overseas	Japan	
Albumin is beneficial only for diuretic-resistant pulmonary edema or marked edema with marked hypoproteinemia, but there is no evidence of improved prognosis.	2	B	None*	59-63

\*No clinical study was available.

## ● Commentaries

## Place of albumin in the treatment of pulmonary edema or marked edema

Cases of pulmonary edema or marked edema are first managed with sodium and fluid restriction plus loop diuretics. However, if patients do not respond to high doses of diuretics and have comorbid marked hypoalbuminemia (albumin level  $\leq 2.0$  g/dl), the combination of a diuretic and a hypertonic albumin product is considered<sup>59)60)</sup>. It should be noted that this combination therapy is a matter of dispute and patients who benefit from the therapy may be limited<sup>61)62)</sup>. There is no evidence that albumin products improve prognosis<sup>63)</sup>.

● Recommendation

In patients with treatment-resistant pulmonary edema or marked edema, the use of a hypertonic albumin product is considered only in the case of marked hypoalbuminemia (2B).

**ix) Markedly decreased circulating plasma volume**

● Statement

CQ9. Is the use of albumin effective in acute pancreatitis etc. with markedly decreased circulating plasma volume?	Grade	Evidence Level		Reference
		Overseas	Japan	
Albumin administration is recommended in patients with shock as a result of markedly decreased circulating plasma volume secondary to acute pancreatitis, intestinal obstruction, etc.	2	D	D	64

● Commentaries

Circulating plasma volume is decreased when systemic inflammatory response induced by pancreatitis causes increased vascular permeability or reduced colloid osmotic pressure associated with loss of proteins, which facilitates the loss of extracellular fluid into the abdominal and thoracic cavities as well as the pancreatic area. Although the Clinical Practice Guidelines for the Management of Acute Pancreatitis 2010<sup>64)</sup> state “the practical regimen, including the ratio of crystalloids and colloids to be used, should be individualized on the basis of an overall assessment of central venous pressure, blood pressure, urinary output, hematocrit, serum total protein level, and others,” there is no clear evidence regarding the efficacy of albumin in acute pancreatitis. In addition, caution should be exercised because albumin administered in cases of increased vascular permeability extravasates and induces fluid retention, thus possibly leading to prolonged edema. However, shock secondary to markedly decreased circulating plasma volume is eligible for isotonic albumin products, as hypovolemic shock is.

● Recommendation

An isotonic albumin product should be used in cases of shock secondary to decreased circulating plasma volume associated with medical disorders, such as acute pancreatitis (2D).

**x) Cerebral ischemia (head injury)**

● Statement

CQ10 Is the use of albumin effective in cerebral ischemia (head injury)?	Grade	Evidence Level		Reference
		Overseas	Japan	
1. It cannot be said that albumin is effective for fluid resuscitation in patients with traumatic brain injury or initial treatment of acute stroke. In the former, worsened prognosis has been noted.	1	A	None*	65,66
2. Albumin is effective to maintain circulating blood volume in vasospasm after subarachnoid hemorrhage.	2	C	None*	67-69

\*No clinical study was available.

● Commentaries

1. Efficacy of albumin in cerebral ischemia (head injury) and prognosis

Among patients with traumatic brain injury who received fluid resuscitation for decreased circulating blood volume, albumin was associated with a higher mortality than normal saline, especially with the difference reaching significance in patients with severe brain injury<sup>65)</sup>. In addition, it has been noted that a hypertonic albumin product at a high dose (2 g/kg) for the initial treatment of acute stroke does not improve neurological prognosis and may increase the incidence of pulmonary edema or cerebral hemorrhage<sup>66)</sup>.

Crystalloids are preferentially used to maintain normal circulating blood volume in cerebral vasospasm after subarachnoid hemorrhage. Although albumin products are the second choice in cases of non-response to crystalloids, they have no direct effect on cerebral vasospasm and play a supplementary role by maintaining circulating blood volume<sup>67)</sup>. Triple-H therapy (the combination of hypervolemia, hemodilution, and induced hypertension) has been proposed for the improvement of disturbed cerebral circulation induced by cerebral vasospasm, but effects of aggressive fluid therapy for circulating blood volume expansion are controversial and maintenance of normal circulating blood volume has recently been favored<sup>68)69)</sup>.

● Recommendation

1. Albumin is not recommended for fluid resuscitation in patients with traumatic brain injury or initial treatment of acute stroke (strong recommendation against use, 1A).

2. The use of isotonic albumin should be considered to maintain circulating blood volume in cases of vasospasm after subarachnoid hemorrhages that do not respond to crystalloids (2C).

**xi) Heart surgery with cardiopulmonary bypass**

● Statement

CQ11. Is the use of albumin effective during heart surgery with cardiopulmonary bypass?	Grade	Evidence Level		Reference
		Overseas	Japan	
The benefit of using albumin as a priming solution during open-heart surgery with cardiopulmonary bypass has not been proven.	2	D	D	70-73, 75

● Commentaries

Albumin has long been used as a priming solution in the cardiopulmonary bypass circuit during open-heart surgery with cardiopulmonary bypass. The use has two major purposes, i.e., to reduce the activation of platelets or complements by coating the blood contact surface of the circuit and to prevent fluid leakage to the extravascular compartment by maintaining the colloid osmotic pressure during the extracorporeal circulation. For the former, the reduction of the activation of platelets or complements is now achieved using the blood contact surface of the circuit coated with heparin or macromolecular polymers. Therefore, albumin is used mainly for the latter purpose (maintaining the colloid osmotic pressure).

A randomized, controlled trial comparing albumin and crystalloid as a priming solution for cardiopulmonary bypass reported that the postoperative fluid balance was better in the albumin group<sup>70</sup>. However, there were no significant differences in postoperative increase in body weight, although albumin was associated with a postoperative decrease in body weight and it has been reported that there are no statistical differences in postoperative blood loss, blood transfusion volume, length of stay in ICU, length of stay in hospital, or mortality<sup>71)~73)</sup>. Although a Japanese retrospective study reported that albumin as a priming solution should be used with caution<sup>74)</sup>, it is considered that some use of albumin is inevitable in children with hemodilution<sup>75)</sup>.

● Recommendation

Because there are almost no studies providing evidence of the efficacy and benefits of isotonic albumin in length of stay and mortality when used as a priming solution during open-heart surgery with cardiopulmonary bypass, albumin should be used with caution (2D).

**xii) Hypoalbuminemia with stable hemodynamics during the perioperative period**

● Statement

CQ12. Is the use of albumin is effective in hemodynamically stable patients with hypoalbuminemia during the perioperative period?	Grade	Evidence Level		Reference
		Overseas	Japan	
The use of albumin is not effective in hemodynamically stable patients with hypoalbuminemia during the perioperative period.	2	C	None*	76, 77

\*No clinical study was available.

● Commentaries

During the perioperative period, hypoalbuminemia may occur secondary to increased vascular permeability, body fluid dilution resulting from blood transfusion or reduced albumin production in the liver. Although it is well documented that hypoalbuminemia is a poor prognostic factor<sup>76)</sup>, it remains inconclusive whether the use of albumin can improve the patient's prognosis. Many studies designed to examine the effect of albumin during the perioperative period include critically ill patients, such as ICU patients, but exclude patients with stable hemodynamics. The result of a Chinese, prospective, single-center, controlled trial comparing albumin with normal saline after gastrointestinal surgery indicated that there were no differences in terms of recovery of serum albumin

levels or clinical outcomes<sup>77)</sup>. In addition, the efficacy of the use of albumin remains unknown even in critically ill patients, suggesting that more care should be taken in hemodynamically stable patients.

● Recommendation

The use of albumin is not recommended in hemodynamically stable patients with hypoalbuminemia during the perioperative period (weak recommendation against use, 2C).

**xiii) Pregnancy-induced hypertension**

● Statement

CQ13. Is the use of albumin effective in pregnancy-induced hypertension?	Grade	Evidence Level		Reference
		Overseas	Japan	
The efficacy of the use of albumin in pregnancy-induced hypertension is not proven.	2	D	D	78,79

● Commentaries

In pregnancy-induced hypertension, the presence of proteinuria, extravasation, etc. frequently cause hypoproteinemia. When hypertension becomes more marked, circulating plasma volume decreases, leading to hemoconcentration. For that reason, albumin products were used for volume expansion in the 1970s. However, excessively high doses of albumin products increase the risk of pulmonary edema due to extravasation in patients with pregnancy-induced hypertension, who have increased vascular permeability. Thus, albumin is indicated in cases in which the use of an antihypertensive drug reduces diuresis, leading to oliguria. Three trials conducted to date included a limited sample size of 61 subjects and found no evidence of efficacy. Reliable data volume and methodologies are needed<sup>78)</sup>.

In summary, albumin is indicated in only limited cases of pregnancy-induced hypertension and instead excessive administration may worsen disease conditions<sup>79)</sup>.

● Recommendation

Isotonic albumin may be indicated in cases in which the use of an antihypertensive drug reduces diuresis, leading to oliguria. Excessive administration may worsen disease conditions (2D).

**xiv) Inflammatory bowel disease**

● Statement

CQ14. Is the use of albumin effective in inflammatory bowel disease?	Grade	Evidence Level		Reference
		Overseas	Japan	
The efficacy of albumin in inflammatory bowel disease is not proven.	2	None*	None*	None*

\*No clinical study was available.

● Commentaries

Hypoalbuminemia in patients with inflammatory bowel disease occurs due to undernutrition, inflammation, loss of proteins from the intestinal tract, etc. Although albumin is a useful indicator of nutrition or prognosis<sup>80)81)</sup>, no studies have been reported in which the clinical benefit of albumin in hypoalbuminemia was evaluated. In principle, hypoalbuminemia is managed with treatment of underlying disease or nutrition therapy<sup>82)</sup>, and the use of albumin is not recommended.

● Recommendation

The use of albumin is not recommended in inflammatory bowel disease (weak recommendation against use, 2 None).

**xv) Nutritional support as a source of protein**

## ● Statement

CQ15. Is the use of albumin effective as a source of protein for nutritional support?	Grade	Evidence Level		Reference
		Overseas	Japan	
1. The use of albumin as a source of protein for nutritional support is of limited value.	2	C	None*	83-85
2. The use of albumin does not improve the prognosis of patients with hypoalbuminemia who are on total parenteral nutrition.	2	C	None*	86-88

\*No clinical study was available.

## ● Commentaries

1. Serum albumin level is a prognostic factor in critically ill patients.

Decreased serum albumin level on hospital admission is considered to be associated with the patient's prognosis<sup>83)84)</sup>. However, hypoalbuminemia is affected by not only the severity of underlying disease but also malnutrition due to debilitating illness secondary to complications, mental stress, etc., and therefore cannot be completely regarded as a predictor of the patient's prognosis. Instead, the measurement of serum albumin levels is a useful indicator of changes in nutritional status in patients under long-term follow-up<sup>85)86)</sup>.

2. The use of albumin as a source of protein for nutritional support is of no value.

After dosing, albumin is slowly metabolized in the body and the majority of the dose is consumed as a source of calories. Albumin has an extremely low bioavailability and only a small fraction of the dose is metabolized into amino acids as materials for protein regeneration in the liver. Because only extremely small amounts of the essential amino acids tryptophan, isoleucine, and methionine are formed, albumin is of little value as nutritional support. The use of albumin in postoperative hypoproteinemia or malignancies is of no nutritional value with the exception of inducing a transient rise in plasma protein levels and providing colloid osmotic effects. From a standpoint of nutritional support, administration of amino acids and energy supplement with parenteral nutrition or enteral nutrition is nutritionally effective in producing proteins. In hospitalized patients who cannot take anything by mouth and require nutritional management, the early use of enteral nutrition, as compared with the early use of parenteral nutrition, is associated with a lower incidence of infections or noninfectious complications and a shorter length of stay in hospital, but with no differences in ultimate mortality. The use of albumin products is not indicated for hypoalbuminemia and the early use of enteral nutrition or parenteral nutrition is beneficial<sup>87)</sup>.

3. The use of albumin does not improve the prognosis of patients with hypoalbuminemia who are on parenteral nutrition.

The administration of albumin to intensive care unit (ICU) patients with hypoalbuminemia who are receiving parenteral nutrition does not improve morbidity or mortality<sup>88)89)</sup>. Instead, considering the risk of increased infectious (e.g., sepsis) or non-infectious complications, the routine use of albumin products in hypoalbuminemia should be avoided because it is merely expensive and does not improve the patients' prognosis.

## ● Recommendation

1. The use of albumin as a source of protein is of limited value in nutritional support and the early use of enteral nutrition or parenteral nutrition is efficient in hypoalbuminemia (weak recommendation against use, 2C).

2. Although serum albumin level is an independent prognostic factor in hospitalized patients, the use of albumin should be avoided because it has no positive effects on the incidence of complications or the length of stay in hospital and prognosis. (weak recommendation against use, 2C)

**xvi) Terminally ill patients**

## ● Statement

CQ16. Does the use of albumin improve the prognosis of terminally ill patients?	Grade	Evidence Level		Reference
		Overseas	Japan	
The use of albumin does not improve the prognosis of terminally ill patients with hypoproteinemia.	2	C	None*	87,90

\*No clinical study was available.

## ● Commentaries

Use of albumin for hypoproteinemia in terminally ill patients

Causes of hypoproteinemia in terminally ill patients include i) reduced protein synthesis, ii) changes in biodistribution due to dehydration etc., iii) increased catabolism, and iv) loss of protein from the body. In particular, reduced protein synthesis in the liver is involved, including an eating disorder or disorder of digestion and absorption for protein components due to underlying disease. High-calorie nutrition containing amino acids, which are materials of protein, using the early use of enteral or parenteral nutrition is important<sup>87)</sup>. Although the use of albumin products produces an immediate rise in serum albumin levels, it is of limited value in nutritional support because albumin has extremely low bioavailability and only a small fraction of the dose is metabolized into amino acids as materials for protein regeneration in the liver. Thus, the indication of albumin for hypoproteinemia in terminally ill patients is limited and includes symptomatic treatment to facilitate osmotic diuresis in severe edema or pulmonary edema. The use of albumin does not improve the prognosis of terminally ill patients with merely hypoproteinemia<sup>90)</sup> and instead should be avoided because it may reduce the production of inflammatory cytokines (e.g., interferon- $\gamma$  and TNF- $\alpha$ ) from peripheral blood mononuclear cells or T-lymphocytes and increase the incidence of infections due to its immunosuppressive effects, resulting in a poor prognosis<sup>91)</sup>. In addition, unnecessary use of fluid therapy or albumin should be avoided from the viewpoint of sanctity of life in terminally ill patients<sup>92)</sup>.

## ● Recommendation

There are no reports where the use of albumin improves the prognosis of terminally ill patients, but instead the use of albumin has been reported to increase the incidence of infections. The use of albumin should be also avoided in terminally ill patients because of concerns for immunosuppression. (Weak recommendation against use, 2C)

**xvii) Pathological conditions that are not eligible for other plasma expanders**

## ● Statement

CQ17. Is the use of albumin recommended in pathological conditions that are not eligible for other plasma expanders?	Grade	Evidence Level		Reference
		Overseas	Japan	
Albumin is effective in cases in which it is difficult to use plasma substitutes other than albumin.	1	B	None*	93, 94

\*No clinical study was available.

## ● Commentaries

Plasma substitutes other than albumin include hydroxyethyl starch (HES) products and dextran products. They have been used for decreased circulating blood volume that are observed in surgery/trauma, burn treatment, etc., but have been noted to cause blood coagulation disorders, acute renal failure, and other problems. Thus, the use of albumin products is necessary in cases requiring high-dose administration. In addition, albumin is administered when allergic symptoms are observed, including congestive heart failure, renal impairment with oliguria and anaphylaxis.

In a clinical trial, patients with severe sepsis who received an HES product, as compared with those who received Ringer's acetate, had a higher risk of death at 90 days and were more likely to receive renal-replacement therapy<sup>93)</sup>. There is a report that an HES product, as compared with albumin, increased the risk of postoperative blood loss necessitating blood transfusion and reoperation for bleeding when administered for fluid management in adult cardiopulmonary bypass surgery<sup>94)</sup>. However, the 3rd generation HES130/0.41 product has excellent safety and efficacy profiles and remains to be studied.



● Recommendation

Albumin is used in cases in which it is difficult to use plasma substitutes other than albumin. (1B)

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Akemi Wakisaka: None

	Supervision	Funding	Formulation of CQs	Primary Selection of Published Papers	Secondary Selection of Published Papers*	Preparation of Commentaries	Determination of the Evidence Level and Grade of Recommendation
Shigeyoshi Makino		○	○	○	○	○	○
Tadashi Matsushita		○					
Yuji Yonemura			○		○	○	○
Satoshi Yasumura	○		○	○	○	○	○
Shuichi Kino			○		○	○	○
Takehiro Kono			○	○	○	○	○
Asashi Tanaka			○		○	○	○
Masanori Matsumoto			○	○	○	○	○
Akemi Wakisaka			○				

\*Includes additional hand-searched papers.

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Table Evidence-based Guidelines for the Use of Albumin Products Japan Society of Transfusion Medicine and Cell Therapy

Grade of Recommendation	Hypertonic Albumin Product	Isotonic Albumin Product
Recommended	<ul style="list-style-type: none"> <li>■ Liver cirrhosis               <ul style="list-style-type: none"> <li>① Type 1 hepatorenal syndrome</li> <li>② Spontaneous bacterial peritonitis</li> <li>③ Large-volume paracentesis</li> <li>④ Management of refractory ascites</li> </ul> </li> <li>■ Therapeutic plasma exchange not requiring the replacement of coagulation factors (with dilution)</li> </ul>	<ul style="list-style-type: none"> <li>■ Therapeutic plasma exchange not requiring replacement of coagulation factors</li> <li>■ Pathological conditions that are not eligible for other plasma expanders</li> </ul>
Usually not used	<ul style="list-style-type: none"> <li>■ Nephritic syndrome with refractory edema or pulmonary edema</li> <li>■ Pulmonary edema or marked edema due to hypoproteinemia</li> </ul>	<ul style="list-style-type: none"> <li>■ Hemorrhagic shock</li> <li>■ Severe burns</li> <li>■ Severe sepsis</li> <li>■ Extracorporeal circulation with unstable hemodynamics</li> <li>■ Markedly decreased circulating plasma volume (e.g., pregnancy-induced hypertension, acute pancreatitis)</li> <li>■ Heart surgery with cardiopulmonary bypass</li> <li>■ Vasospasm after subarachnoid hemorrhage</li> </ul>
Inappropriate use	<ul style="list-style-type: none"> <li>■ Hypoalbuminemia with stable hemodynamics during the perioperative period</li> <li>■ Nutritional support as a source of protein</li> <li>■ Terminally ill patients</li> </ul>	
Contraindication	<ul style="list-style-type: none"> <li>■ Brain injury (cerebral ischemia)</li> </ul>	

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## 科学的根拠に基づいたアルブミン製剤の使用ガイドライン

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