10TH ANNUAL

DIGESTIVE DISEASES: NEW ADVANCES

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Decompensated Cirrhosis: When Can We Use Albumin

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Disclosures

- Sammy Saab, MD, MPH
  - Speakers Bureau: AbbVie, Gilead, Exelixis, Eisai, Intercept, Takeda, Mallinckrodt, Salix

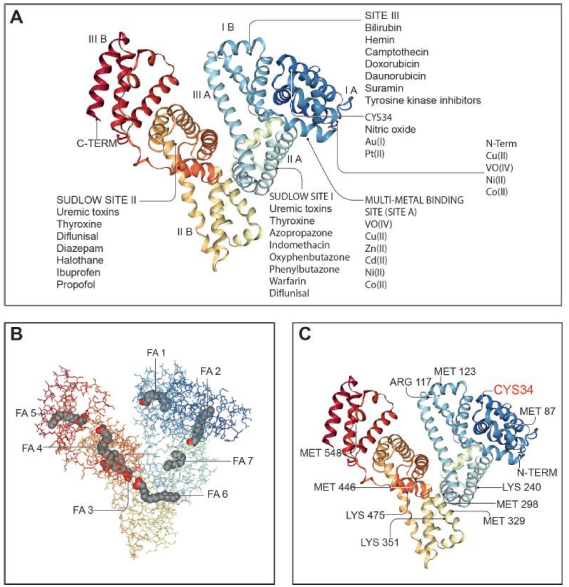
Learning Objectives

- Describe the important role of albumin in human liver physiology and how its function is altered in patients with advanced liver disease
- Understand the critical role of albumin replacement in improving outcomes in patients with decompensated cirrhosis
- Analyze limitations of albumin replacement therapy in patients with decompensated liver disease

Human Serum Albumin

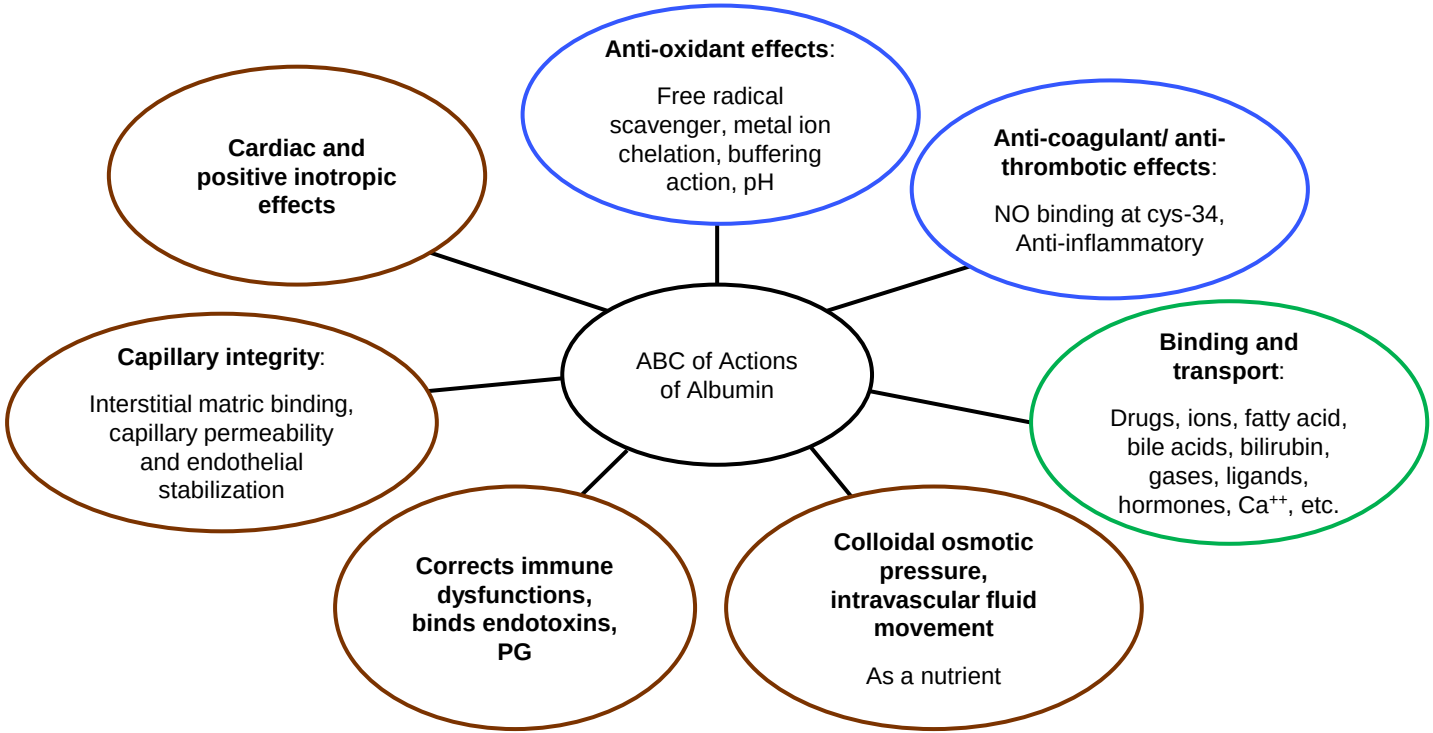
- Human serum albumin (HSA) is the most abundant plasma protein of the body
- HSA modulates plasma oncotic pressure and fluid distribution between body compartments
- Many of the physiological functions of HSA rely on its ability to reversibly bind to an extremely wide range of ligands

Endogenous and Exogenous Binding Sites in the Albumin Molecule



Bhattacharya AA et al. *J Mol Biol*. 2000; Bernardi M et al. *Gut*. 2020; Jagdish RK et al. *Hepatology.* 2021.

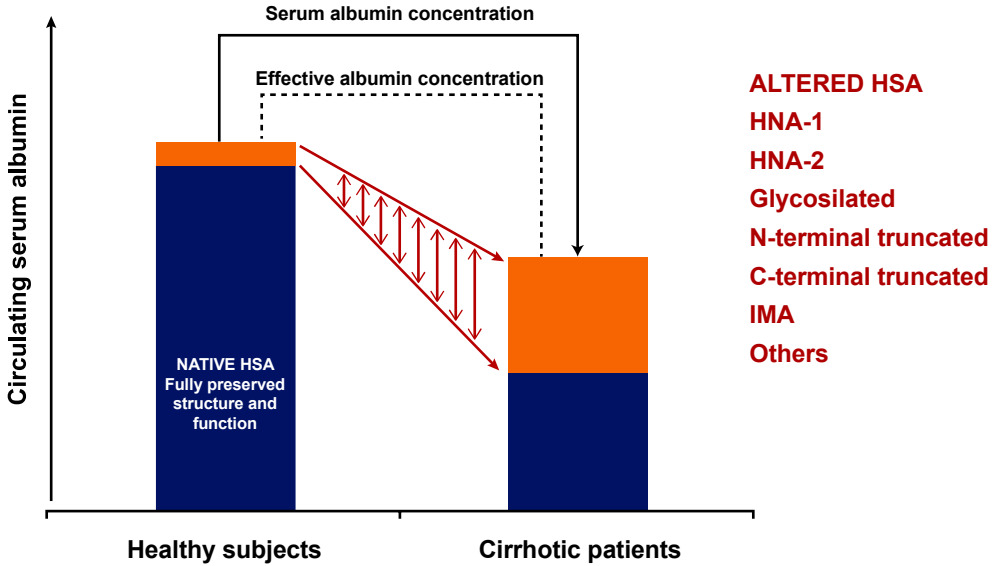
Albumin Has Multiple Important Roles in the Body



Bernardi M et al. *Gut*. 2020; Jagdish RK et al. *Hepatology.* 2021;
Campos Munoz A et al. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan. Available from: https://www.ncbi.nlm.nih.gov/books/NBK534241/?report=classic.

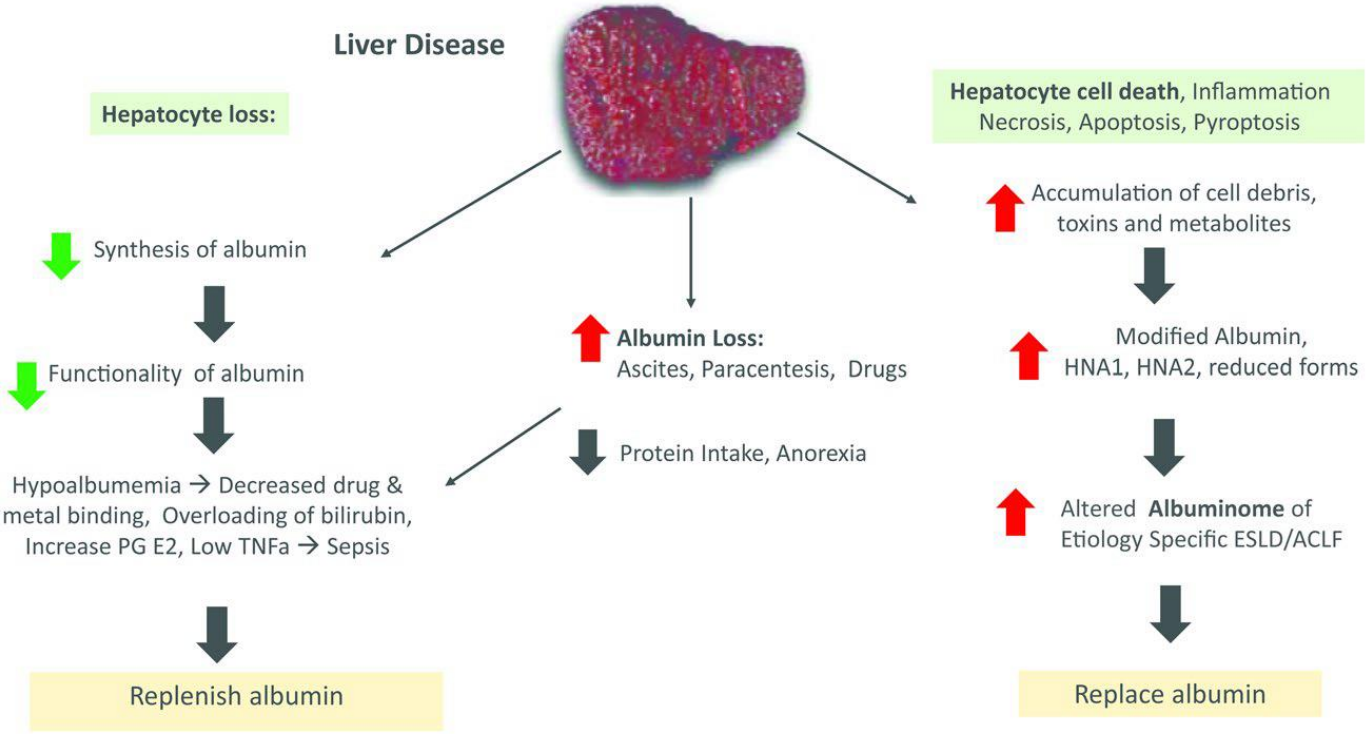
Albumin in Chronic Liver Disease: Quantitative and Functional Changes

- As chronic liver disease progresses, quantitative and functional changes occur in albumin



Zaccherini G et al. *Acta Gastroenterol Belg*. 2019.

Need for Albumin Replacement in Chronic Liver Disease



ESLD, end-stage liver disease; PGE2, prostaglandin E2.

Jagdish RK et al. *Hepatology.* 2021

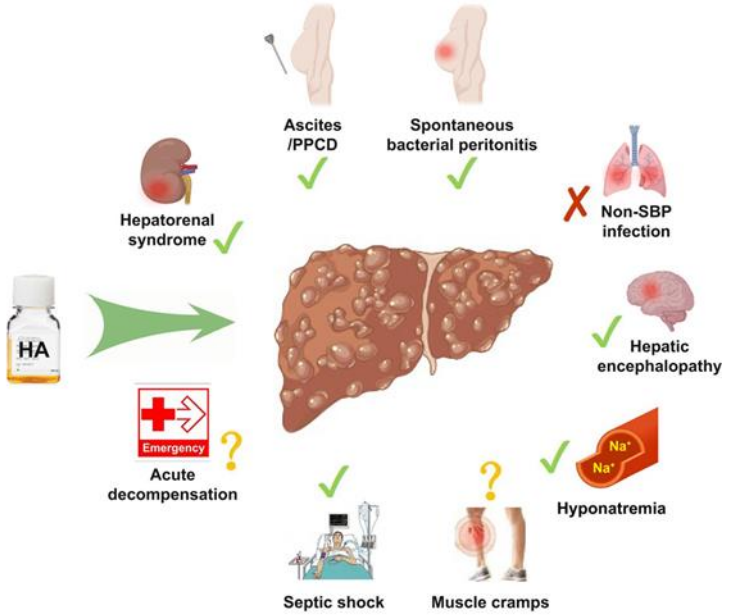
Current Uses of Albumin

- Albumin infusions are used over the short or long-term for:
  - Preventing different complications of decompensated cirrhosis
  - Treating different complications of decompensated cirrhosis
  - Improving quality of life

Jagdish RK et al. *Hepatology.* 2021.

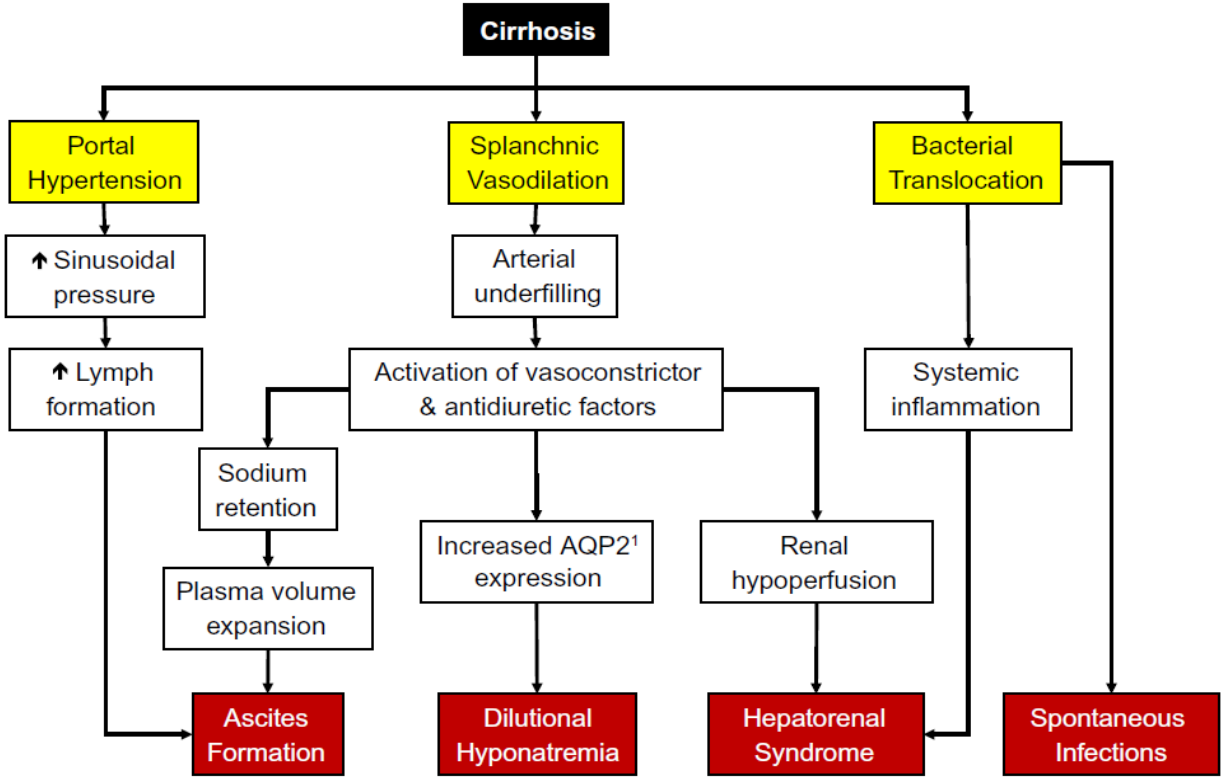
International Position Statement on the Use of Albumin Infusion for Cirrhosis-Related Complications

- Thirty-three investigators from 19 countries contributed to the position statement.
- Twelve position statements were proposed on the use of human albumin (HA) in liver cirrhosis.
- Short-term HA infusion should be recommended for managing hepatorenal syndrome, large volume paracentesis, and spontaneous bacterial peritonitis.
- Long-term HA infusion can be considered for managing ascites in specific settings.
- Pulmonary edema should be closely monitored in patients receiving HA infusion.



Bai Z, et al. *JHEP Reports* 2023

Complications of Cirrhosis



Biggins SW et al. *Hepatology*. 2021

Long Term Albumin Infusion

Placebo Controlled Studies Using Albumin as Disease-Modifying Agent in Cirrhosis

Study	Albumin Administration Regimen	Primary Endpoints	Secondary Endpoints
Romanelli et al.	Diuretics plus albumin at 25 g/week in first year and 25 g every 2 weeks thereafter versus diuretics alone	Survival in albumin-treated patients was greater (P = 0.0078) with lower probability of ascites recurrence (51% vs. 94%, P < 0.0001)	Albumin infusion improved survival by 16 months
Caraceni et al.	40 g twice a week for 2 weeks, then 40 g weekly for 18 months versus SMT for 18 months	Mortality reduced (P = 0.028) with albumin, with absolute risk deduction of 0.11	Albumin prevented recurrence of ascites, HRS, HE, infections, admissions
Sola et al.	40 g albumin every 15th day plus midodrine (15-30 mg/day) vs. placebo for 1 year	Incidence of complications, same in groups (P = 0.402)	No difference in 1-year mortality (P = 0.527)
Di Pascoli et al.	20 g of albumin twice per week in refractory ascites	Mortality reduced in albumin vs. SMT (41.6% vs. 65.5%, P = 0.032)	Albumin reduced emergency hospitalization, with longer hospital-free period

SMT ~ standard medical treatment; HRS ~ hepatorenal syndrome; HE ~ hepatic encephalopathy

Adapted from Jagdish et al. *Hepatol* 2021; Romanelli et al World J Gastroenterol 2006; Caraceni et al *Lancet* 2018; Sola et al *J Hepatol* 2018; Di Pascoli M et al. *Liver Int*. 2019.

Albumin Treatment in Cirrhosis and Refractory Ascites

- In 70 patients with cirrhosis and refractory ascites, the effect of long-term albumin administration on emergent hospitalization and mortality was assessed
- Study arms:
  - Non-random assignment to receive long-term administration of human albumin at the doses of 20 g twice per week (n = 45), in addition to standard medical of care
  - Standard of medical care (n=30)
- Long-term treatment with albumin was found to improve survival and reduce the probability of emergent hospitalizations

Di Pascoli M et al. *Liver Int*. 2019.

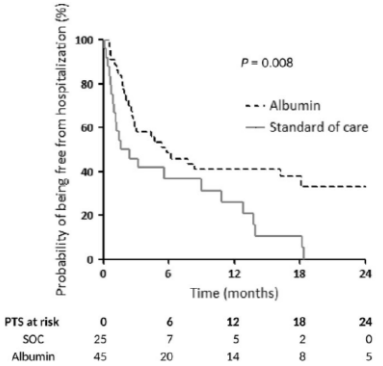
Albumin Treatment in Cirrhosis and Refractory Ascites: Emergent Hospitalizations Due to Complications

Probability of emergent hospitalization due to cirrhosis complications during the 24-month follow-up

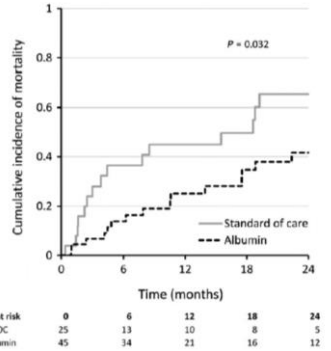
Complication	Albumin (%)	Standard of care (%)	*P*
HRS	22.5%	57.7%	0.084
HE	26.9%	64.5%	0.016
Ascites	37.1%	71.0%	0.002
SBP	7.9%	50.6%	0.004
Non-SBP infection	27.2%	88.6%	0.001
Variceal bleeding	2.4%	4.5%	0.603

HE, hepatic encephalopathy; HRS, hepatorenal syndrome; SBP, spontaneous bacterial peritonitis.
Di Pascoli M et al. *Liver Int*. 2019.

24-month probability of emergent hospitalization reduced



24-month mortality reduced



Albumin Infusions in Hospitalized Patients with Cirrhosis

Methods

- Randomized, multicenter, open label
- Hospitalized decompensated patients with albumin <3.0
- Goal albumin 3.0

Composite end point

- New infection
- Kidney dysfunction
- Death

Endpoints

Variable	Albumin Group (N=380)	Standard-Care Group (N=397)	Adjusted Odds Ratio (95% CI)	P Value
Composite primary end-point – no. (%)	113 (29.7)	120 (30.2)	0.98 (0.71-1.33)	0.87
Components of composite primary end point – no. (%)				
Incidence of new infection	79 (20.8)	71 (17.9)	1.22 (0.85-1.75)	
Incidence of kidney dysfunction	40 (10.5)	57 (14.4)	0.68 (0.44-1.11)	
Incidence of death	30 (7.9)	33 (8.3)	0.95 (0.56-1.59)	
Death at 28 days	53 (14.0)	62 (15.6)	0.86 (0.57-1.30)	
Death at 3 mo	92 (24.2)	93 (23.4)	1.05 (0.74-1.48)	
Death at 6 mo	132 (34.7)	119 (30.0)	1.27 (0.93-1.73)	
Total median albumin infused per patient (IQR)-g	200 (140-280)	20 (0-120)	143 (127-158)	

China L et al. *NEJM*. 2021.

Acute Kidney Injury

Albumin Treatment in HRS-AKI

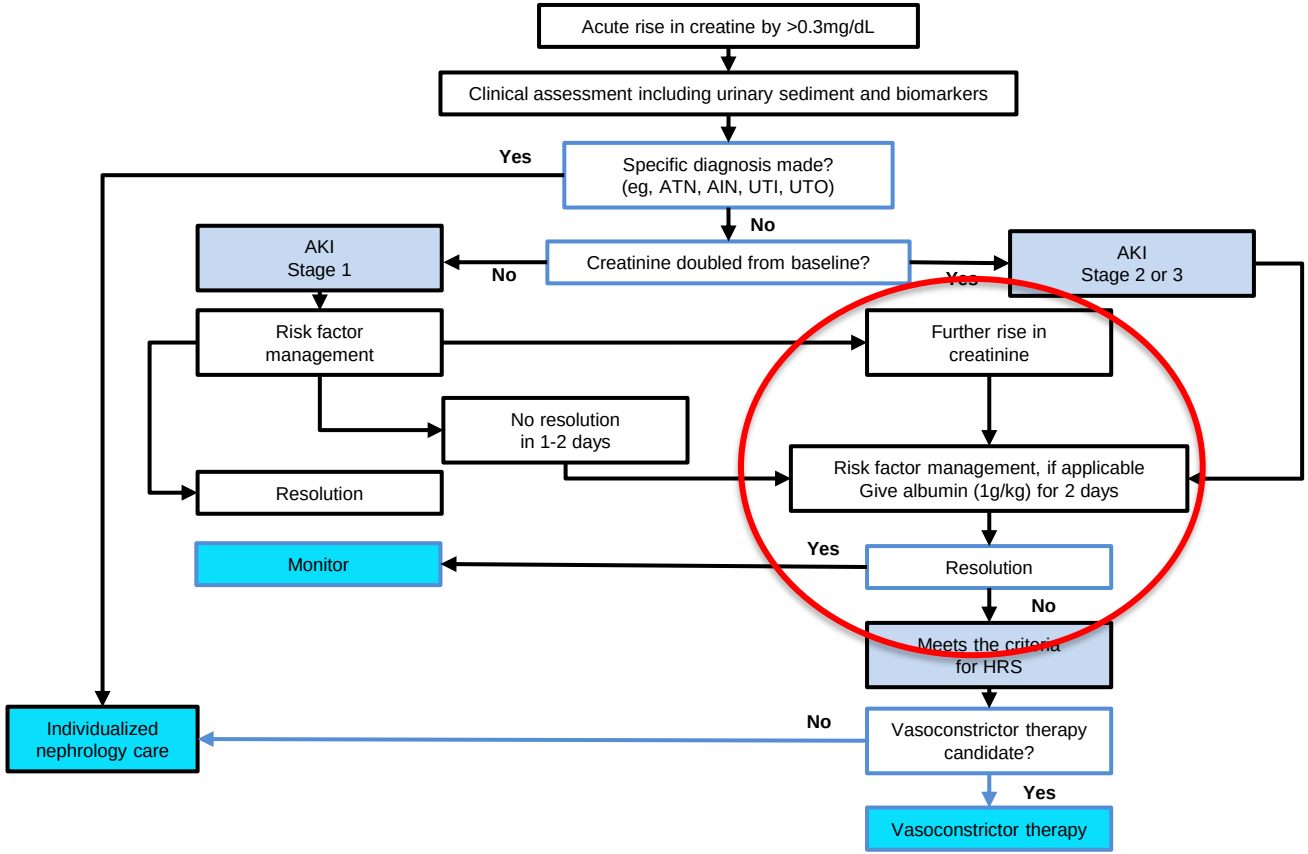
- The recommended treatment for HRS-AKI* consists of albumin and a vasoconstrictor
  - Data suggests that combinations of terlipressin and albumin, and noradrenaline and albumin, were more effective than albumin therapy alone to achieve a complete reversal of HRS
- However, the optimal albumin dose remains poorly characterized
- A meta-analysis was performed and 19 clinical studies (574 total patients) on albumin + vasoconstrictor treatment for HRS-AKI were identified and analyzed
- Data suggests a dose–response relationship between infused albumin and survival in patients with HRS-AKI
- Further studies are warranted

*Previously identified as Type 1 HRS

Biggins SW et al. *Hepatology*. 2021; Garcia-Tsao G et al. *Hepatology*. 2008; Salerno F et al. *BMC Gastroe*nterol. 2015.

AASLD Proposed Algorithm for Diagnosis and Management of AKI in Cirrhosis

AKI Stage	Description
1	Increase of creatinine ≥0.3 mg/dL up to 2-fold of baseline
2	Increase in creatinine between 2-fold and 3-fold of baseline
3	Increase in creatinine >3-fold of baseline or creatinine >4 mg/dL with an acute increase ≥0.3 mg/dL or initiation of RRT



Biggins SW et al. *Hepatology*. 2021.

Criteria to Diagnose HRS-AKI

Cirrhosis with ascites
Diagnosis of AKI according to International Club of Ascites-Acute Kidney Injury† criteria
No response after 2 consecutive days of diuretic withdrawal and plasma volume expansion with albumin infusion (1 g/kg body weight per day)
Absence of shock
No current or recent use of nephrotoxic drugs (NSAIDs, aminoglycosides, or iodinated contrast media)
No signs of structural kidney injury, as indicated by proteinuria (>500 mg per day), microhematuria (>50 red blood cells per high-power field), and/or abnormal renal ultrasonography

Biggins SW et al. *Hepatology*. 2021

†Increase in serum creatinine ≥0.3 mg/dL from baseline within 48 hours or a percent increase in serum creatinine of ≥50% which is known or presumed to have occurred within the preceding 7 days.

Ascites

Treatment of Grade 3 Ascites

First-Line Treatment	**LVP**	• **There is no limit for the amount of ascites that can be removed in a single session** • **However, the use of albumin is particularly important if more than 5 L of ascites are removed to prevent the development of PPCD**
	Albumin	• **Albumin infusion at the time of LVP of >5 L is recommended to mitigate the risk of PPCD; the risk of PPCD may increase with >8 L of fluid evacuated in one single session** • **Give 1 unit of 25% albumin for each liter of ascites removed**

Grade 1	**Mild ascites**	**Only detected by ultrasound**
Grade 2	**Moderate ascites**	**Moderate symmetric distension of the abdomen**
Grade 3	**Large or gross ascites**	**Marked distension of the abdomen**

Biggins SW et al. *Hepatology*. 2021.
PPCD, Post-paracentesis circulatory dysfunction

Albumin Infusion in Patients with SBP

- Renal failure develops in 30 to 40 percent of patients with SBP and is a major cause of death.
- Risk may be decreased with an infusion of intravenous 25 % albumin solution that is administered within six hours of diagnosis (1.5 g/kg body weight; maximum dose: 100 g) and on day 3 (1 g/kg body weight; maximum dose:100 g).

TABLE 2. CLINICAL OUTCOME ACCORDING TO THE ASSIGNED TREATMENT.*

OUTCOME VARIABLE	CEFOTAXIME (N=63)	CEFOTAXIME PLUS ALBUMIN (N=63)	P VALUE
Resolution of infection — no. (%)†	59 (94)	62 (98)	0.36
Duration of antibiotic therapy — days	6±1	5±1	0.48
Paracentesis for ascites after resolution of infection — no. (%)‡	16 (25)	14 (22)	0.83
Hospital stay — days	13±1	14±1	0.48
Renal impairment — no. (%)	21 (33)	6 (10)	0.002
Death — no. (%)			
In hospital§	18 (29)	6 (10)	0.01
At three months¶	26 (41)	14 (22)	0.03

Biggins SW et al. *Hepatology*. 2021. Sort P et al. N Engl J Med 1999

Albumin for Hyponatremia in Patients with Cirrhosis

Methods

- Hospitalized cirrhotic patients included in the NACSELD (North American Consortium for End-Stage Liver Disease) cohort with hyponatremia (Na <130mmol/L) were divided into those receiving intravenous albumin or not.

Results

- 1126 patients with hyponatremia
  - 777 received 225 (IQR 100,400) g of albumin
  - 349 did not receive albumin
- Use of intravenous albumin lead to hyponatremia resolution (69% vs 61%, p=0.008)

Bajaj JS, et al. *Am J Gastroenterol* 2018.

Use of Albumin in the Treatment of Hepatic Encephalopathy

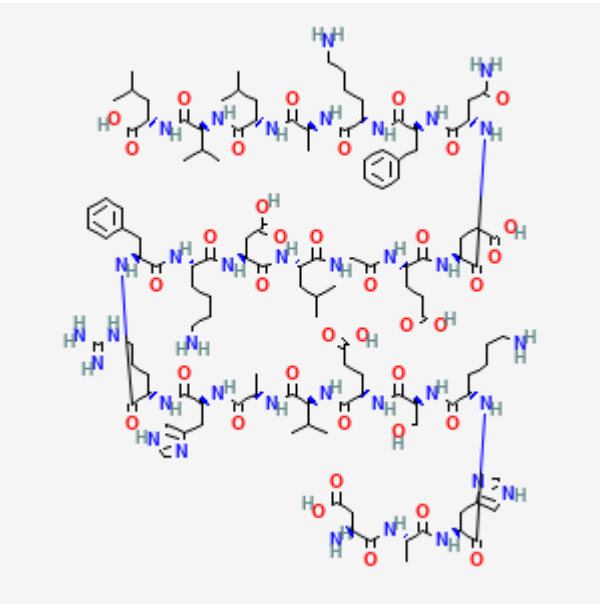
Study	Population	Albumin Administration Regimen	Primary Endpoints
Jalan R et al	Patients with diuretic-induced grade 2 or more HE	4.5% albumin vs colloid for volume expansion guided by CVP.	Improvement of HE Grade at 2 to 4 and was sustained at 72 hours ($P < 0.05$)
Simon-Talero M et al	Acute episode of grade 2 or more HE	Albumin (1.5g/kg) on day 1 and albumin (1g/kg) on day 3 vs isotonic saline.	No change in HE at day 4 (57.7% vs 53.3%; p >0.05) but improvement in survival at 90 (60% vs 40%; P = 0.02)
Ventura-Cots M et al	Acute episode of grade 2 or more HE	Albumin (1.5g/kg) on day 1 and albumin (1g/kg) on day 3 vs placebo	Decreased 90 day mortality in competing risk analysis (11% vs 30%, P = 0.02)
Riggio et al	Patients s/p TIPS without HE	Albumin (1/g/kg) for 2 days after TIPS, the albumin (0.5g.kg) at day 4th and 7th, then weekly for 3 weeks vs historical control	No difference in overt HE during first month (34% vs 31%) or during follow-up (39% vs 48%)

HE ~ hepatic encephalopathy; CVP ~ central venous pressure.; TIPS ~ Transjugular intrahepatic portosystemic shunt

Jalan R et al. *Clin Science* 2004; Simon-Talero M et al. *J Hepatol* 2013; Ventura-Cots M et al. *J Clin Med* 2021; Riggio et al *Metab Brain Dis* 2016.

Albumin as Pharmacological Therapy

- There are two formulations available that differ on the albumin concentration; albumin 5% and 25%; in general terms:
  - Hyperoncotic (Albumin 25%) is the therapeutic choice when either sodium or fluid is restricted or in cases of oncotic deficiencies
  - Isooncotic (Albumin 5%) use is more common in situations of volume loss as dehydration
- Concentration, the rate of infusion, and dosage depend on the patient's clinical situation



Campos Munoz A et al. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan. Available from: https://www.ncbi.nlm.nih.gov/books/NBK534241/?report=classic.

Frequently Asked Questions Surrounding HSA Administration

Frequently Asked Question	Recommendation
What are the target serum albumin levels during HSA treatment?	• Correcting albumin based on fluid status is more important than achieving goal albumin levels. HSA use should be guided by functional (volume status, treatment response) rather than quantitative endpoints
What are the most common AEs?	• Because it is difficult to identify the optimum HSA dose, the most common risks of HSA administration are pulmonary edema and fluid overload • Pulmonary edema is precipitated by HSA-induced increases in plasma volume, especially when infused rapidly.
How are AEs managed?	• The HSA dose and rate of infusion should be adjusted according to the patient's volume status, which requires evaluation after each HSA dose • Evaluation should include signs of cardiopulmonary dysfunction and fluid status after each dose of HSA: Blood pressure, pulse, oxygenation, escalating oxygen requirements, respiratory rate, development of peripheral edema, and renal function • Upon the first clinical sign(s) of cardiovascular overload (headache, dyspnea, jugular venous distention, and increased blood pressure), the infusion must be slowed or stopped immediately, and furosemide can be considered for volume management • Clinicians should also be mindful of the sodium content in HSA preparations, which is included for isotonicity. As a result, hypernatremia occurs in patients administered HSA over several days and this may contribute to associated pulmonary edema.
Which patients are at increased risk of AEs?	• The use of HSA must be done with caution in conditions where hypervolemia and its consequences could represent a special risk to the patient, such as pulmonary hypertension with right heart failure, congestive heart failure, pulmonary edema, renal, and postrenal anuria. • In patients with HRS-AKI, the additive effects provided by vasoconstrictors and HSA infusion provide benefits but this may further complicate the AE profile. These patients should be closely monitored for the possible development of side effects of vasoconstrictors and HSA, including ischemic complications and pulmonary edema. • Assessing intravascular volume status by measuring the inferior vena cava diameter and percent collapsibility with inspiration using conventional ultrasound machines or at bedside using point-of-care ultrasound could be a useful tool in guiding HSA infusion.

Kugelmas M et al. Expert. *Am J Health Syst Pharm*. 2023; Pyrsopoulos NT, et al. In preparation 2023

Albumin Adds to Accuracy of MELD Score Predicting Liver-Related Mortality

- MELD=9.57×loge(creatinine)+3.78×loge(bilirubin)+11.20×loge(INR)+6.43

- MELDNa=MELD+[1.32×(137−Na)]−[0.033×MELD×(137−Na)

- MELD 3.0 = 1.33 (if female) + [4.56 × $\log_e$ (bilirubin)] + [0.82 × (137 – Na)] – [0.24 × (137 – Na) × $\log_e$(bilirubin)] + [9.09 × $\log_e$(INR)] + [11.14 × $\log_e$(creatinine)] + [1.85 × (3.5 – albumin)] – [1.83 × (3.5 – albumin) × $\log_e$(creatinine)] + 6

Conclusions

- Serum albumin in decompensated cirrhosis undergoes structural and functional abnormalities
- Albumin has an important role in the management of patients with decompensated liver disease who develop Acute Kidney Injury, Spontaneous Bacteria Peritonitis, and Refractory Ascites.
- Further investigations are needed to
  - Confirm the beneficial effects of long-term albumin,
  - Clarify dosing and administration schedule and
  - Identify patients who would benefit most