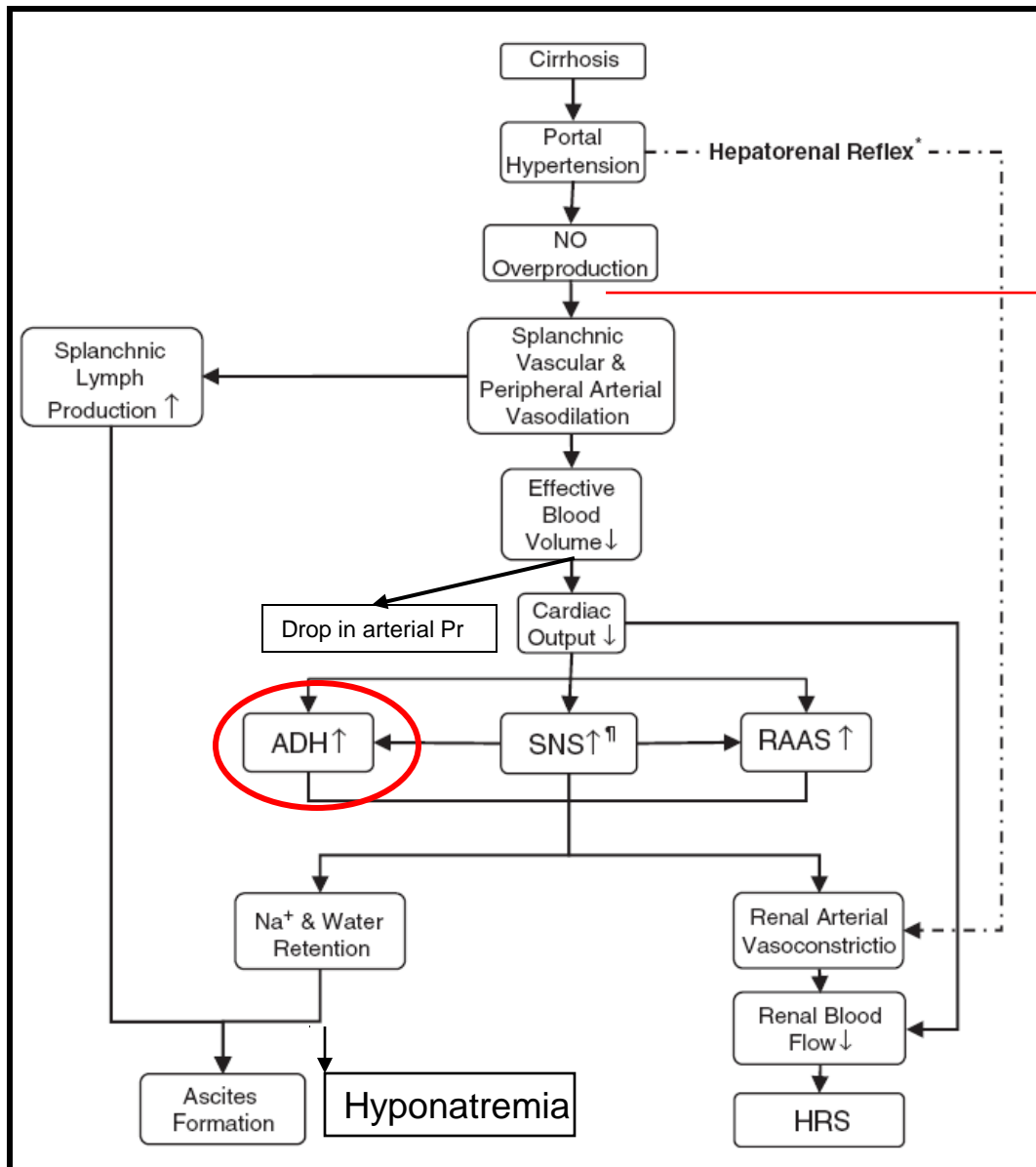


Fluid & hyponatremia management in cirrhotic patients

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Pathophysiology



As the disease progress

Hyponatremia: definition & prevalence

- Hyponatremia in cirrhosis is currently defined as a reduction in serum sodium below 130 mmol/L.
- The prevalence of hyponatremia of < 130 mmol/L, is 21.6% (1)
- If the cutoff level of 135 mmol/L is used (a significant proportion of patients with cirrhosis have a serum sodium concentration >130 mmol/L but < 135 mmol/L), the prevalence increases up to **49.4%** (2)

1- Ginés P, et al. *HEPATOLOGY* 1998; 28: 851-864.

2- Angeli P, et al. *HEPATOLOGY* 2006; 44: 1535-1542.

Hyponatremia: definition & prevalence

- Those patients with Na levels between 130 – 135 mmol/l are not considered to have hyponatremia with the current definition but they show pathogenic and clinical features similar to those of patients with serum sodium < 130 mmol/L.

Angeli P, et al. *HEPATOLOGY* 2006; 44: 1535-1542.

Types of hyponatremia in cirrhosis

	<i>Hypovolemic hyponatremia</i>	<i>Hypervolemic hyponatremia Or dilutional hyponatremia</i>
%	Less common in cirrhotic patients	More common in advanced cirrhotic patients
Causes	<u>losses of ECF</u> , from the kidneys (because of overdiuresis due to treatment with excessive doses of diuretics) or from the gastrointestinal tract.	marked impairment of <u>renal solute-free water excretion</u> , resulting in disproportionate renal retention of water with respect to sodium retention.
Features	Contraction of plasma volume, low ECF volume, <i>lack of edema and ascites</i> , signs of dehydration, and prerenal renal failure	Expanded ECF volume and plasma volume with <i>ascites and edema</i> (BUT effective arterial hypovolemia)

Why avoiding hyponatremia is important in cirrhotic patients?

- Hyponatremia has been associated with increase risk for hepatic encephalopathy
- Hyponatremia is a frequent finding in patients with cirrhosis and bacterial infections.
- Hyponatremia, in the majority of patients, occurs in close association with renal failure and correlates with a poor prognosis.
- Low serum sodium levels are a very common finding in patients with hepatorenal syndrome.

Follo A, et al. *HEPATOLOGY* 1994; 20: 1495-1501.

Ginès A, et al. *Gastroenterology* 1993; 105: 229-236

Why avoiding hyponatremia is important in cirrhotic patients?

- Severe hyponatraemia, in patients awaiting liver transplantation, may increase the risk of central pontine myelinolysis during fluid resuscitation in surgery.

Abbasoglu O, et al. *Clin Transplant* 1998; 12: 263-269

- In adults patients with cirrhosis, hyponatremia impairs quality of life because patients require a restriction of daily fluid & Na intake → poorly tolerated.

Proposed mechanism of hyponatremia in hepatic encephalopathy

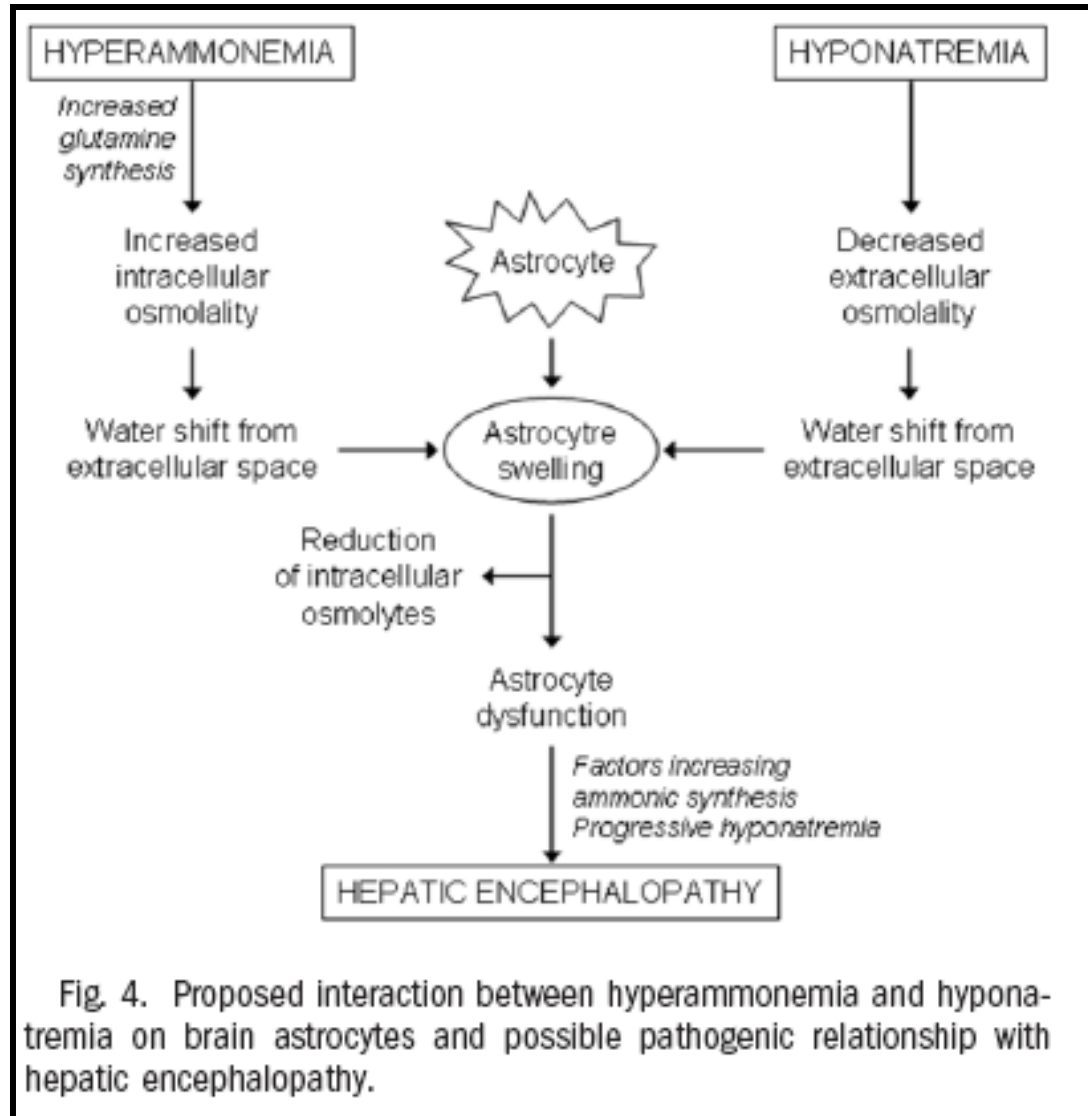
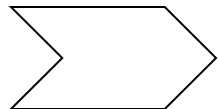


Fig. 4. Proposed interaction between hyperammonemia and hyponatremia on brain astrocytes and possible pathogenic relationship with hepatic encephalopathy.

Management of hypovolemic hyponatremia

- The distinction between hypovolemic and hypervolemic hyponatremia is very important from a therapeutic perspective.
- Patients with ***hypovolemic hyponatremia*** must be treated with saline solutions aimed at increasing plasma volume and normalizing the low total body sodium along with the removal of the precipitating factor (usually diuretics).



Management of hypervolemic hyponatremia (with ascites)

- Hypervolemic hyponatremia should be managed with interventions aimed at increasing renal solute-free water excretion with the final goal of reducing the excess of water with respect to sodium in the circulation.
- Since hyponatremia is almost always associated with edema & ascites, part of the presentation will include management of ascites

Dietary salt restriction

- Salt restriction has a role more in managing patients with **ascites & normal Na**
- Restriction of sodium in diet is limited to 1 to 2mEq/kg/day for infants and children, and 1 to 2 g/day (44 to 88 mEq of sodium/day) in adolescents.
- Only 10 to 20% of patients with ascites will respond to sodium restriction alone (those with a relatively normal serum sodium and a urinary sodium of > 15 mEq/24 h)
- Dietary intervention should be offered in consultation with an experienced pediatric dietitian because it may affect the total calories intake.

Dietary salt restriction

- Certain drugs, especially those in the effervescent tablet form, have high sodium contents. IV antibiotics generally contain 2.1–3.6 mmol of sodium per gram

(Moore & Aithal. *Gut* 2006;**55**(Supplement 6):vi1-vi12)

Fluid restriction

- There is real controversy in adult studies about using fluid restriction as a method to treat those patients → efficacy is limited.
- ? Children
- Most experts agree that there is **NO role for water restriction** in patients with **uncomplicated ascites** (not infected & not associated with HRS)
- Significant water restriction may result in further increases in circulating ADH, impaired free water clearance which may lead to hyponatraemia and a further decline of renal function

Moore & Aithal. *Gut* 2006;55(Supplement 6):vi1-vi12

Gines & Guevara. *Hepatology* 2008; 48:1002-1010

When fluid restriction is recommended?

- **Water restriction should be reserved for those who are:**
 - Clinically *euvolaemic* with
 - *Severe hyponatraemia (< 120 mmmol/L)* &
 - Not currently taking diuretics &
 - *Serum creatinine is normal.*

(Moore & Aithal. *Gut* 2006;55(Supplement 6):vi1-vi12)

Diuretics

- The goal of diuresis is a negative fluid balance of 10 cc/kg/day or 500-750 cc/day in aduloscents/adults.
- When peripheral edema is present, high dose of diuretics is safe as peripheral edema buffers any intravascular volume reduction.
(not common in young children)
- Because of the priority of maintaining growth in pediatric patients, diuretics may be the initial therapy for treatment of cirrhotic patients with ascites (in compare to salt/fluid restriction).

Diuretics

- Some studies recommend starting with spironolactone –DOCx- (aldosterone antagonist) till reach its max dose & then to add furosemide (loop diuretic) if the effect is not adequate, but other studies suggest to start with the combination therapy.
- If ***weight loss and diuresis*** are inadequate, the doses of both spironolactone and furosemide should be increased simultaneously, maintaining the ratio of 5:2

• *Electrolytes, Urea, Creatinine should be measured frequently at first then regularly as long as the patient on diuretics.*

Over diuresis is associated with intravascular depletion → renal impairment, hepatic encephalopathy & hyponatremia



Guidelines on the management of ascites in cirrhosis

K P Moore and G P Aithal

Gut 2006;55;vi1-vi12

- **Serum Na: 126–135 mmol/l & normal serum creatinine →**
Continue diuretic therapy but observe serum electrolytes. Water restriction is not required
- **Serum Na: 121–125 mmol/l, normal serum creatinine → ??**
International opinion is to continue diuretic therapy, The authors opinion is to stop diuretic therapy or adopt a more cautious approach.
- **Serum Na: 121–125 mmol/l, serum creatinine elevated (>150 $\mu\text{mol/l}$ or >120 $\mu\text{mol/l}$ and rising) →** Stop diuretics and give volume expansion (NS or Colloids: 5 %, 25 % albumin)

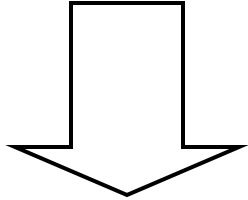


Guidelines on the management of ascites in cirrhosis

K P Moore and G P Aithal

Gut 2006;55;vi1-vi12

- Serum sodium **120 mmol/l** → stop diuretics & volume expansion with colloids or saline (controversy).
- Important to avoid increasing serum sodium by >10 mmol/l per 24 hours.



Giving NS or albumin in patients with significant hyponatremia may worsen the ascites but it is better to have ascites with normal renal functions than to develop potentially irreversible renal failure.

When high Na content fluid is indicated?

- In general it is preferable to avoid infusion of fluids which contain salt in patients with ascites because it is associated with increasing ascites & edema
- But it may be appropriate and indicated to give volume expansion with a crystalloid or colloid if:
 - Renal impairment with severe hyponatraemia
 - Development of hepatorenal syndrome

Vaptans

- Aquaretics (Vaptans) are vasopressin receptor antagonists that act on the distal tubule of the kidney
- At least 3 RCTs showed that vaptans increase solute-free water excretion and improve serum sodium concentration in patients with hypervolemic hyponatremia.

Table 3. Summary of the Studies Assessing the Effects of Vaptans on Serum Sodium Concentration in Patients with Cirrhosis, Ascites, and Hyponatremia

Authors	Compound	Dosage (Number of Patients)	Duration of Treatment	Baseline Serum Sodium	End-of-Treatment Serum Sodium	Responders (% of Patients)*
Wong et al. ³⁸	Lixivaptan	Placebo (8)	7 days	127 ± 1	126 ± 1	NR
		25 mg bid (8)		126 ± 1	129 ± 2	NR
		125 mg bid (10)		122 ± 2	127 ± 3	NR
		250 mg bid (7)		125 ± 1	132 ± 1	NR
Gerbes et al. ³²	Lixivaptan	Placebo (20)	7 days	127 ± 3	128 ± 4	5%
		100 mg (22)		128 ± 4	130 ± 7	45%
		200 mg (18)		126 ± 4	132 ± 7	67%
Ginès et al. ³³	Satavaptan	Placebo (28)	14 days	126 ± 4	128 ± 7	26%
		5 mg (28)		127 ± 5	131 ± 6	50%
		12.5 mg (26)		128 ± 4	133 ± 5	54%
		25 mg (28)		126 ± 6	134 ± 6	82%

Vaptans

Vaptans-Side effects

- Thirst is the frequent reported side effect (up to 29%)
- Potential theoretical concerns of the administration of vaptans in patients with cirrhosis include the following:
 - (1) hypernatremia due to a markedly negative fluid balance,
 - (2) a rapid increase in serum sodium concentration, and
 - (3) renal failure due to depletion of the intravascular volume.
- There is only one study that report a long term sustained effect of vaptan (at 1 year), with no significant side effects. (only in abstract)

Ginès P. Wong F, Watson H. Abstracts of the 42nd Annual Meeting of the European Association for the Study of the Liver (2007). *J Hepatol* 2007; 46

- Whether treatment using vaptans improves overall morbidity and mortality is not yet known.

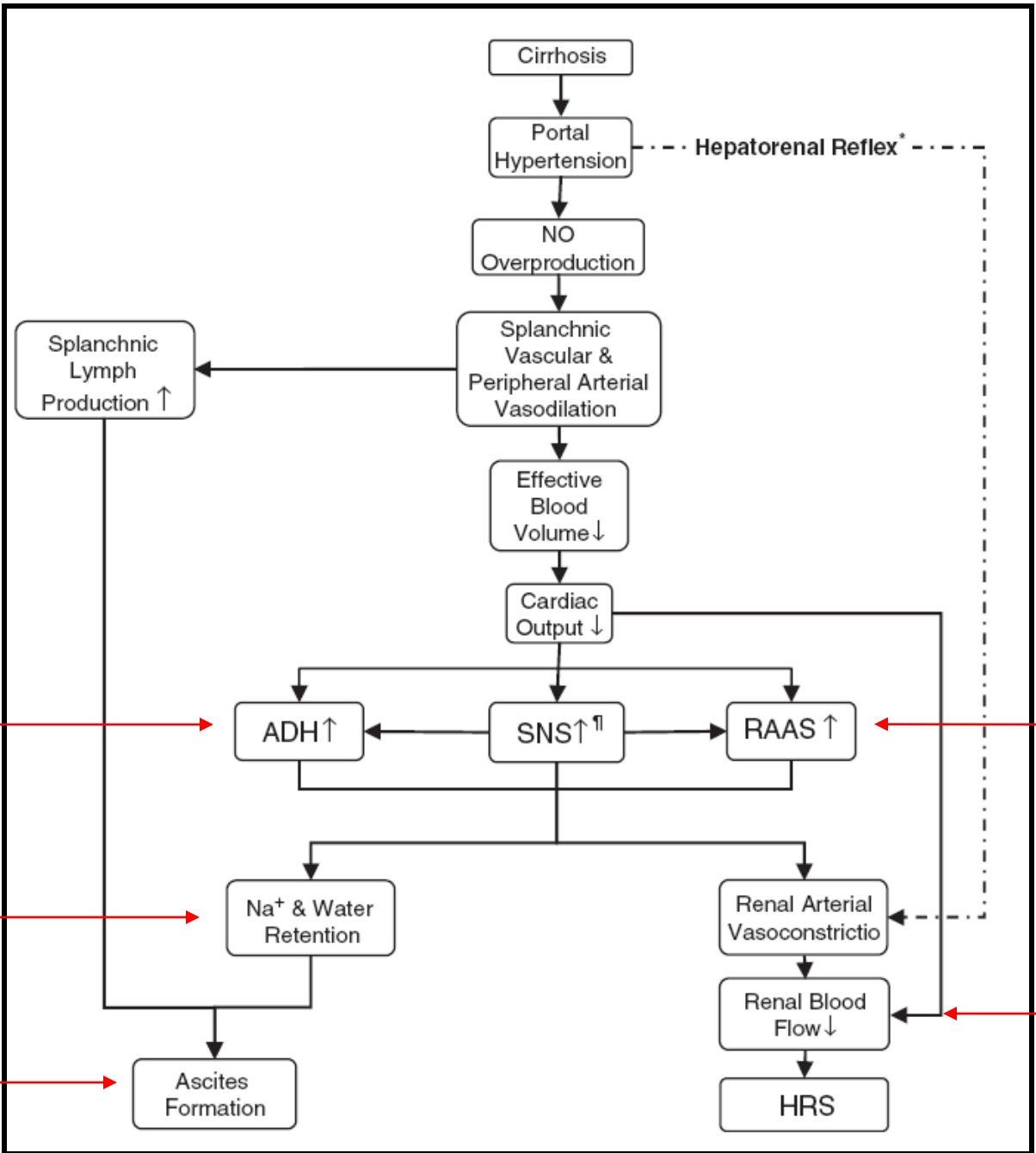
(Moore & Aithal. *Gut* 2006;55(Supplement 6):vi1-vi12)



Ascites classification

Table 1 Classification of ascites

Severity ⁴	
Grade 1 (mild)	Not clinically evident, diagnosed on ultrasound
Grade 2 (moderate)	Proportionate sensible abdominal distension
Grade 3 (severe)	Noticeable tense distension of abdomen
Uncomplicated ⁵	Not infected or associated with HRS
Refractory ⁶	Cannot be mobilized, early recurrence after LVP, not prevented satisfactorily with medical treatment (after 1 week)
Diuretic-resistant	No response to intensive diuretic treatment
Diuretic-intractable	Drug-induced adverse effects preclude diuretic treatment



Vaptants

Salt restriction & Water restriction

Paracentesis

Spirolactone: Aldosterone antagonist

Volume support with NS or albumin

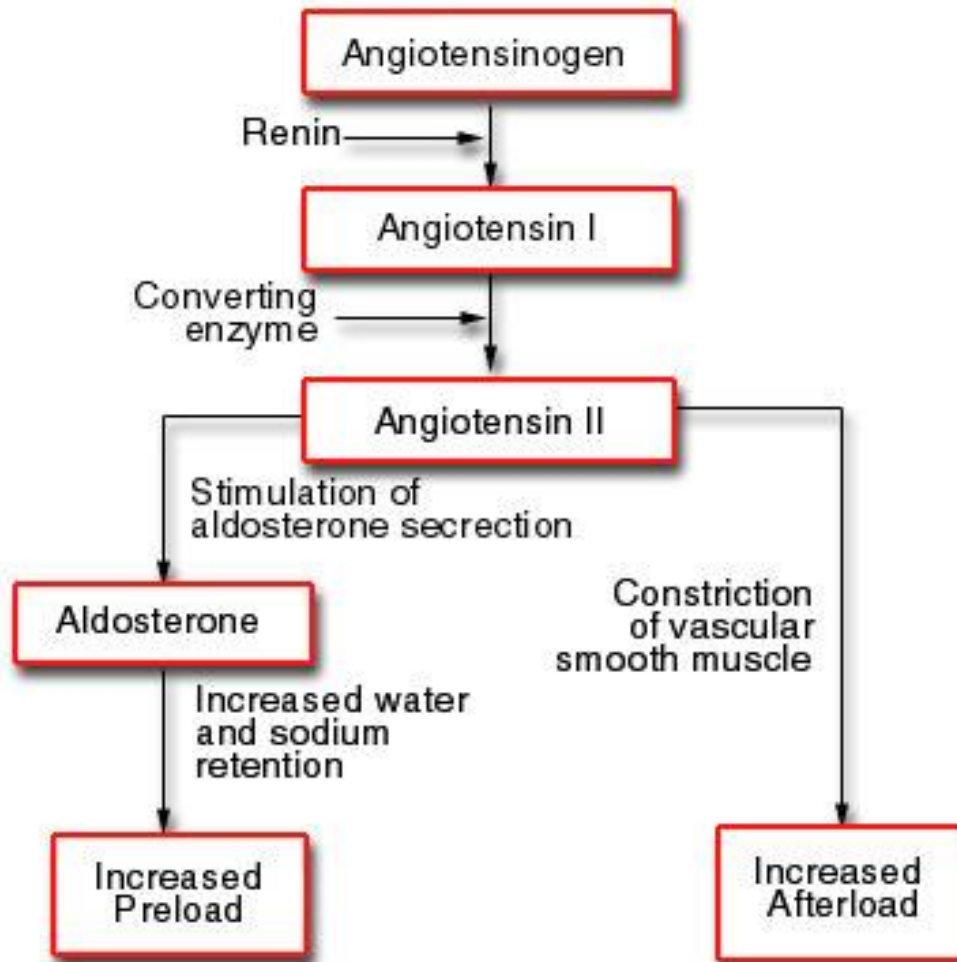


Table 1. Variations in Colloids and Crystalloids Formulations

Solution	pH	Na⁺	Cl⁻	K⁺	Ca⁺⁺	Lactate	Glucose	Osmolality	Other
.9% normal saline	5.0	154	154	0	0	0	0	308	0
LR	6.5	130	109	4	3	28	0	275	0
5% dextrose in water (D ₅ W)	4.0	0	0	0	0	0	50 g/L	252	0
.45% normal saline with dextrose (D ₅ 1/2 NS)	4.5	77	77	0	0	0	50 g/L	406	0
Albumin (5%)	6.4-7.4	130-160	130-160	< 1	0	0	0	309	50 g/L albumin
Albumin (25%)	6.4-7.4	130-160	130-160	< 1	0	0	0	312	250 g/L albumin
Hetastarch 6%	5.5	154	154	0	0	0	0	310	60 g/L starch
Pentastarch 10%	5.0	154	154	0	0	0	0	326	100 g/L starch
Dextran-40 (10% solution)	3.5-7.0	154	154	0	0	0	0	311	100 g/L dextran
Dextran-70 (6% solution)	3.0-7.0	154	154	0	0	0	0	310	60 g/L dextran
<i>Haemacel</i> 3.5%	7.4	145	145	5	6.25	0	0	293	35 g/L gelatin
<i>Gelofusine</i>	7.4	154	125	0	0	0	0	308	40 g/L gelatin

Table 3 Diagnostic criteria for HRS by the International Ascites Club

Major criteria

- Chronic or acute liver disease with advanced hepatic failure and portal hypertension
- Low glomerular filtration rate (serum creatinine >1.5 mg/dl (133 mmol/l) or 24-h creatinine clearance <40 ml/min)
- Absence of shock, ongoing bacterial infection, current treatment with nephrotoxic drugs, gastrointestinal fluid losses, renal fluid losses >500 g/day; >1000 g/day (in the case of oedema)
- No sustained improvement in renal function (serum creatinine <1.5 mg/dl (133 mmol/l) or 24-h creatinine clearance <40 ml/min)
- Proteinuria <500 mg/dl
- No ultrasonographic sign of primary renal disease

Minor criteria (additional criteria)

- Urine volume <500 ml/day
 - Urine sodium <10 mEq/l
 - Urine osmolality $>$ plasma osmolality
 - Urine red blood cells <50 per high-power field
 - Serum sodium <130 mEq/l
-