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Review Article

Albumin administration in internal medicine: A journey between effectiveness and futility[☆]Enrico Pompili^{a,b}, Giacomo Zaccherini^{a,b}, Maurizio Baldassarre^{a,c}, Giulia Iannone^{a,b}, Paolo Caraceni^{a,b,*}^a Department of Medical and Surgical Sciences, Alma Mater Studiorum University of Bologna, Italy^b Unit of Semeiotics, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Italy^c Centre for Applied Biomedical Research (CRBA), Alma Mater Studiorum of Bologna, Italy

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ABSTRACT

Albumin is the most abundant circulating protein and provides about 70% of the plasma oncotic power. The molecule also carries many other biological functions (binding, transport and detoxification of endogenous and exogenous compounds, antioxidation, and modulation of inflammatory and immune responses).

Hypoalbuminemia is a frequent finding in many diseases, representing usually only a biomarker of poor prognosis rather than a primary pathophysiological event. Despite that, albumin is prescribed in many conditions based on the assumption that correction of hypoalbuminemia would lead to clinical benefits for the patients. Unfortunately, many of these indications are not supported by scientific evidence (or have been even disproved), so that a large part of albumin use is nowadays still inappropriate.

Decompensated cirrhosis is the clinical area where albumin administration has been extensively studied and solid recommendations can be made. Besides prevention and treatment of acute complications, long-term albumin administration in patients with ascites has emerged in the last decade has a potential new disease-modifying treatment. In non-hepatological settings, albumin is widely used for fluid resuscitation in sepsis and critical illnesses, with no clear superiority over crystalloids. In many other conditions, scientific evidence supporting albumin prescription is weak or even absent.

Thus, given its high cost and limited availability, action is needed to avoid the use of albumin for inappropriate and futile indications to ensure its availability in those conditions for which albumin has been demonstrated to have a real effectiveness and an advantage for the patient.

Human albumin is the most abundant circulating protein and accounts for approximately 50–60% of all total plasma proteins in healthy individuals. The molecule is composed of 585 amino acids organised into three homologous domains (I, II and III), each of which containing two distinct subdomains. The liver is the only site of production, with the hepatocytes entering into the blood circulation about 9–12 gs of albumin every day [1,2]. In physiological conditions, albumin synthesis

involve only 20–30% of hepatocytes, therefore there is a large functional reserve allowing to increase it by 3–4 times when needed. The catabolism of the molecule is ubiquitous and takes place at the level of vascular endothelia, muscle, skin and kidney at a daily rate that equals hepatic synthesis. The circulatory half-life of the protein is about 16–18 h, since every hour 4–5% of albumin leaves the intravascular compartment, and then returns to it via the lymphatic system. The overall half-life is about

Abbreviations: ACLF, acute-on-chronic liver failure; AKI, acute kidney injury; HE, hepatic encephalopathy; HRS, Hepatorenal syndrome; LVP, large-volume paracentesis; MELD, Model for End-stage Liver Disease; PPCD, post-paracentesis circulatory dysfunction; RCT, randomized clinical trial; SBP, spontaneous bacterial peritonitis; SMT, standard medical treatment.

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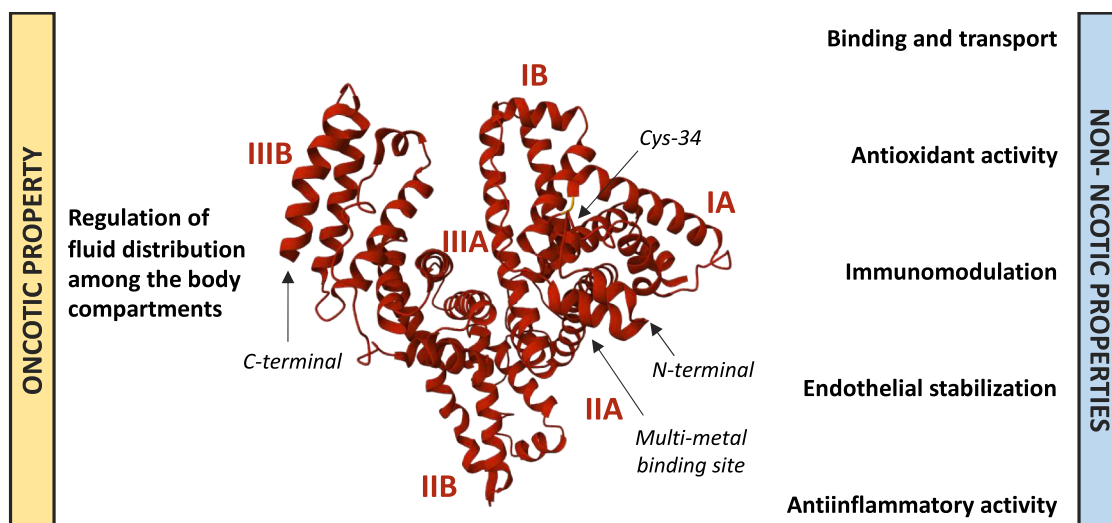


Fig. 1. Properties and structure of the albumin molecule. Binding and transport of endogenous and exogenous (including drugs) compounds occur at the site I, II and III. Antioxidant activity occurs mostly at the cysteine-34 (Cys-34) residue, at the N-terminal and at the multi-metal binding site.

14–20 days in healthy adults [1,2].

Albumin has been always recognized for providing approximately 75% of the oncotic pressure of the blood: two thirds of its oncotic property is due to the molecular mass and high concentration in the bloodstream, while the remaining one third to the presence of negative charges on its surface that attract positive ions, such as sodium, and consequently water (Gibbs-Donnan effect). This makes albumin the most important modulator of fluid distribution among the different body compartments [1–4].

In the last few decades, it has become evident that albumin is also provided of many other biological functions unrelated to the oncotic power (Fig. 1). Albumin binds and transports many endogenous (i.e., unconjugated bilirubin, fatty acids, cholesterol, bile acids and thyroxine) and exogenous (i.e., drugs) compounds. It represents the most abundant circulating antioxidant able to scavenge both oxygen and nitrogen reactive species [2–4]. Besides its capacity of antagonizing oxidative stress, albumin modulates inflammation and the immune response through several other mechanisms (i.e., binding prostaglandin E₂ and stimulating immune cells) [5,6]. Finally, it has been reported a role in the haemostasis and pH regulation [2–4].

In few words, taking into consideration both the high serum concentration and all its pleiotropic properties, it appears evident that albumin contributes to many physiological processes of our organisms.

1. Hypoalbuminemia: a prognostic biomarker or a target of therapy?

The normal range of serum albumin concentration has been set between 3.5 and 5 g/dl by using the current laboratory assays. In a large cohort study, at least 90% of healthy male subjects have a serum albumin concentration higher than 4 g/dl up to 80 years old and less than 1% presents a level below 3.5 g/dl [7].

Hypoalbuminemia (<3.5 g/dl) is a quite frequent finding in many acute and chronic diseases and acts as an independent predictor of poor outcomes. In older patients, hypoalbuminemia has been linked to in-hospital complications, longer hospital stays, surgical complications, hospital readmissions, and poorer survival [8–12]. A large study in about 15,000 patients hospitalized for acute illnesses showed that hypoalbuminemia at admission is a stronger predictor of death, length of stay, and hospital readmission [13]. Hypoalbuminemia is a negative prognostic factor in patients with either solid or hematological malignancies [14,15]. Serum albumin concentration has been also included in

several prognostic scores (i.e. Child-Pugh, ALBI, GLOBE) in patients with liver diseases [16–18]. More recently, hypoalbuminemia independently predicted a worse prognosis in patients with SARS-CoV-2 pneumoniae [19].

If the prognostic meaning of hypoalbuminemia is incontrovertible, the opposite can be said regarding the link between its correction by exogenous albumin administration and improvement of outcomes.

The therapeutic use of albumin dates to World War II when it was administered to expand plasma volume in critically injured patients. In the following decades, besides its role as plasma-expander, the administration of albumin has been extended to a wide range of clinical conditions, usually associated to hypoalbuminemia, based on the assumption that its correction would lead to clinical benefits for the patients. Unfortunately, many of these indications are not supported by solid scientific evidence (or have been even disproved), so that a large part of the therapeutic use of albumin is nowadays still inappropriate.

If we also consider that albumin, as any other blood derivative, is a finite product and therefore of limited availability, and its production is expensive, it appears evident that the therapeutic use of albumin should be limited to the clinical indications where solid scientific evidence has been shown effectiveness in improving clinical outcomes.

2. Albumin and liver cirrhosis: “the perfect drug for the perfect disease”

Human albumin administration is likely the therapeutic intervention most studied in patients with decompensated liver cirrhosis. The potential benefits of administering albumin to patients with ascites have been initially evaluated about 60 years ago [20]. Afterwards, a large number of randomized clinical trials (RCTs) have shown that albumin is effective in preventing or treat some acute complications of cirrhosis, but not others [21]. Furthermore, in the last decade, long-term administration has been shown to be a new modality of albumin treatment able to act as a disease-modifier in patients with cirrhosis and ascites [21]. Finally, international surveys indicate that hepatologists prescribe albumin also for indications supported neither by guidelines nor by any solid scientific evidence [22–24].

One might wonder why albumin is so attractive to researchers and clinicians dealing with patients with decompensated cirrhosis. The answer is likely based on the assumption that the pleiotropic functions of albumin could target the pathophysiological mechanisms so precisely in no other disease as in decompensated cirrhosis.

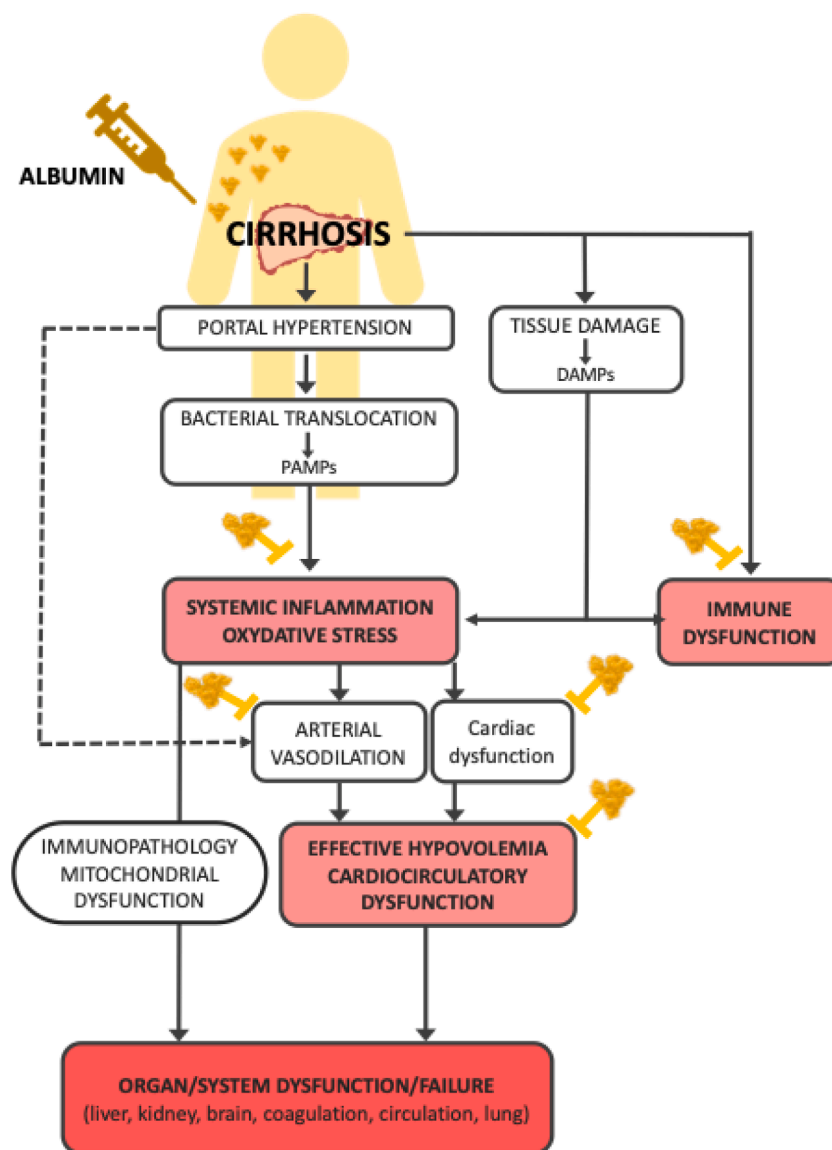


Fig. 2. Pathophysiology of decompensated cirrhosis and potential positive effects of albumin administration. PAMPs: pathogen-associated molecular patterns, DAMPs: damage-associated molecular patterns.

2.1. Pathophysiological rationale for the use of albumin in decompensated cirrhosis

Effective hypovolemia due to splanchnic vasodilation and, in the advanced stage of the disease, to cardiac dysfunction has been for decades the key pathophysiological event in decompensated cirrhosis [25]. Thus, albumin administration given for maintaining the integrity of arterial circulation by correcting effective hypovolemia or avoiding further deterioration has been proved to be beneficial in some severe complications of cirrhosis [4,21]. However, it is now clear that systemic inflammation and immune dysfunction are other major pathophysiological drivers of decompensated cirrhosis, particularly in the very advanced stage or when acute-on-chronic liver failure ensues (ACLF) [26,27]. Systemic inflammation induced by the substances translocated from the gut and by those released from the damaged liver is at the base of the cardiocirculatory dysfunction of decompensated cirrhosis. It also directly promotes organ dysfunction and failure through mechanisms, such as immunopathology and mitochondrial dysfunction [26,27]. Several evidence indicate that the non-oncotic properties of the molecule can mediate the beneficial effects of albumin by modulating the inflammatory and immune responses [27,28] (Fig. 2).

Moreover, in patients with decompensated cirrhosis, the albumin molecule undergoes both quantitative and qualitative changes. Hypoalbuminemia results mainly from the reduced synthesis in the diseased liver and the enhanced catabolism due to the structural alterations of the molecule; however, the hemodilution related to the expanded total plasma volume also contributes to its reduced plasma levels [4]. Besides that, the persisting inflammatory state of advanced cirrhosis induces molecular, structural and conformational changes of albumin that adversely affect its binding, transport and detoxification capacities [29–33]. Thus, the circulating albumin in these patients is not only low, but it is also dysfunctional.

Taken all together, these factors provide the rationale for administering exogenous albumin with the objective of restoring the physiological functions of the molecule able to counteract the major pathophysiological drivers in patients with decompensated cirrhosis (Fig. 2).

2.2. Therapeutic use of albumin in decompensated cirrhosis

Many interventional studies have investigated the efficacy and safety of albumin in decompensated cirrhosis. Both positive and negative

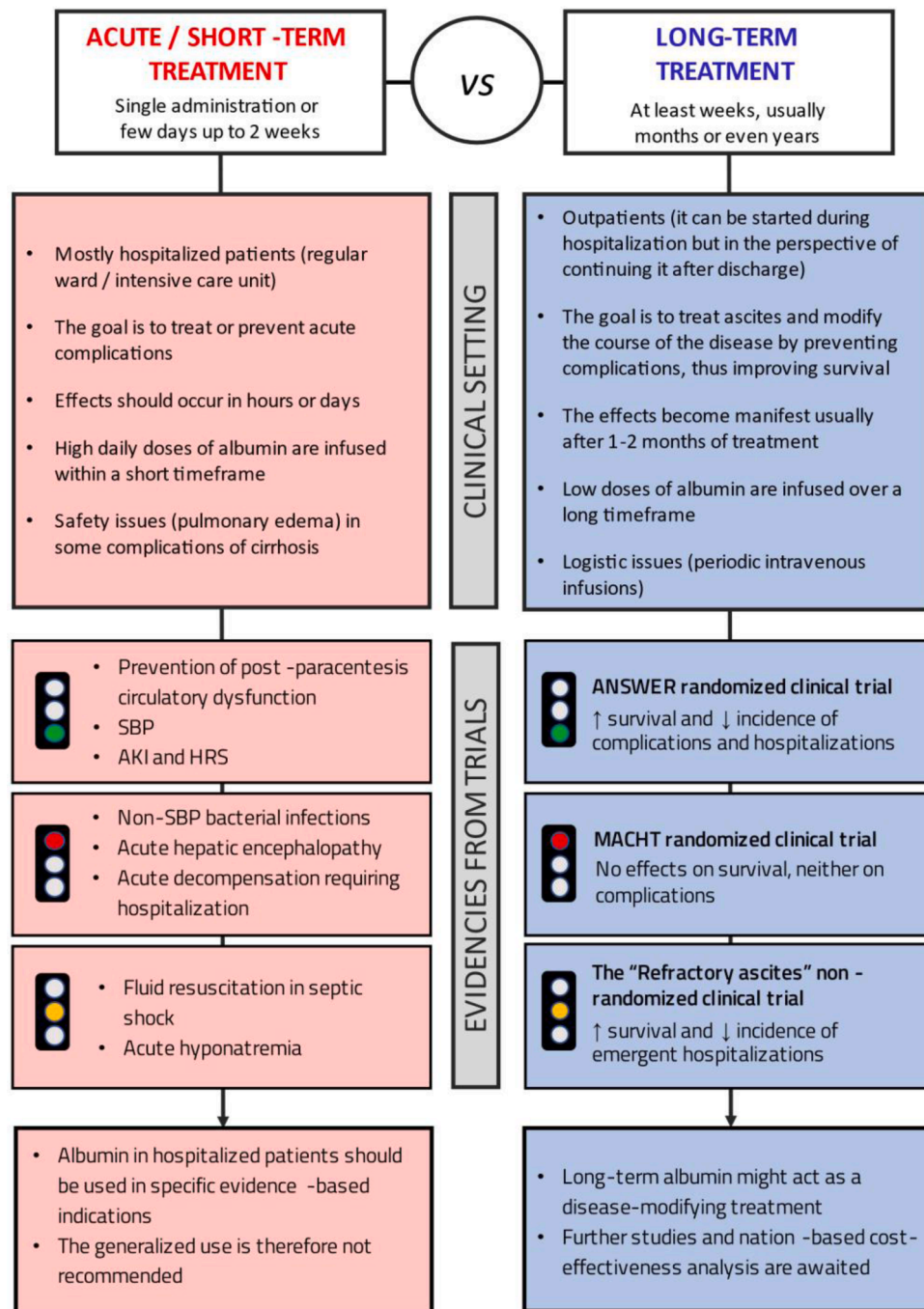


Fig. 3. Differences in acute/short term and long-term albumin treatment in patients with decompensated cirrhosis.

results have been reported likely due to the high heterogeneity of the trials in terms of clinical indications, patient phenotypes, and doses and schedules of albumin administration. From the studies available, a clear distinction can be made by differentiating acute or short-term treatment from long-term treatment (Fig. 3).

2.2.1. Acute or short-term albumin treatment

Treatment can be defined acute or short-term when albumin is given as a single administration or for few days up to a maximum of 2 weeks [21]. It is usually applied in hospitalized patients, both in regular wards or in intensive care units, with the goal of treating or preventing an acute complication of cirrhosis. To be effective, albumin is expected to act quite fast and therefore high amounts of albumin are infused in a relatively short timeframe. Such an approach can raise safety issues in

patients at high-risk of volume overload, particularly pulmonary edema.

2.2.1.1. Evidence-based indications recommended by international guidelines. Acute or short-term albumin administration has been proved to be effective in specific conditions which can be frequently encountered in patients with decompensated cirrhosis (Table 1).

Large-volume paracentesis (LVP), which has been arbitrarily defined as the removal of at least 5 litres of ascitic fluid in a single session, is the first-line treatment for patients with decompensated cirrhosis complicated by massive or tense ascites or with refractory ascites [34,35]. LVP can induce *post-paracentesis circulatory dysfunction* (PPCD), which can be diagnosed by an increase of the plasma renin activity of at least 50% above the pre-paracentesis value occurring up to 6 days after paracentesis [36]. PPCD is characterized by a further exacerbation of

Table 1

Clinical indications for acute/short term albumin administration in patients with decompensated cirrhosis supported by scientific international guidelines.

Indication	Albumin doses	Outcomes
LVP (≥ 5 liters)	6–8 g per liter of ascites removed	Prevention of PPCD (<i>RCTs and metaanalyses</i>) Improvement of survival (<i>only metaanalyses</i>)
SBP (with antibiotics)	1.5 g/kg at diagnosis and 1 g/kg on the 3rd day	Prevention of renal failure (<i>RCTs and metaanalyses</i>) Improvement of survival (<i>RCTs and metaanalyses</i>)
Treatment of HRS (with vasoconstrictors)	20–40 g/day until vasoconstrictors are stopped or up to a maximum of 14 days	Resolution of HRS (<i>RCTs and metaanalyses</i>) Improvement of survival (<i>only metaanalyses</i>)
AKI grade 1B or higher	1 g/kg (maximum 100 g/day) for two consecutive days	Resolution of AKI (<i>expert consensus</i>)

AKI: acute kidney injury; HRS: hepatorenal syndrome; LVP: large volume paracentesis; PPCD: post-paracentesis circulatory dysfunction; RCT: randomized clinical trial; SBP: spontaneous bacterial peritonitis.

effective hypovolemia, leading to renal impairment, dilutional hyponatremia, rapid reaccumulation of ascites, and death [34–38]. Albumin administration after LVP is able to prevent PPCD with a more efficient extent than crystalloids and synthetic colloids [39,40]. Albumin should be also given after lower-volume paracentesis (<5 litres) in patients with ACLF [38], renal impairment or severe circulatory dysfunction [34,35]. Plasma expansion with a mixture of albumin and crystalloids or synthetic colloids to spare albumin has not been tested and therefore should be avoided.

Spontaneous bacterial peritonitis (SBP) is a bacterial infection of ascites diagnosed by a neutrophil count >250/mm³ in the ascitic fluid, in the absence of any clear abdominal infectious foci [41]. Despite the advancement in antibiotic therapy, SBP is associated to about 20% in-hospital mortality as a result of the risk of developing renal failure, sepsis and septic shock [34,42,43]. A seminal RCT showed that administration of albumin, together with antibiotic therapy, significantly reduces the incidence of renal failure and improves mortality compared to antibiotic alone [42]. Current EASL and AASLD guideline support the use of albumin in addition to antibiotics. However, albumin administration may not be necessary in patients not presenting severe liver failure (serum bilirubin <4 mg/dL) or renal dysfunction (serum creatinine <1 mg/dL), as the risk of renal failure and death in these cases is low [34,35,42,44].

Acute Kidney Injury (AKI) is defined by an increase in serum creatinine of at least 0.3 mg/dL within 48 h or at least a 50% increase in serum creatinine that is known or presumed to have occurred within the preceding 7 days [45]. AKI is frequent in decompensated cirrhosis being diagnosed in 25–50% of hospitalized patients and is associated to a worsening of prognosis [46]. *Hepatorenal syndrome (HRS)* is peculiar of patients with cirrhosis and represents about 15–40% of all AKI cases [45, 46]. Diagnosis of HRS-AKI is challenging and is usually made following a diagnostic algorithm including plasma volume expansion with albumin (Fig. 4) [45–48]. Briefly, patients with AKI stage 2 and 3 and those with stage 1b those not responding to management of risk factors should receive high-dose albumin for 2 consecutive days [47]. Non-responding patients, if they meet the criteria for HRS, should be treated with terlipressin and albumin according to the results of several RCTs showing the reversal of AKI-HRS in about 30–50% of cases [49–51]. Norepinephrine represents a valid alternative [52,53], but its administration usually requires admission to ICU and a recent report has shown that it is less effective than terlipressin at least in patients with ACLF [54]. Finally, caution should be applied in patients with HRS-AKI in presence of risk factors for pulmonary edema due to the concomitant effects of albumin (pre-load increase related to plasma expansion) and terlipressin

(after-load increase due to the rise in peripheral vascular resistances associated to a negative inotropic effect on myocardium) [55].

2.2.1.2. Indications not supported by scientific evidence. A single RCT on acute episodes of hepatic encephalopathy (HE) and 3 RCTs on bacterial infections unrelated to SBP showed that short-term administration of albumin on top of standard medical treatment (SMT) does not improve neither the resolution of these clinical events nor patient survival [56–59], while an increased incidence of pulmonary edema has been reported, particularly in patients with severe pneumoniae [58,59].

A paradigmatic example of short-term albumin treatment comes from the ATTIRE study, a large multicenter randomized trial recently performed in United Kingdom, which evaluated the efficacy and safety of albumin in patients admitted to the hospital for acute onset or worsening of complications of cirrhosis and at least moderate hypoalbuminemia [60]. Albumin was given with a personalized daily dosing protocol followed to achieve and maintain the target level of 3 g/dl until discharge or up to a maximum of 14 days. Median length of albumin treatment was about 8 days. The results of the ATTIRE study are without any doubt negative since no differences between the experimental and control groups were observed for both the primary end-point (a composite of infection from any cause, kidney dysfunction and death from day 3 to 15 or up to discharge) and all the secondary end-points (i.e., 28 days, 3 months and 6 months survival and the incidence of each of the 3 components of the primary end-point). Again, a significantly higher incidence of pulmonary edema was reported in patients receiving albumin.

Thus, it appears evident that a generalized use of albumin in hospitalized patients with decompensated cirrhosis cannot be recommended and prescription should be instead guided by the scientific evidence available to avoid unnecessary consumption of albumin. Unfortunately, even in presence of international guidelines and recommendations [34, 35,61], surveys in Europe and United States have shown that a part of albumin is prescribed by hepatologists for non evidence-based indications, including hypoalbuminemia per se or nutritional support [22–24].

2.2.2. Long-term albumin treatment

The use of albumin as a long-term treatment in patients with cirrhosis and ascites has been proposed for many years, but only in 2018 three clinical trials have provided novel and important data [62–64]. Long-term treatment lasts at least weeks, usually months or even years. It is usually performed in outpatients, but it can be started during hospitalization but always in the perspective of continuing after discharge. The goal is to modify the course of the disease by preventing the development of complications and the benefit usually becomes manifest after weeks of treatment. Since albumin doses are lower and distributed over time no safety issues have been reported. Logistic issues related to the periodic intravenous infusions could be instead expected (Fig. 3).

The ANSWER study is an Italian, open-label, multicentre RCT that included 431 patients, presenting at least moderate uncomplicated ascites despite diuretic therapy, to receive either standard medical treatment (SMT) plus albumin (40 g twice weekly for 2 weeks, and then 40 g weekly up to a maximum of 18 months) or SMT alone [62].

Albumin treatment induced a significant improvement of the 18-month overall survival, which was the primary end-point of the study, eased the management of ascites by reducing more than 50% the incidence of paracentesis, significantly reduced the incidence rate of many severe complications of cirrhosis, so that liver-related hospital admissions and days spent in hospital were significantly lower in patients receiving albumin. This was associated with a better quality of life as compared to those treated with only SMT. Furthermore, albumin administration resulted to be cost-effective at least in the Italian Health care system. Finally, a recent post-hoc analysis showed the rate of correction of hyponatremia was significantly higher in the albumin

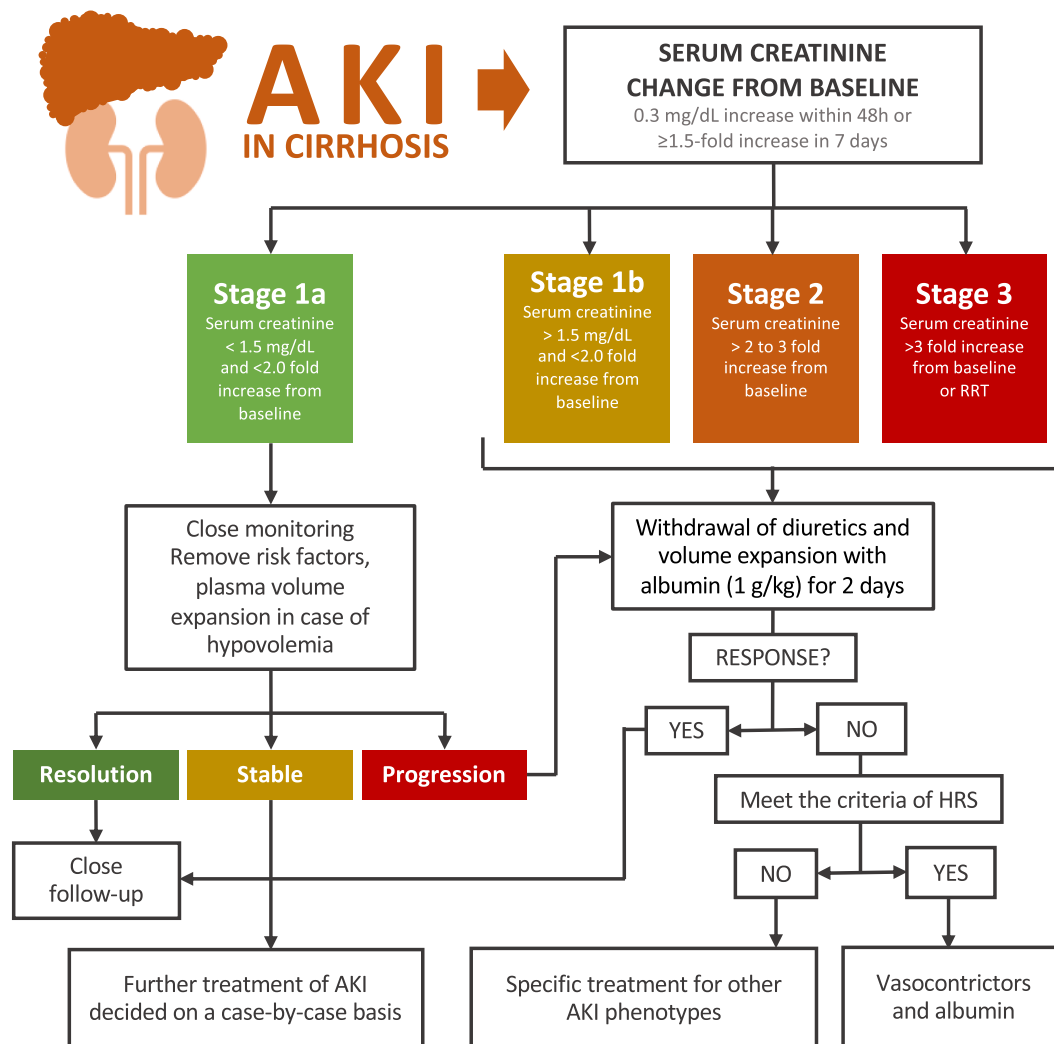


Fig. 4. Definition and stages of acute kidney injury (AKI). Diagnostic and treatment algorithm for AKI and hepatorenal syndrome (HRS) in patients with cirrhosis. Adapted from [45,47]. Diagnostic criteria for HRS are: 1. presence of cirrhosis, acute liver failure or acute-on-chronic liver failure; 2. increase in serum creatinine ≥ 0.3 mg/dl within 48 h or $\geq 50\%$ from baseline value and/or urinary output ≤ 0.5 ml/kg body weight ≥ 6 h; 3. no regression of AKI to a lower stage after at least 2 days of diuretic withdrawal and volume expansion with albumin; 4. absence of shock; 5. no current or recent treatment with nephrotoxic drugs; 6. absence of parenchymal disease as indicated by proteinuria >500 mg/day, microhematuria (>50 red blood cells per high power field), urinary injury biomarkers (if available) and/or abnormal renal ultrasonography.

Table 2

Long-term albumin treatment in patients with cirrhosis and ascites: differences between the ANSWER and MACHT trials. Adapted by [21]. MELD: Model for End stage Liver Disease.

	MACHT [64]	ANSWER [62]
Design	Randomized double-blind placebo-controlled	Randomized open-label
Severity of disease	MELD score: 17	MELD score: 12
Dosage and timing of albumin administration	40 gs every 2 weeks	40 gs twice a week for 2 weeks then 40 gs once a week
Median length of albumin treatment	63 days	14.5 months
Impact of treatment on serum albumin concentration	No differences between interventional and control group	Significant increase from baseline in the interventional group
Outcomes	No effect on 12-month mortality or incidence of complications	Significant improvement of 18-month overall survival and incidence of complications

group as compared to those treated only with SMT [65].

Very similar positive results have been also reported in a single-center, open-label, non-randomized clinical trial assessing 2 years of albumin administration (40 gs weekly) in patients with refractory ascites [63].

The third trial is a Spanish, double-blind, placebo-controlled multi-centre RCT that assessed albumin (40 g every days) plus midodrine (15–30 mg/day) up to 1 year in 196 patients with cirrhosis and ascites waiting for liver transplantation (MACHT) [64]. The results were without any doubt negative showing no differences in the incidence of any complication of cirrhosis (primary endpoint) or survival.

Why the results from the ANSWER and MACHT trials are so variant? The differences have recently been analysed in a review co-authored by the principal investigators of the two RCTs studies [21] (Table 2).

Besides the design of the study (open-label vs double-blind), which can have introduced a confounding bias, the major difference resides on the impact of albumin treatment on median serum albumin concentration: while a significant increase above baseline (from 3.1 to 3.8 g/dL) was observed in the ANSWER study, this was not the case in the MACHT

study (from 3.1 to 3.2 g/dL) due to the lower dose and frequency (about half) and length of administration (only 2 months) [62,64]. Thus, it appears that two conditions, strictly interrelated, must be achieved to unveil the clinical benefits of long-term treatment: administering enough albumin and for enough time to significantly increase serum albumin concentration.

Based on the ANSWER study, long-term albumin administration has been included among the medical options for the treatment with ascites by the Italian Association for the Study of the Liver (AISF) [66]. It should be acknowledged, however, that Italy represents a sort of “unicum” with respect to other countries since this treatment is reimbursed by the National Health System and is currently standard of care in many hepatological centers. Indeed, a strong international scientific debate is currently ongoing about long-term albumin administration in patients with ascites, which represents not only a novel indication, but also carries logistic and economic issues inherent to the need for chronic periodic intravenous infusions that could render its applicability in clinical practice problematic.

It would be unrealistic to propose long-term albumin administration for all patients with ascites which represent a very heterogeneous population. At present, the clinical phenotype of cirrhosis who can benefit mostly from this approach appears to be represented by patients with relatively stable conditions and at least moderate non complicated ascites despite a moderate dosage of diuretics. Patients who had recently resolved an acute complication of the disease yet still presenting with ascites are also amenable to treatment and those with refractory ascites, because by adding albumin some of these patients may become responsive to diuretics [63].

Thus, other RCTs on long-term albumin treatment are needed to clarify these issues. Recently, a double-blind, placebo-controlled RCT comparing the impact of weekly albumin infusion at the dose (1.5 g/kg) or saline over 5 weeks reported an improving in cognitive function and quality of life in individuals with prior hepatic encephalopathy [67]. Furthermore, the results of a large multicenter open-label RCT assessing the “effects of long-term administration of human albumin on subjects with decompensated cirrhosis and ascites” (PRECIOSA study; NCT03451292) are expected during 2024.

3. Albumin and critical illnesses

Albumin infusion has long been proposed for the treatment of sepsis, septic shock, and more generally for fluid replacement in critically ill patients admitted to the intensive care unit (ICU). Over the past decades, several trials and meta-analyses have investigated the benefit of albumin administration over other fluid replacements.

The SAFE trial, which was conducted about 20 years ago in critically ill patients admitted to ICU, showed that patients receiving 4% albumin solution or normal saline had similar outcomes at 28 days in terms of mortality, organ failure, and days spent in the ICU [68]. However, a post-hoc analysis of patients with severe sepsis showed that albumin therapy was associated with a reduced odds ratio of death [69]. More recently, the ALBIOS trial showed that patients with sepsis or septic shock treated with 20% albumin solution albumin titrated to achieve a serum concentration of 30 g/dL, in combination with crystalloids, versus crystalloids alone had a similar 90-day survival, but a post-hoc analysis in the subgroup of subjects with septic shock showed that albumin treatment was associated with lower 90-day mortality [70]. Finally, a RCT in septic cancer patients admitted to the ICU, who received a bolus of albumin in lactated Ringer’s solution versus lactated Ringer’s solution alone during the first 6 h of fluid resuscitation, showed no significant improvement in mortality at either 7 or 28 days [71].

Several meta-analyses have been performed on the use of albumin-containing solutions for the resuscitation of critically-ill patients providing controversial results over time [72–75]. The more recent studies have shown that albumin administration is safe, but a clear survival benefit compared to crystalloids has not been clearly

demonstrated [72–74].

Based on these results and taking also into account the high cost of albumin compared to crystalloids and the limitations for the use of starches due to their low safety profile, the 2021 International guideline of the Surviving Sepsis Campaign does not recommend albumin infusion as a first choice for fluid resuscitation in patients with sepsis or septic shock, but suggests, with a low level of evidence, the use of albumin in patients who have received a large volume of crystalloids [76]. Albumin may be preferred also in patients who may not tolerate high volumes of crystalloids, such as those with cirrhosis. In these patients, albumin solutions (5 or 20%) were more effective than crystalloids in reverting arterial hypotension during septic shock, although heterogenous results were reported about the impact on short-term survival [77,78].

3.1 Therapeutic plasma exchange (TPE). TPE represents a therapeutic option in those clinical conditions that require the removal of harmful substances from the bloodstream and/or the administration of substances present in donor plasma [79,80]. In this area, albumin and plasma are the main replacement fluids, preferred over crystalloids. Compared with plasma, the use of albumin has several advantages, including reduced allergic and immunological reactions, a reduced risk of transmitting infections, and compatibility with all blood groups [79]. On the other hand, TPE with albumin can lead to depletion of coagulation factors and immunoglobulins and a risk of acidosis (due to the acidity of the molecule) [79]. Recently, the American Society for Apheresis (ASFA) guidelines have classified some pathologies for which TPE is the first line of therapy, others for which it is the second line, or others whose role is not well defined [80]. The main pathologies for which TPE is recognized as a first-line treatment (alone or in combination with other types of treatment) are Guillain-Barre syndrome, myasthenia gravis, chronic inflammatory demyelinating polyradiculoneuropathy, N-methyl D-aspartate receptor (NMDAR) encephalitis, Goodpasture syndrome, ANCA-associated vasculitis, hyperviscosity syndrome (especially in Waldstrom’s macroglobulinemia), thyroid storm. Finally, in thrombotic thrombocytopenic purpura and acute liver failure, TPE with plasma substitute is preferred to albumin because of the need to administer other substances present in plasma such as ADAMST13 and coagulation factors [79,80].

4. Other uses of albumin not supported by solid scientific evidence

Nephrotic syndrome with edema: Although the benefit of the co-administration of albumin and diuretics, when albumin values are lower than 2.5 g/dl or in case of kidney injury, has been reported [81], recent meta-analyses indicate the need of high-quality RCTs before drawing any conclusion regarding the use of albumin in nephrotic syndrome [82,83].

Protein-losing enteropathy. Albumin is frequently used, particularly in patients with very low serum levels, although there is a lack of scientific evidence on this topic [84].

Severe burns: Infusion of crystalloids alone can induce over-resuscitation with an increased risk of mortality due the large amount needed and a colloid rescue with plasma or albumin is indicated [85]. A recent meta-analysis of burn resuscitation indicated that 5% albumin as early as 8 h after burn injury, in those who are projected to receive a massive resuscitation fluids, reduces the total amount of crystalloid in the first 24 h, decreases the intra-abdominal pressure, and reduces the development of abdominal compartment syndrome [86,87].

Cardiac surgery: Positive effects of the use of albumin as compared to crystalloids during cardiac surgery, including maintenance of haemodynamic, reduced risk of thrombocytopenia, reduction of volume overload, have been reported [88]. However, the recent ALBICS trial did not show a reduction in major events 90 days after cardiac surgery with the use of albumin rather than Ringer acetate [89].

Transplantation. Albumin supplementation is used in peri- and post-operative liver transplantation as fluid replacement or to control ascites

Table 3
More frequent inappropriate uses of albumin in medicine.

Correction of hypoalbuminemia per se
Malnutrition
Protein-losing nephropathies or enteropathies (exception may be represented by generalized edemas and very low serum albumin levels)
Brain traumatic injuries
Acute pancreatitis
Major surgery (exception may be represented by patients with advanced cirrhosis)
Edema in cancer patients Paracentesis of malignant ascites

and edema. Again, the studies available provide controversial results showing either improvement or no benefit in organ function [90–92]. Regarding renal transplantation, albumin does not appear to improve the outcome and early graft function compared to crystalloids, neither intraoperatively nor in the immediate postoperative period [93].

5. Inappropriate use of albumin

As reported by several studies worldwide [93–99], a great number of albumin prescriptions, from 50% up to 90%, are not supported by clinical evidence, guidelines and recommendations (Table 3). The use of albumin for nutritional reasons or correction of hypoalbuminemia *per se* are examples of inappropriateness in various settings (general surgery, internal medicine, geriatrics, oncology). In all these diseases, hypoalbuminemia acts as a biomarker of poor nutritional status and in general of negative prognosis rather than a primary pathophysiological event [100], so that albumin supplementation is not effective and therefore should be avoided.

Cancer patients sometimes receive albumin for edema in the last part of their life even if paradoxically this could worsen congestion due to the increased permeability of their capillary bed [101]. Similarly, it is not indicated albumin infusions post-paracentesis [102], as it is recommended in cirrhosis.

Finally, administration of albumin also in trauma is not indicated [68,103,104], particularly in the setting of patients with traumatic brain injury where a post-hoc analysis of the SAFE study showed an increase in mortality compared to saline [105].

6. Conclusions

There are only a limited number of areas in which the use of albumin has been proved to be effective and safe. Unfortunately, its prescription is very commonly inappropriate both in regular wards and intensive care units: in some circumstances, improper use of albumin is linked to contradictory scientific evidence or to absence of guidelines; in others, it is related to the subjective perception of physicians of the potential benefits to the patients despite the lack of supporting scientific evidence.

As the production of albumin from plasma donors is limited and likely insufficient to cover the total request of this hemoderivative from all over the world, action is needed to avoid the use for inappropriate and futile indications by promoting serious educational and regulatory policies to control the appropriateness of prescription, in order to ensure the availability of this strategic therapy for those conditions for which albumin has been demonstrated to have a real effectiveness and a benefit for the patient.

References

- [1] Peters T. All about albumin: biochemistry, genetics, and medical applications. Academic Press; 1996. <https://doi.org/10.1093/clinchem/43.10.2014a>.
- [2] Fanali G, Di Masi A, Trezza V, Marino M, Fasano M, Ascenzi P. Human serum albumin: from bench to bedside. *Mol Aspects Med* 2012;33:209–90. <https://doi.org/10.1016/j.mam.2011.12.002>.
- [3] Arroyo V, García-Martínez R, Salvatella X. Human serum albumin, systemic inflammation, and cirrhosis. *J Hepatol* 2014;61:396–407. <https://doi.org/10.1016/j.jhep.2014.04.012>.
- [4] Bernardi M, Angeli P, Claria J, Moreau R, Gines P, Jalan R, et al. Albumin in decompensated cirrhosis: new concepts and perspectives. *Gut* 2020;69:1127–38. <https://doi.org/10.1136/gutjnl-2019-318843>.
- [5] O'Brien AJ, Fullerton JN, a Massey K, Auld G, Sewell G, James S, et al. Immunosuppression in acutely decompensated cirrhosis is mediated by prostaglandin E2. *Nat Med* 2014;20:1–8. <https://doi.org/10.1038/nm.3516>.
- [6] Casulleras M, Flores-Costa R, Duran-Güell M, Alcaraz-Quiles J, Sanz S, Titos E, et al. Albumin internalizes and inhibits endosomal TLR signaling in leukocytes from patients with decompensated cirrhosis. *Sci Transl Med* 2020;12. <https://doi.org/10.1126/scitranslmed.aax5135>.
- [7] Campion EW, DeLabry LO, Glynn RJ. The effect of age on serum albumin in healthy males: report from the normative aging study. *J Gerontol* 1988;43. <https://doi.org/10.1093/geronj/43.1.M18>.
- [8] Garwe T, Albrecht RM, Stoner JA, Mitchell S, Motghare P. Hypoalbuminemia at admission is associated with increased incidence of in-hospital complications in geriatric trauma patients. *Am J Surg* 2016;212:109–15. <https://doi.org/10.1016/j.amjsurg.2015.06.013>.
- [9] Nair S, Herten H, Pitchumoni CS. Hypoalbuminemia is a poor predictor of survival after percutaneous endoscopic gastrostomy in elderly patients with dementia. *Am J Gastroenterol* 2000;95:133–6. [https://doi.org/10.1016/S0002-9270\(99\)00732-7](https://doi.org/10.1016/S0002-9270(99)00732-7).
- [10] Bohl DD, Shen MR, Hannon CP, Fillingham YA, Darrith B, Della Valle CJ. Serum albumin predicts survival and postoperative course following surgery for geriatric hip fracture. *JBJS* 2017;99:2110. <https://doi.org/10.2106/JBJS.16.01620>.
- [11] Sullivan DH, Roberson PK, Bopp MM. Hypoalbuminemia 3 months after hospital discharge: significance for long-term survival. *J Am Geriatr Soc* 2005;53:1222–6. <https://doi.org/10.1111/j.1532-5415.2005.53369.x>.
- [12] Reuben DB, Ix JH, Greendale GA, Seeman TE. The predictive value of combined hypoalbuminemia and hypocholesterolemia in high functioning community-dwelling older persons: macarthur studies of successful aging. *J Am Geriatr Soc* 1999;47:402–6. <https://doi.org/10.1111/j.1532-5415.1999.tb07230.x>.
- [13] Herrmann FR, Safran C, Levkoff SE, Minaker KL. Serum albumin level on admission as a predictor of death, length of stay, and readmission. *Arch Intern Med* 1992;152:125–30.
- [14] Namendys-Silva SA, González-Herrera MO, Texcocano-Becerra J, Herrera-Gómez A. Hypoalbuminemia in critically ill patients with cancer: incidence and mortality. *Am J Hosp Palliat Med* 2011;28:253–7. <https://doi.org/10.1177/1049909110384841>.
- [15] Komrokji RS, Corrales-Yepez M, Kharfan-Dabaja MA, Al Ali NH, Padron E, Rollison DE, et al. Hypoalbuminemia is an independent prognostic factor for overall survival in myelodysplastic syndromes. *Am J Hematol* 2012;87:1006–9. <https://doi.org/10.1002/ajh.23303>.
- [16] Child CG, Turcotte JG. Surgery and portal hypertension. *Major Probl Clin Surg* 1964;1:1–85.
- [17] Johnson PJ, Berhane S, Kagebayashi C, Satomura S, Teng M, Reeves HL, et al. Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach—the ALBI grade. *J Clin Oncol* 2015;33:550–8. <https://doi.org/10.1200/JCO.2014.57.9151>.
- [18] Lammers WJ, Hirschfield GM, Corpechot C, Nevens F, Lindor KD, Janssen HLA, et al. Development and validation of a scoring system to predict outcomes of patients with primary biliary cirrhosis receiving ursodeoxycholic acid therapy. *Gastroenterology* 2015;149:1804–12. <https://doi.org/10.1053/j.gastro.2015.07.061>. e4.
- [19] Arnau-Barrés I, Pascual-Dapena A, López-Montesinos I, Gómez-Zorrilla S, Sorlí L, Herrero M, et al. Severe hypoalbuminemia at admission is strongly associated with worse prognosis in older adults with SARS-CoV-2 infection. *J Clin Med* 2021;10:5134. <https://doi.org/10.3390/jcm10215134>.
- [20] Wilkinson P, Sherlock S. The effect of repeated albumin infusions in patients with cirrhosis. *Lancet* 1962;2:1125–9. <https://doi.org/10.1001/jama.1963.03700060177138>.
- [21] Caraceni P, O'Brien A, Gines P. Long-term albumin treatment in patients with cirrhosis and ascites. *J Hepatol* 2022;76:1306–17. <https://doi.org/10.1016/j.jhep.2022.03.005>.
- [22] Bajaj JS, O'Leary JG, Wong F, Kamath PS. Variations in albumin use in patients with cirrhosis: an AASLD members survey. *Hepatol Baltim Md* 2015;62:1923–4. <https://doi.org/10.1002/hep.27789>.
- [23] Garioud A, Cadranet JF, Pauwels A, Noursbaum JB, Thévenot T, Dao T, et al. Albumin use in patients with cirrhosis in france: results of the ALBU-LIVE survey: a case for better EASL guidelines diffusion and/or revision. *J Clin Gastroenterol* 2017;51:831–8. <https://doi.org/10.1097/MCG.0000000000000735>.
- [24] Caraceni P, Pavesi M, Baldassarre M, Bernardi M, Arroyo V. The use of human albumin in patients with cirrhosis: a European survey. *Expert Rev Gastroenterol Hepatol* 2018;12:625–32. <https://doi.org/10.1080/17474124.2018.1460203>.
- [25] Schrier RW, Arroyo V, Bernardi M, Epstein M, Henriksen JH, Rodés J. Peripheral arterial vasodilation hypothesis: a proposal for the initiation of renal sodium and water retention in cirrhosis. *Hepatology* 1988;8:1151–7. <https://doi.org/10.1002/hep.1840080532>.
- [26] Arroyo V, Angeli P, Moreau R, Jalan R, Clària J, Trebicka J, et al. The systemic inflammation hypothesis: towards a new paradigm of acute decompensation and multiorgan failure in cirrhosis. *J Hepatol* 2021;74:670–85. <https://doi.org/10.1016/j.jhep.2020.11.048>.
- [27] Bernardi M, Moreau R, Angeli P, Schnabl B, Arroyo V. Mechanisms of decompensation and organ failure in cirrhosis: from peripheral arterial vasodilation to systemic inflammation hypothesis. *J Hepatol* 2015;63:1272–84. <https://doi.org/10.1016/j.jhep.2015.07.004>.

- [28] Fernández J, Clària J, Amorós A, Aguilar F, Castro M, Casulleras M, et al. Effects of albumin treatment on systemic and portal hemodynamics and systemic inflammation in patients with decompensated cirrhosis. *Gastroenterology* 2019; 157:149–62. <https://doi.org/10.1053/j.gastro.2019.03.021>.
- [29] Domenicali M, Baldassarre M, Giannone FA, Naldi M, Mastroberro M, Biselli M, et al. Posttranscriptional changes of serum albumin: clinical and prognostic significance in hospitalized patients with cirrhosis. *Hepatology* 2014;60:1851–60. <https://doi.org/10.1002/hep.27322>.
- [30] Baldassarre M, Domenicali M, Naldi M, Laggetta M, Giannone FA, Biselli M, et al. Albumin homodimers in patients with cirrhosis: clinical and prognostic relevance of a novel identified structural alteration of the molecule. *Sci Rep* 2016;6:35987. <https://doi.org/10.1038/srep35987>.
- [31] Clària J, Stauber RE, Coenraad MJ, Moreau R, Jalan R, Pavesi M, et al. Systemic inflammation in decompensated cirrhosis: characterization and role in acute-on-chronic liver failure. *Hepatology* 2016;64:1249–64. <https://doi.org/10.1002/hep.28740>.
- [32] Jalan R, Schnurr K, Mookerjee RP, Sen S, Cheshire L, Hodges S, et al. Alterations in the functional capacity of albumin in patients with decompensated cirrhosis is associated with increased mortality. *Hepatology* 2009;50:555–64. <https://doi.org/10.1002/hep.22913>.
- [33] Baldassarre M, Naldi M, Zaccherini G, Bartoletti M, Antognoli A, Laggetta M, et al. Determination of effective albumin in patients with decompensated cirrhosis: clinical and prognostic implications. *Hepatology* 2021;74:2058–73. <https://doi.org/10.1002/hep.31798>.
- [34] Angeli P, Bernardi M, Villanueva C, Francoz C, Mookerjee RP, Trebicka J, et al. EASL clinical practice guidelines for the management of patients with decompensated cirrhosis. *J Hepatol* 2018;69:406–60. <https://doi.org/10.1016/j.jhep.2018.03.024>.
- [35] Biggins SW, Angeli P, Garcia-Tsao G, Ginès P, Ling SC, Nadim MK, et al. Diagnosis, evaluation, and management of ascites, spontaneous bacterial peritonitis and hepatorenal syndrome: 2021 practice guidance by the american association for the study of liver diseases. *Hepatology* 2021;74:1014. <https://doi.org/10.1002/hep.31884>.
- [36] Gines A, Fernandez-Esparrach G, Monescillo A, Vila C, Domenech E, Abecasis R, et al. Randomized trial comparing albumin, dextran 70, and polygeline in cirrhotic patients with ascites treated by paracentesis. *Gastroenterology* 1996; 111:1002–10. [https://doi.org/10.1016/S0016-5085\(96\)70068-9](https://doi.org/10.1016/S0016-5085(96)70068-9).
- [37] Ruiz-del-Arbol L, Monescillo A, Jimenez W, Garcia-Plaza A, Arroyo V, Rodes J. Paracentesis-induced circulatory dysfunction: mechanism and effect on hepatic hemodynamics in cirrhosis. *Gastroenterology* 1997;113:579–86. <https://doi.org/10.1053/gast.1997.v113.pm9247479>.
- [38] Arora V, Vijayaraghavan R, Maiwall R, Sahney A, Thomas SS, Ali R, et al. Paracentesis-induced circulatory dysfunction with modest-volume paracentesis is partly ameliorated by albumin infusion in acute-on-chronic liver failure. *Hepatology* 2020;72:1043. <https://doi.org/10.1002/hep.31071>.
- [39] Ginès P, Titió L, Arroyo V, Planas R, Panés J, Viver J, et al. Randomized comparative study of therapeutic paracentesis with and without intravenous albumin in cirrhosis. *Gastroenterology* 1988;94:1493–502. [https://doi.org/10.1016/0016-5085\(88\)90691-9](https://doi.org/10.1016/0016-5085(88)90691-9).
- [40] Bernardi M, Caraceni P, Navickis RJ, Wilkes MM. Albumin infusion in patients undergoing large-volume paracentesis: a meta-analysis of randomized trials. *Hepatology* 2012;55:1172–81. <https://doi.org/10.1002/hep.24786>.
- [41] Rimola A, García-Tsao G, Navasa M, Piddock LJV, Planas R, Bernard B, et al. Diagnosis, treatment and prophylaxis of spontaneous bacterial peritonitis: a consensus document. *J Hepatol* 2000;32:142–53. [https://doi.org/10.1016/S0168-8278\(00\)80201-9](https://doi.org/10.1016/S0168-8278(00)80201-9).
- [42] Sort P, Navasa M, Arroyo V, Aldeguer X, Planas R, Ruiz-del-Arbol L, et al. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. *N Engl J Med* 1999;341:403–9. <https://doi.org/10.1056/NEJM199908053410603>.
- [43] Kim JJ, Tsukamoto MM, Mathur AK, Ghomri YM, Hou LA, Sheibani S, et al. Delayed paracentesis is associated with increased in-hospital mortality in patients with spontaneous bacterial peritonitis. *Am J Gastroenterol* 2014;109:1436–42. <https://doi.org/10.1038/ajg.2014.212>.
- [44] Poca M, Concepción M, Casas M, Álvarez-Urturi C, Gordillo J, Hernández-Gea V, et al. Role of albumin treatment in patients with spontaneous bacterial peritonitis. *Clin Gastroenterol Hepatol* 2012;10:309–15. <https://doi.org/10.1016/j.cgh.2011.11.012>.
- [45] Angeli P, Ginès P, Wong F, Bernardi M, Boyer TD, Gerbes A, et al. Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the international club of ascites. *J Hepatol* 2015;62:968–74. <https://doi.org/10.1016/j.jhep.2014.12.029>.
- [46] Nadim MK, Garcia-Tsao G. Acute kidney injury in patients with cirrhosis. *N Engl J Med* 2023;388:733–45. <https://doi.org/10.1056/NEJMra2215289>.
- [47] Angeli P, Garcia-Tsao G, Nadim MK, Parikh CR. News in pathophysiology, definition and classification of hepatorenal syndrome: a step beyond the International Club of Ascites (ICA) consensus document. *J Hepatol* 2019;71: 811–22. <https://doi.org/10.1016/j.jhep.2019.07.002>.
- [48] Ginès P, Solà E, Angeli P, Wong F, Nadim MK, Kamath PS. Hepatorenal syndrome. *Nat Rev Dis Primer* 2018;4:1–17. <https://doi.org/10.1038/s41572-018-0022-7>.
- [49] Wong F, Pappas SC, Curry MP, Reddy KR, Rubin RA, Porayko MK, et al. Terlipressin plus albumin for the treatment of type 1 hepatorenal syndrome. *N Engl J Med* 2021;384:818–28. <https://doi.org/10.1056/NEJMoa2008290>.
- [50] Martín-Llahí M, Pépin MN, Guevara M, Díaz F, Torre A, Monescillo A, et al. Terlipressin and albumin vs albumin in patients with cirrhosis and hepatorenal syndrome: a randomized study. *Gastroenterology* 2008;134:1352–9. <https://doi.org/10.1053/j.gastro.2008.02.024>.
- [51] Sanyal AJ, Boyer T, Garcia-Tsao G, Regenstein F, Rossaro L, Appenrodt B, et al. A randomized, prospective, double-blind, placebo-controlled trial of terlipressin for type 1 hepatorenal syndrome. *Gastroenterology* 2008;134:1360–8. <https://doi.org/10.1053/j.gastro.2008.02.014>.
- [52] Alessandria C, Ottobrelli A, Debernardi-Venon W, Todros L, Cerenzia MT, Martini S, et al. Noradrenaline vs terlipressin in patients with hepatorenal syndrome: a prospective, randomized, unblinded, pilot study. *J Hepatol* 2007;47: 499–505. <https://doi.org/10.1016/j.jhep.2007.04.010>.
- [53] Singh V, Ghosh S, Singh B, Kumar P, Sharma N, Bhalla A, et al. Noradrenaline vs. terlipressin in the treatment of hepatorenal syndrome: a randomized study. *J Hepatol* 2012;56:1293–8. <https://doi.org/10.1016/j.jhep.2012.01.012>.
- [54] Arora V, Maiwall R, Rajan V, Jindal A, Muralikrishna Shashtry S, Kumar G, et al. Terlipressin is superior to noradrenaline in the management of acute kidney injury in acute on chronic liver failure. *Hepatol Baltim Md* 2020;71:600–10. <https://doi.org/10.1002/hep.30208>.
- [55] Allegretti AS, Subramanian RM, Francoz C, Olson JC, Cárdenas A. Respiratory events with terlipressin and albumin in hepatorenal syndrome: a review and clinical guidance. *Liver Int* 2022;42:2124–30. <https://doi.org/10.1111/liv.15367>.
- [56] Simón-Talero M, García-Martínez R, Torrens M, Augustin S, Gómez S, Pereira G, et al. Effects of intravenous albumin in patients with cirrhosis and episodic hepatic encephalopathy: a randomized double-blind study. *J Hepatol* 2013;59: 1184–92. <https://doi.org/10.1016/j.jhep.2013.07.020>.
- [57] Guevara M, Terra C, Nazar A, Solà E, Fernández J, Pavesi M, et al. Albumin for bacterial infections other than spontaneous bacterial peritonitis in cirrhosis. A randomized, controlled study. *J Hepatol* 2012;57:759–65. <https://doi.org/10.1016/j.jhep.2012.06.013>.
- [58] Fernández J, Angeli P, Trebicka J, Merli M, Gustot T, Alessandria C, et al. Efficacy of Albumin Treatment for Patients with Cirrhosis and Infections Unrelated to Spontaneous Bacterial Peritonitis. *Clin Gastroenterol Hepatol* 2020;18:963–73. <https://doi.org/10.1016/j.cgh.2019.07.055>.
- [59] Thévenot T, Bureau C, Oberti F, Anty R, Louvet A, Plessier A, et al. Effect of albumin in cirrhotic patients with infection other than spontaneous bacterial peritonitis. A randomized trial. *J Hepatol* 2015;62:822–30. <https://doi.org/10.1016/j.jhep.2014.11.017>.
- [60] China L, Freemantle N, Forrest E, Kallis Y, Ryder SD, Wright G, et al. A randomized trial of albumin infusions in hospitalized patients with cirrhosis. *N Engl J Med* 2021;384:808–17. <https://doi.org/10.1056/NEJMoa2022166>.
- [61] Caraceni P, Angeli P, Prati D, Bernardi M, Alessandria C, Riggio O, et al. AISF-SIMTI position paper: the appropriate use of albumin in patients with liver cirrhosis. *Dig Liver Dis* 2016;48:4–15. <https://doi.org/10.1016/j.dld.2015.11.008>.
- [62] Caraceni P, Riggio O, Angeli P, Alessandria C, Neri S, Foschi FG, et al. Long-term albumin administration in decompensated cirrhosis (ANSWER): an open-label randomised trial. *The Lancet* 2018;391:2417–29. [https://doi.org/10.1016/S0140-6736\(18\)30840-7](https://doi.org/10.1016/S0140-6736(18)30840-7).
- [63] Di Pascoli M, Fasolato S, Piano S, Bolognesi M, Angeli P. Long-term administration of human albumin improves survival in patients with cirrhosis and refractory ascites. *Liver Int* 2019;39:98–105. <https://doi.org/10.1111/liv.13968>.
- [64] Solà E, Solé C, Simón-Talero M, Martín-Llahí M, Castellote J, García-Martínez R, et al. Midodrine and albumin for prevention of complications in patients with cirrhosis awaiting liver transplantation. A randomized placebo-controlled trial. *J Hepatol* 2018;69:1250–9. <https://doi.org/10.1016/j.jhep.2018.08.006>.
- [65] Zaccherini G, Baldassarre M, Tufoni M, Nardelli S, Piano S, Alessandria C, et al. Correction and prevention of hyponatremia in patients with cirrhosis and ascites: post hoc analysis of the ANSWER study database. *Off J Am Coll Gastroenterol ACG* 2023;118:168. <https://doi.org/10.14309/ajg.0000000000001995>.
- [66] Caraceni P, Angeli P, Prati D, Bernardi M, Berti P, Bannardello F, et al. AISF-SIMTI position paper on the appropriate use of albumin in patients with liver cirrhosis: a 2020 update. *Blood Transfus* 2021. <https://doi.org/10.2450/2020.0414-20>.
- [67] Fagan A, Gavis EA, Gallagher ML, Mousel T, Davis B, Puri P, et al. A double-blind randomized placebo-controlled trial of albumin in outpatients with hepatic encephalopathy: HEAL study. *J Hepatol* 2023;78:312–21. <https://doi.org/10.1016/j.jhep.2022.09.009>.
- [68] The SAFE study investigators. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med* 2004;350:2247–56. <https://doi.org/10.1056/NEJMoa040232>.
- [69] SAFE Study Investigators, Finfer S, McEvoy S, Bellomo R, McArthur C, Myburgh J, et al. Impact of albumin compared to saline on organ function and mortality of patients with severe sepsis. *Intensive Care Med* 2011;37:86–96. <https://doi.org/10.1007/s00134-010-2039-6>.
- [70] Caironi P, Tognoni G, Masson S, Fumagalli R, Pesenti A, Romero M, et al. Albumin replacement in patients with severe sepsis or septic shock. *N Engl J Med* 2014;370:1412–21. <https://doi.org/10.1056/NEJMoa1305727>.
- [71] Park CHL, de Almeida JP, de Oliveira GQ, Rizk SI, Fukushima JT, Nakamura RE, et al. Lactated ringer's versus 4% albumin on lactated ringer's in early sepsis therapy in cancer patients: a pilot single-center randomized trial. *Crit Care Med* 2019;47:e798. <https://doi.org/10.1097/CCM.0000000000003900>.
- [72] Martin GS, Bassett P. Crystalloids vs. colloids for fluid resuscitation in the Intensive Care Unit: a systematic review and meta-analysis. *J Crit Care* 2019;50: 144–54. <https://doi.org/10.1016/j.jccr.2018.11.031>.
- [73] Lewis SR, Pritchard MW, Evans DJ, Butler AR, Alderson P, Smith AF, et al. Colloids versus crystalloids for fluid resuscitation in critically ill people. *Cochrane*

- Database Syst Rev 2018;8:CD000567. <https://doi.org/10.1002/14651858.CD000567.pub7>.
- [74] Haase N, Perner A, Hennings LI, Siegemund M, Lauridsen B, Wetterslev M, et al. Hydroxyethyl starch 130/0.38-0.45 versus crystalloid or albumin in patients with sepsis: systematic review with meta-analysis and trial sequential analysis. *BMJ* 2013;346:f839. <https://doi.org/10.1136/bmj.f839>.
- [75] Delaney AP, Dan A, McCaffrey J, Finfer S. The role of albumin as a resuscitation fluid for patients with sepsis: a systematic review and meta-analysis. *Crit Care Med* 2011;39. <https://doi.org/10.1097/CCM.0b013e3181ffe217>.
- [76] Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. *Crit Care Med* 2021;49:e1063–143. <https://doi.org/10.1097/CCM.0000000000005337>.
- [77] Phillips CA, Maiwall R, Sharma MK, Jindal A, Choudhury AK, Kumar G, et al. Comparison of 5% human albumin and normal saline for fluid resuscitation in sepsis induced hypotension among patients with cirrhosis (FRISC study): a randomized controlled trial. *Hepato Int* 2021;15:983–94. <https://doi.org/10.1007/s12072-021-10164-z>.
- [78] Maiwall R, Kumar A, Pasupuleti SSR, Hidam AK, Tevethia H, Kumar G, et al. A randomized-controlled trial comparing 20% albumin to plasmalyte in patients with cirrhosis and sepsis-induced hypotension [ALPS trial]. *J Hepato Int* 2022;77:670–82. <https://doi.org/10.1016/j.jhep.2022.03.043>.
- [79] Bauer PR, Ostermann M, Russell L, Robba C, David S, Ferreyro BL, et al. Plasma exchange in the intensive care unit: a narrative review. *Intensive Care Med* 2022;48:1382–96. <https://doi.org/10.1007/s00134-022-06793-z>.
- [80] Padmanabhan A, Connelly-Smith L, Aqini N, Balogun RA, Klingel R, Meyer E, et al. Guidelines on the use of therapeutic apheresis in clinical practice – evidence-based approach from the writing committee of the american society for apheresis: the eighth special issue. *J Clin Apheresis* 2019;34:171–354. <https://doi.org/10.1002/jca.21705>.
- [81] Lee TH, Kuo G, Chang CH, Huang YT, Yen CL, Lee CC, et al. Diuretic effect of co-administration of furosemide and albumin in comparison to furosemide therapy alone: an updated systematic review and meta-analysis. *PLoS One* 2021;16:e0260312. <https://doi.org/10.1371/journal.pone.0260312>.
- [82] Hedin E, Bijelić V, Barrowman N, Geier P. Furosemide and albumin for the treatment of nephrotic edema: a systematic review. *Pediatr Nephrol* 2022;37:1747–57. <https://doi.org/10.1007/s00467-021-05358-4>.
- [83] Ho JJ, Adnan AS, Kueh YC, Ambak NJ, Van Rostenberghe H, Jummaat F. Human albumin infusion for treating oedema in people with nephrotic syndrome. *Cochrane Database Syst Rev* 2019. <https://doi.org/10.1002/14651858.CD009692.pub2>.
- [84] Elli L, Topa M, Rimondi A. Protein-losing enteropathy. *Curr Opin Gastroenterol* 2020;36:238–44. <https://doi.org/10.1097/MOG.0000000000000629>.
- [85] Lawrence A, Faraklas I, Watkins H, Allen A, Cochran A, Morris S, et al. Colloid Administration Normalizes Resuscitation Ratio and Ameliorates “Fluid Creep.” *J Burn Care Res* 2010;31:40–7. <https://doi.org/10.1097/BCR.0b013e3181cb8c72>.
- [86] Ivy ME, Atweh NA, Palmer J, Possenti PP, Pineau M, D’Aiuto M. Intra-abdominal hypertension and abdominal compartment syndrome in burn patients. *J Trauma* 2000;49:387–91. <https://doi.org/10.1097/00005373-200009000-00001>.
- [87] Jeschke MG, van Baar ME, Choudhry MA, Chung KK, Gibran NS, Logsetty S. Burn injury. *Nat Rev Dis Primer* 2020;6:11. <https://doi.org/10.1038/s41572-020-0145-5>.
- [88] Verheij J, van Lingen A, Beishuizen A, Christiaans HMT, de Jong JR, Girbes ARJ, et al. Cardiac response is greater for colloid than saline fluid loading after cardiac or vascular surgery. *Intensive Care Med* 2006;32:1030–8. <https://doi.org/10.1007/s00134-006-0195-5>.
- [89] Pesonen E, Vlasov H, Suojaranta R, Hiippala S, Schramko A, Wilkman E, et al. Effect of 4% albumin solution vs ringer acetate on major adverse events in patients undergoing cardiac surgery with cardiopulmonary bypass: a randomized clinical trial. *JAMA* 2022;328:251. <https://doi.org/10.1001/jama.2022.10461>.
- [90] Johnson PN, Romanelli F, Smith KM, Ranjan D, Butler JS, Clifford TM. Analysis of morbidity in liver transplant recipients following human albumin supplementation: a retrospective pilot study. *Prog Transplant Aliso Viejo Calif* 2006;16:197–205. <https://doi.org/10.1177/152692480601600303>.
- [91] Mukhtar A, EL Masry A, Moniem AA, Metini M, Fayed A, Khater YH. The impact of maintaining normal serum albumin level following living related liver transplantation: does serum albumin level affect the course? A pilot study. *Transplant Proc* 2007;39:3214–8. <https://doi.org/10.1016/j.transproceed.2007.06.084>.
- [92] Ertmer C, Kampmeier TG, Volkert T, Wolters H, Rehberg S, Morelli A, et al. Impact of human albumin infusion on organ function in orthotopic liver transplantation - a retrospective matched-pair analysis. *Clin Transplant* 2015;29:67–75. <https://doi.org/10.1111/ctr.12486>.
- [93] Abdallah E, El-Shishtawy S, Mosbah O, Zeidan M. Comparison between the effects of intraoperative human albumin and normal saline on early graft function in renal transplantation. *Int Urol Nephrol* 2014;46:2221–6. <https://doi.org/10.1007/s11255-014-0785-z>.
- [94] Jahangard-Rafsanjani Z, Javadi MR, Torkamandi H, Alahyari S, Hajhossein Talasaz A, Gholami K. The evaluation of albumin utilization in a teaching university hospital in iran. *Iran J Pharm Res IJPR* 2011;10:385–90.
- [95] Casuccio A, Nalbome E, Immordino P, La Seta C, Sanfilippo P, Tuttolomondo A, et al. Appropriateness of requests for human serum albumin at the University Hospital of Palermo, Italy: a prospective study. *Int J Qual Health Care* 2015:mzv005. <https://doi.org/10.1093/intqhc/mzv005>.
- [96] Buckley MS, Knutson KD, Agarwal SK, Lansburg JM, Wicks LM, Saggart RC, et al. Clinical pharmacist-led impact on inappropriate albumin use and costs in the critically ill. *Ann Pharmacother* 2020;54:105–12. <https://doi.org/10.1177/1060028019877471>.
- [97] Buckley MS, Agarwal SK, Lansburg JM, Kopp BJ, Erstad BL. Clinical pharmacist-led impact on inappropriate albumin utilization and associated costs in general ward patients. *Ann Pharmacother* 2021;55:44–51. <https://doi.org/10.1177/1060028020935575>.
- [98] Liunbruno GM, Bennardello F, Lattanzio A, Piccoli PL, Rossetti G. Recommendations for the use of albumin and immunoglobulins. *Blood Transfus* 2009. <https://doi.org/10.2450/2009.0094-09>.
- [99] Coyle T, John SM. Evaluation of albumin use in a community hospital setting: a retrospective study looking at appropriate use and prescribing patterns. *PLoS One* 2021;16:e0257858. <https://doi.org/10.1371/journal.pone.0257858>.
- [100] Soeters PB, Wolfe RR, Hypoalbuminemia SA. Pathogenesis and clinical significance. *J Parenter Enter Nutr* 2019;43:181–93. <https://doi.org/10.1002/jpen.1451>.
- [101] Moujaess E, Fakhoury M, Assi T, Elias H, El Karak F, Ghosn M, et al. The Therapeutic use of human albumin in cancer patients’ management. *Crit Rev Oncol Hematol* 2017;120:203–9. <https://doi.org/10.1016/j.critrevonc.2017.11.008>.
- [102] Cavazzoni E, Bugiantella W, Graziosi L, Franceschini MS, Donini A. Malignant ascites: pathophysiology and treatment. *Int J Clin Oncol* 2013;18:1–9. <https://doi.org/10.1007/s10147-012-0396-6>.
- [103] SAFE Study Investigators, Finfer S, Bellomo R, McEvoy S, Lo SK, Myburgh J, et al. Effect of baseline serum albumin concentration on outcome of resuscitation with albumin or saline in patients in intensive care units: analysis of data from the saline versus albumin fluid evaluation (SAFE) study. *BMJ* 2006;333:1044. <https://doi.org/10.1136/bmj.38985.398704.7C>.
- [104] Vincent JL, Russell JA, Jacob M, Martin G, Guidet B, Wernerman J, et al. Albumin administration in the acutely ill: what is new and where next? *Crit Care Lond Engl* 2014;18:231. <https://doi.org/10.1186/cc13991>.
- [105] The SAFE Study Investigators. Saline or albumin for fluid resuscitation in patients with traumatic brain injury. *N Engl J Med* 2007;357:874–84. <https://doi.org/10.1056/NEJMoa067514>.