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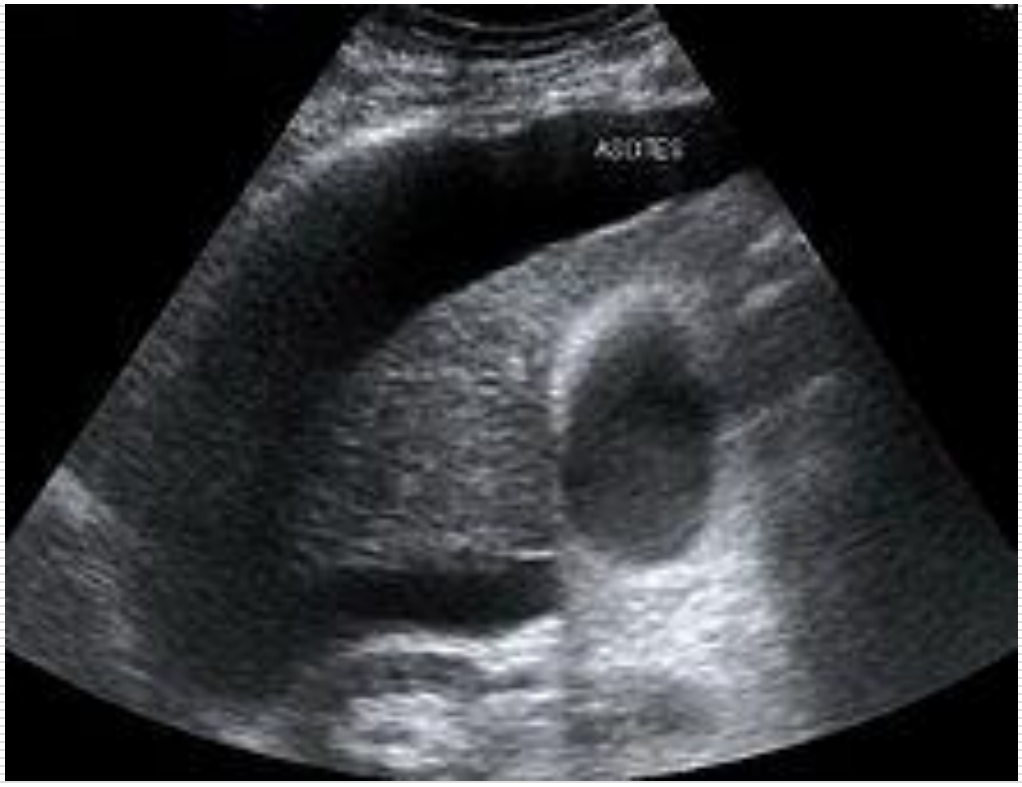
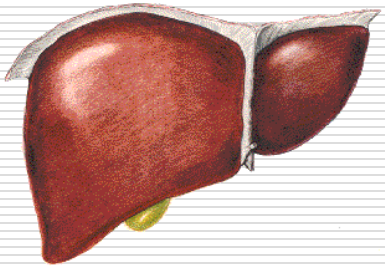

ASCITES

The hepatorenal syndrome



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Azzawyah Kidney Center
2018

History

- The first reports of kidney failure occurring in individuals with chronic liver diseases were from the late 19th century by Frerichs and Flint.
- However, the hepatorenal syndrome was first defined as acute kidney failure that occurred in the setting of biliary surgery.
- The syndrome was soon re-associated with advanced liver disease, and, in the 1950s, was clinically defined by Sherlock, Hecker, Papper and Vessin as being associated with systemic hemodynamic abnormalities and high mortality
- The first systematic attempt to define hepatorenal syndrome was made in 1994 by the International Ascites Club, a group of liver specialists

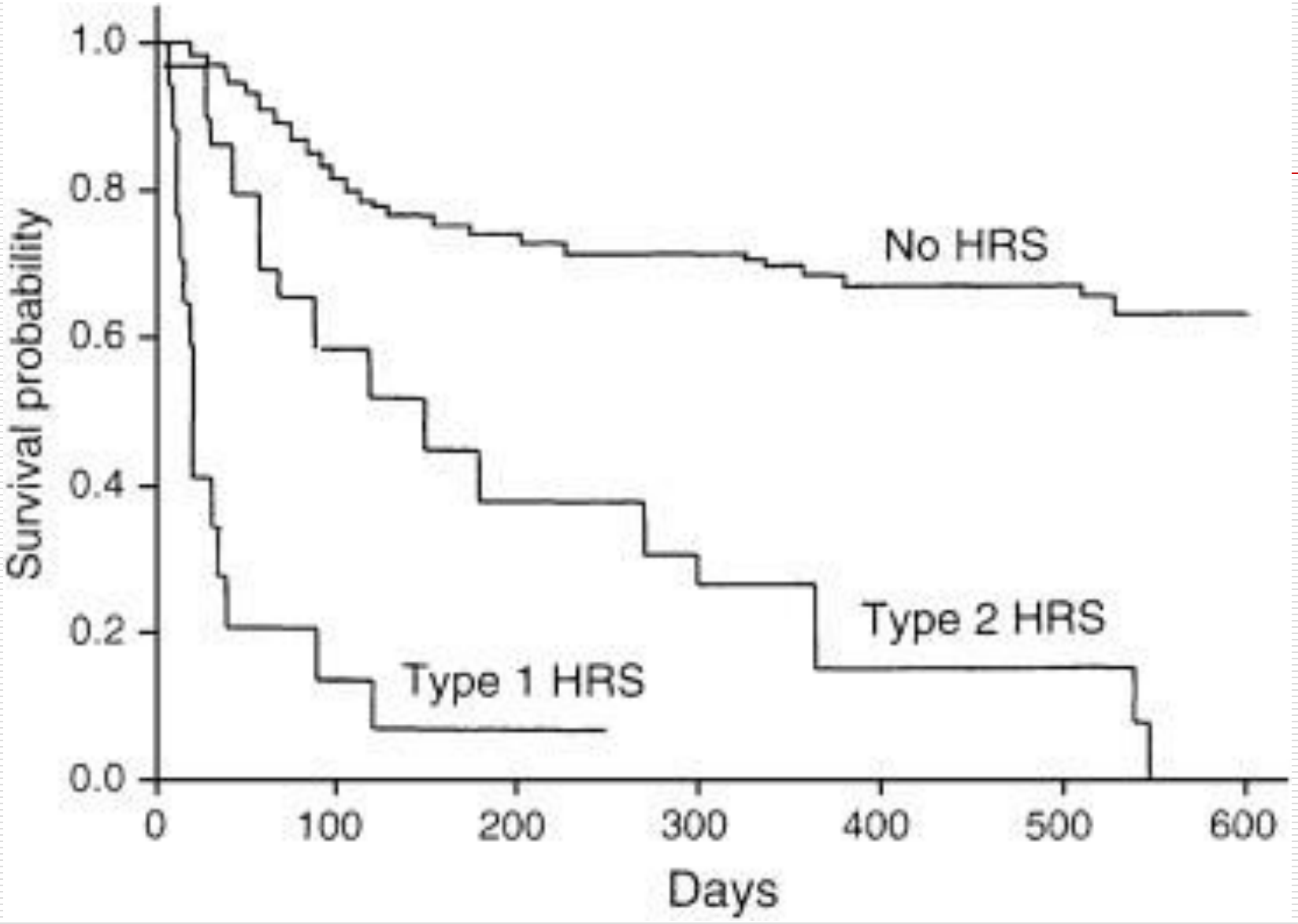
Epidemiology

As the majority of individuals with hepatorenal syndrome have cirrhosis, much of the epidemiological data on HRS comes from the cirrhotic population.
The condition is quite common: approximately 10% of individuals admitted to hospital with ascites have HRS.
A retrospective case series of cirrhotic patients treated with terlipressin suggested that 20.0% of acute kidney failure in cirrhotics was due to type 1 HRS, and 6.6% was due to type 2 HRS.
It is estimated that 18% of individuals with cirrhosis and ascites will develop HRS within one year of their diagnosis with cirrhosis, and 39% of these individuals will develop HRS within five years of diagnosis

Assessing kidney function in pts with cirrhosis

- Cr assays are subject to interference by chromogens, bilirubin being the major one
- There is decreased hepatic production of creatine
- The edematous state that complicates end-stage liver disease leads to large distribution of Cr in the body and lower serum Cr concentration
- Complications such as variceal bleeding, spontaneous bacterial peritonitis or sepsis lead to increased Cr tubular excretion

- HRS is a form of acute or subacute renal failure characterized by severe renal vasoconstriction, which develops in decompensated cirrhosis or ALF
- Nearly half of patients die within 2 weeks of this diagnosis
- The annual incidence of HRS ranges between 8% and 40% in cirrhosis depending on the MELD score
- The frequency of HRS in severe acute alcoholic hepatitis and in fulminant liver failure is about 30% and 55%, respectively


1.0
0.8
0.6
0.4
0.2
0.0
Survival probability
No HRS
Type 2 HRS
Type 1 HRS
0
100
200
300
400
500
600
Days

Classification of the hepatorenal syndrome

- Type 1: cirrhosis with rapidly progressive acute renal failure doubling to level of s cr >2.5 mg/dl , and halving of crcl to level ‹ 20 ml/min over less than 2 wks)

While

- Type 2: is slower in onset & progression and is not associated with an inciting event, defined by increase scr level to of > 1.5 mg/dl, crcl ‹40 ml/min and Una 10 mEq/l

??

- Type 3
- Type 4

Causes of AKI in pts with cirrhosis

- Acute tubular necrosis (41.7%)
- Pre-renal failure (38%)
- **Hepatorenal syndrome (20%)**
- Post-renal failure (0.3%)

HRS Type 1 – Another Diagnostic Approach

1. Cirrhosis (decompensated with ascites)
   a. With precipitating event
   b. Elevated liver enzymes & liver dysfunction
2. Cr >133 umol/L … BUT
3. Rule out OTHER causes of AKI first
   a. Pre-renal: hypovolemia (diuretics), bleeding, shock (septic, cardiogenic, etc.)
   b. Renal: nephrotoxic drugs (e.g. NSAIDS), renal disease assoc with liver dis (GNs)
   c. Post renal obstruction

Major diagnostic criteria for hepatorenal syndrome

- Cirrhosis with ascites.
- Serum creatinine >133 mmol/l (1.5 mg/dl).
- No improvement of serum creatinine (decrease to a level of ≤133 mmol/l) after at least 2 days with diuretic withdrawal and volume expansion with albumin. The recommended dose of albumin is 1 g/kg of body weight per day up to a maximum of 100 g/day.
- Absence of shock.
- No current or recent treatment with nephrotoxic drugs.
- Absence of parenchymal kidney disease as indicated by proteinuria >500 mg/day, microhaematuria (>50 red blood cells per high power field) and/or abnormal renal ultrasonography.

2007 International Ascites Club Revised HRS I Criteria

Gut 2007 Sep:56(9):1310–1318.

Minor diagnostic criteria for hepatorenal syndrome

- Urine volume < 500 mL/24 h
- Urine sodium <10 mEq/L
- Urine osmolality greater than plasma osmolality
- Urine red blood cells < 50 per high power field
- Serum sodium <130 mEq/L

Type 1 hepatorenal syndrome

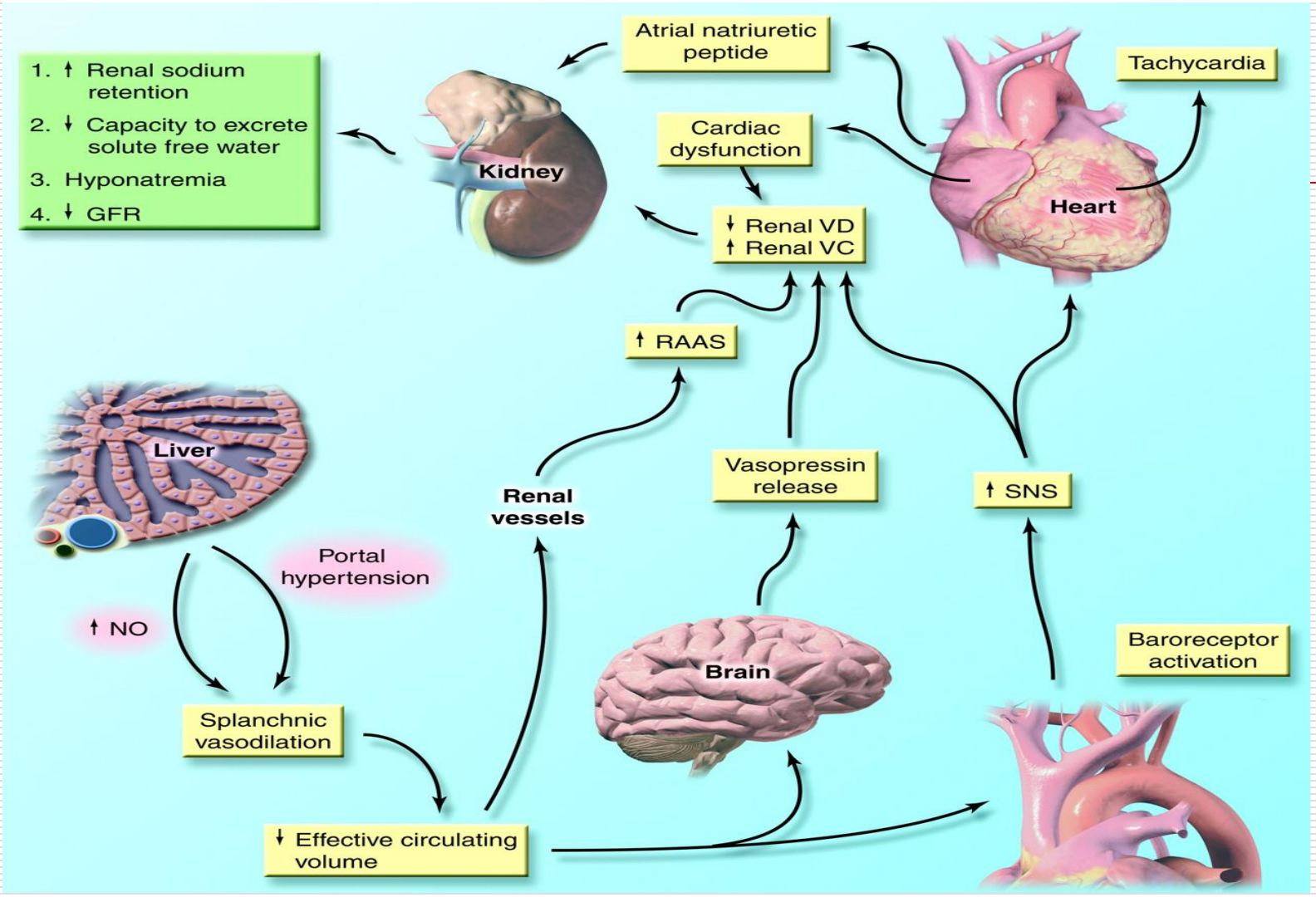
- The serum creatinine level doubles to greater than 2.5 mg/dL within 2 weeks
- It is characterized by its rapid progression and high mortality, with a median survival of only 1 to 2 weeks
- It can be precipitated by spontaneous bacterial peritonitis and variceal hemorrhage
- In some cases acute hepatic injury, superimposed on cirrhosis, may lead to liver failure and HRS

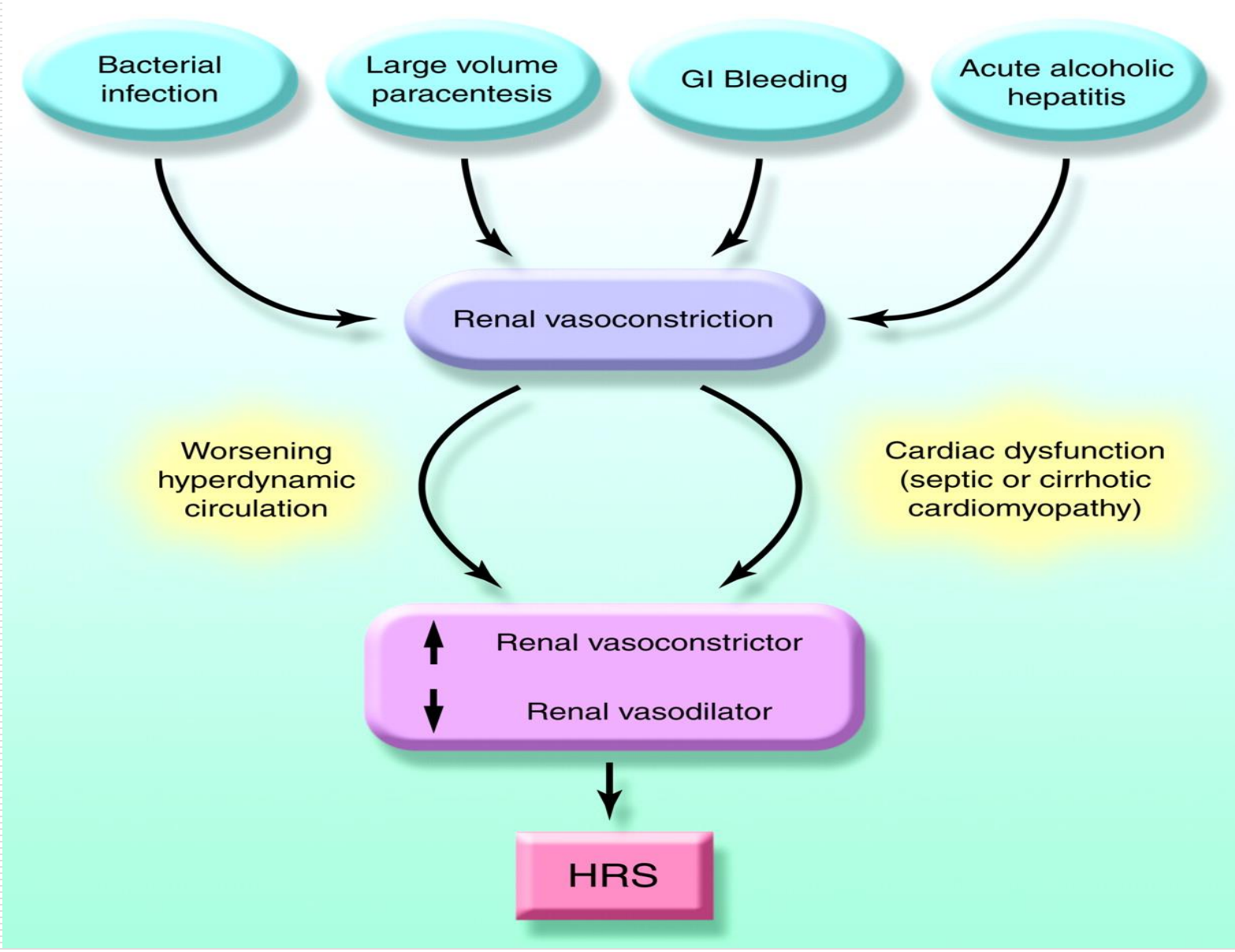
Type 2 hepatorenal syndrome

- Serum creatinine increases slowly and gradually during several weeks or months
- Many patients with type 2 HRS eventually progress to type 1 HRS because of a precipitating factor
- The median survival of type 2 HRS is about 6 months

Pathogenesis

- Portal hypertension leads to arterial vasodilatation and pooling of blood in the splanchnic bed, with a decrease in systemic vascular resistance
- The modulation of cardiac output is relatively unable to prevent the severe reduction of effective circulating volume due to the splanchnic arterial vasodilation
- Activation of the renin-angiotensin-aldosterone system and the sympathetic nervous system and stimulation of antidiuretic hormone release become necessary to maintain arterial blood pressure
- As the liver disease worsens these circulatory changes gradually increase until systemic hemodynamic stability depends on vasoconstriction of the extrasplanchnic vascular beds


1. ↑ Renal sodium retention
2. ↓ Capacity to excrete solute free water
3. Hyponatremia
4. ↓ GFR
Kidney
Atrial natriuretic peptide
Cardiac dysfunction
↓ Renal VD
↑ Renal VC
Heart
Tachycardia
↑ RAAS
Liver
Renal vessels
Vasopressin release
↑ SNS
Portal hypertension
↑ NO
Brain
Baroreceptor activation
Splanchnic vasodilation
↓ Effective circulating volume


Bacterial infection
Large volume paracentesis
GI Bleeding
Acute alcoholic hepatitis
Renal vasoconstriction
Worsening hyperdynamic circulation
Cardiac dysfunction (septic or cirrhotic cardiomyopathy)
Renal vasoconstrictor
Renal vasodilator
HRS

Nitric oxide

- Nitric oxide (NO) is a potent vasodilator that is elevated in the peripheral circulation of patients with cirrhosis
- The imbalance between NO and vasoconstrictors such as endothelin-1 in the renal microcirculation has been proposed to be responsible for the progressive deterioration in kidney function in these patients

- Nitric oxide has a very short half-life; therefore, measurement of the NO metabolites, nitrite and nitrate (NOx), are commonly used to estimate NO levels in the circulation
- Because both metabolites are excreted predominantly by the kidney, decreased renal clearance rather than overproduction could account for the elevated level of NOx in decompensated cirrhosis

- L-Arginine (L-Arg), a nonessential amino acid, is the precursor for NO production by nitric oxide synthase
- The liver is the major site for arginine metabolism, where arginine generated in the urea cycle is rapidly converted to urea and ornithine by arginase-1
- NOS and arginase-1 compete for available arginine and it is possible that the overproduction of NO results from an excess availability of substrate

- Patients with either compensated cirrhosis, cirrhotic patients with ascites, refractory ascites (RA) or chronic hepatorenal syndrome (HRS) type II were included in the sudy
- Normal healthy volunteers, organ donors and chronic renal failure (CRF) patients without liver disease were included as controls

- After adjusting for all demographics and variables, HRS was the only disease state predicting high levels of NOx in the peripheral circulation ($P < 0.001$)
- Multivariate analysis also revealed that HRS was an independent factor predicting high levels of L-Arg ($P = 0.03$)
- Chronic renal failure and stages of progressive renal dysfunction in decompensated cirrhosis were not independently associated with peripheral levels of NOx or L-Arg
- Peripheral levels of NOx reliably reflect NOx levels in the splanchnic circulation, suggesting that peripheral levels of NOx can be used diagnostically as a marker for disease state

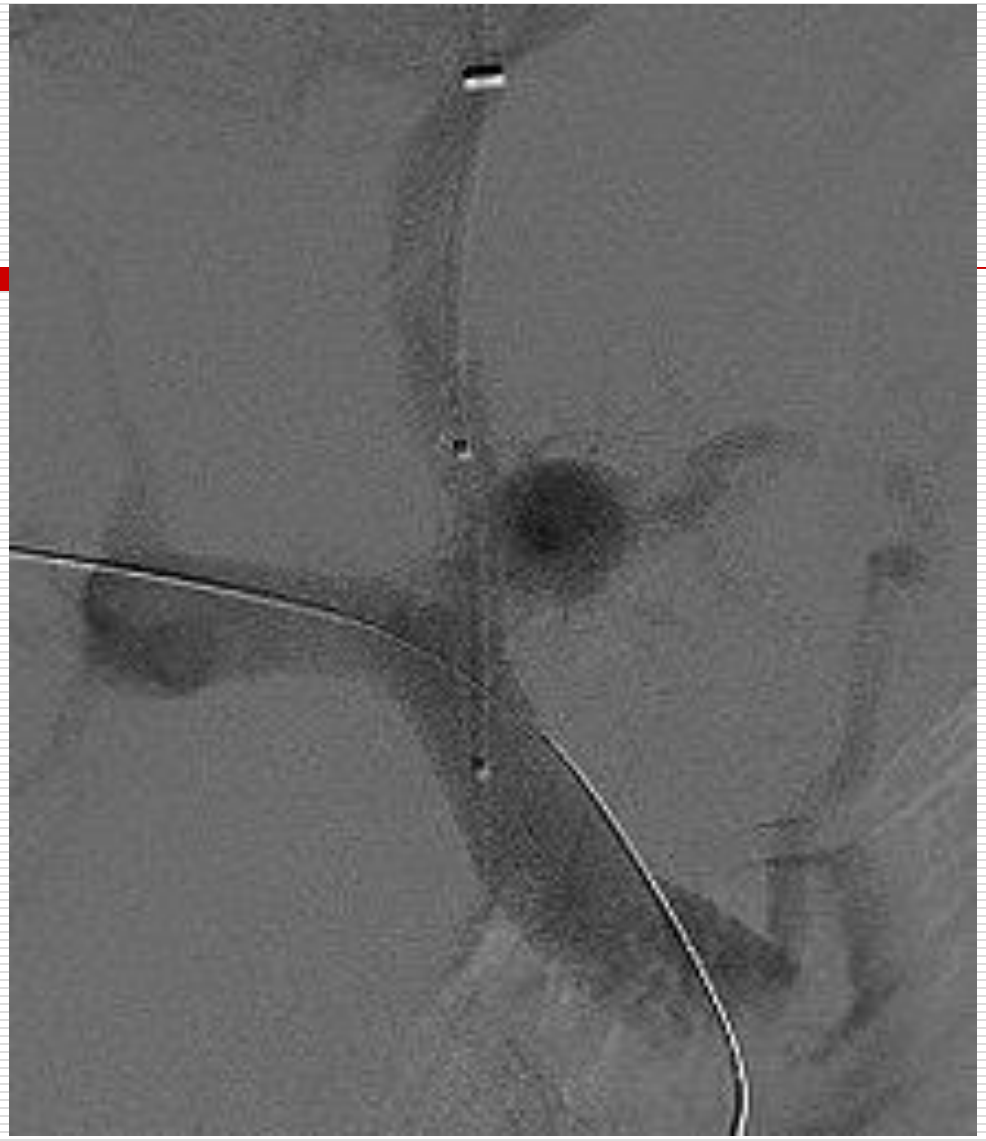
Treatment

Transplantation

The definitive treatment for hepatorenal syndrome is liver transplantation, and all other therapies can best be described as bridges to transplantation.

While liver transplantation is by far the best available management option for HRS, the mortality of individuals with HRS has been shown to be as high as 25% within the first month after transplantation

TIPS



TIPS (Transjugular intrahepatic porto-systemic shunt)

- ✓ Significant suppression of the endogenous vasoconstrictor systems
- ✓ Decrease in creatinine levels
- ✓ More easily controllable ascites

Complications of TIPS for treatment of HRS include the worsening of hepatic encephalopathy (as the procedure involves the forced creation of a porto-systemic shunt, effectively bypassing the ability of the liver to clear toxins), inability to achieve adequate reduction in portal pressure, and bleeding

Liver dialysis

Liver dialysis involves extracorporeal dialysis to remove toxins from the circulation, usually through the addition of a second dialysis circuit that contains an albumin-bound membrane.

The molecular adsorbents recirculation system (MARS) has shown some utility as a bridge to transplantation in patients with hepatorenal syndrome, yet the technique is still nascent.

RRT

Renal replacement therapy may be required to bridge individuals with hepatorenal syndrome to liver transplantation, although the condition of the patient may dictate the modality used.
The use of dialysis, however, does not lead to recuperation or preservation of kidney function in patients with HRS, and is essentially only used to avoid complications of kidney failure until transplantation can take place.
In patients who undergo hemodialysis, there may even be an increased risk of mortality due to low blood pressure in patients with HRS, although appropriate studies have yet to be performed. As a result, the role of RRT in patients with HRS remains unclear.

Medical treatment

Midodrine/octreotide

- Combination therapy with midodrine (a selective alpha-1 adrenergic agonist) and octreotide (a somatostatin analog) may be effective and safe
- Midodrine is a systemic vasoconstrictor and octreotide is an inhibitor of endogenous vasodilator release, combined therapy would improve renal and systemic hemodynamics

- These drugs were used in three pilot studies in a total of 79 patients
- A complete recovery of renal failure was observed in 49% of patients.
- In most patients midodrine administration started at 5-10 mg t.i.d. orally, with the goal of increasing the dose to 12.5 or 15 mg t.i.d. if a reduction of serum creatinine was not observed
- Octreotide administration started at 100 μg subcutaneously t.i.d. with the goal of increasing the dose to 200 μg subcutaneously t.i.d. if a reduction of serum creatinine was not observed

Terlipressin

- Terlipressin, an agonist of the V1 vasopressin receptors, is inactive in its native form, but is transformed into the biologically active form, lysine-vasopressin through enzymatic cleavage of glycyl residues by tissue peptidases
- Because of this modification, terlipressin has a prolonged biological half-life compared with other vasopressin analogues

Terlipressin: Meta Analysis

- Five studies involving 243 patients with HRS were identified
- Pooling of study results showed a significant increase in HRS reversal among patients who received terlipressin versus those who received placebo (the pooled odd ratio OR of HRS reversal was 8.09 p=0.0001)
- The rate of severe ischemic events was higher in study than control patients, (pooled OR=2.907 p=0.032)
- Terlipressin use had no significant impact upon survival (pooled OR for survival rate, 2.064 p=0.07)

- Other agents that have been investigated for use in treatment of HRS include pentoxifylline, acetylcysteine, and misoprostol.
- The evidence for all of these therapies is based on either case series, or in the case of pentoxifylline, extrapolated from a subset of patients treated for alcoholic hepatitis.[1]

Acute treatment

- Stop diuretics

- Volume expansion with albumin
  - 1g/kg body weight; then 20-40 mg daily
  - maximum 100g/d
- Midodrine 7.5-12.5 mg TID (alpha 1 agonist)
- Octreotide 100-200 mcg SC TID
  - Reduced mortality with alb/mid/oct vs. alb controls (43% vs. 71%)
- In the ICU, consider norepinephrine in patients with hemodynamic instability

Chronic treatment

- Hemodialysis vs. CRRT
- TIPS relieves portal HTN
  - Limited evidence for efficacy
- Orthotopic liver transplantation (OLT)
  - Five year survival: 60% vs. 0% (OLT vs. control)
  - May require liver kidney transplant if HD > 8w to avoid post-OLT HD.

Case #1 → Mr. T

55 year old Caucasian business man

Chronic hepatitis C with decompensated cirrhosis (ascites)

EC: Community acquired pneumonia with no bacteremia

- no acute liver decompensation symptoms or signs; no ascites

	Admission	Day 2	Day 4
ALT (N <30)	**45**	**48**	**44**
AST (N <25)	**32**	**35**	**33**
ALP (N<120)	112	**130**	**148**
GGT (N<38)	**50**	**65**	**56**
T. Bili (N<20)	15	20	17
Albumin (N=35-45)	35	32	34
INR (N<1.1)	1.0	1.0	1.0
Creatinine (N<110)	90	**140**	**190**

Is the AKI due to:

1)Hepatorenal syndrome Type 1

OR

2)Other causes of AKI

Case#2 - Mr. ZZ

44 year old motorcycle enthusiast male

Alcoholic liver disease with decompensated cirrhosis (ascites)

EC: Tense ascites with spontaneous bacterial peritonitis (SBP)

	Admission	Day 2	Day 4
ALT (N <30)	40	60	80
AST (N <25)	160	240	300
ALP (N<120)	112	125	122
GGT (N<38)	120	160	280
T. Bili (N<20)	30	55	70
Albumin (N=35-45)	28	25	22
INR (N<1.1)	1.4	1.9	2.5
Creatinine (N<110)	90	140	190

Is the AKI due to:

1) Hepatorenal syndrome Type 1

OR

2) Other causes of AKI

Case#3 - Mrs. kS

A 49-year-old woman is hospitalized for altered mental status. She has alcoholic cirrhosis complicated by ascites. She takes lactulose, but she is now having four to five loose stools per day. She also takes furosemide and spironolactone.

On physical examination, temperature is 36.4 °C (97.5 °F), blood pressure is 102/74 mm Hg, pulse rate is 78/min, and respiration rate is 16/min; BMI is 24. She is disoriented to time and date. The mucous membranes are dry.

Laboratory studies

- INR: 1.3 (normal range, 0.8-1.2)
- Albumin: 2.6 g/dL (26 g/L)
- Total bilirubin: 3.5 mg/dL (59.9 µmol/L)
- Blood urea nitrogen: 38 mg/dL (13.6 mmol/L)
- Creatinine: 2.5 mg/dL (221 µmol/L)
- Urinalysis: Normal

Her baseline creatinine is 1.1. Blood culture results are pending. Her diuretics and lactulose are discontinued.

- Which of the following is the most appropriate treatment for acute kidney injury in this patient?

A) Midodrine

B) Midodrine and octreotide

C) Norepinephrine

D) 25% albumin

- Which of the following is the most appropriate treatment for acute kidney injury in this patient?

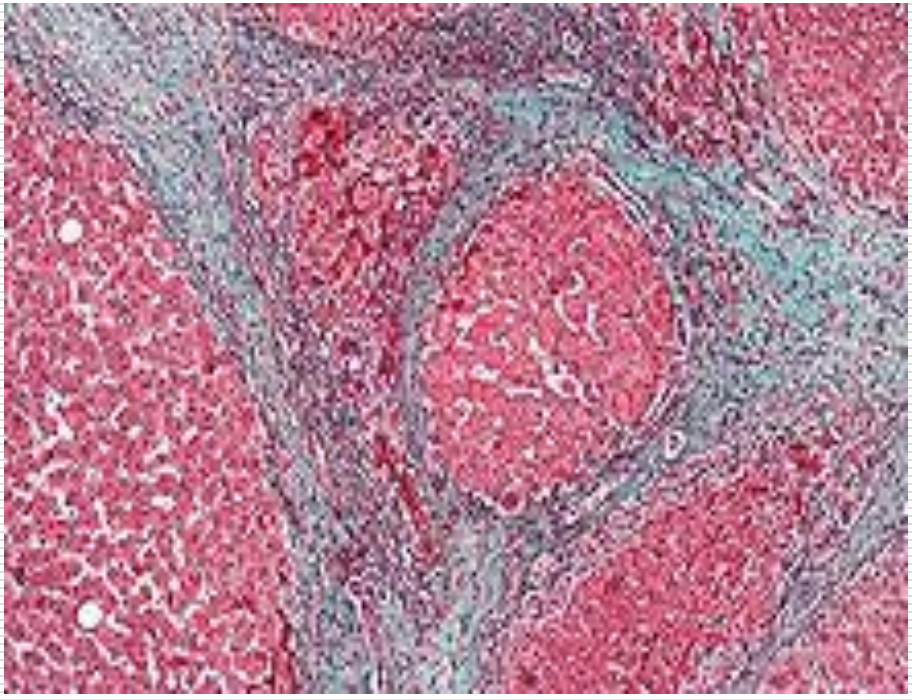
A) Midodrine

B) Midodrine and octreotide

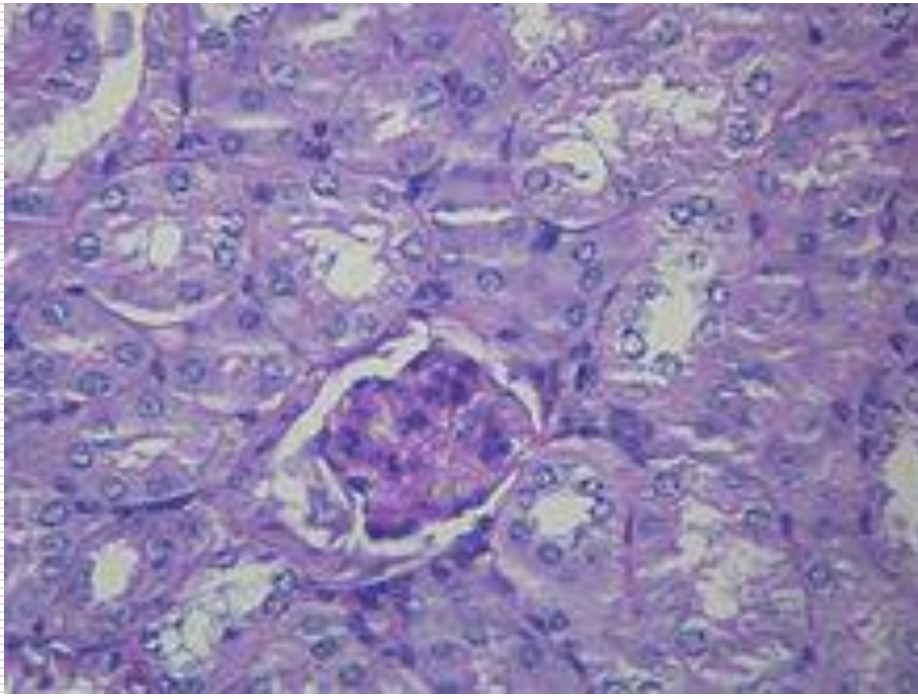
C) Norepinephrine

D) 25% albumin

Histology



(chicken wire appearance)cirrhosis of the liver, the most common cause of HRS.



PAS stain of normal kidney histology

Take Quiz

Which is not usually associated with hepatorenal syndrome?

Answers | Teaching Points

Click Your Answer Below

- End-stage cirrhosis of the liver
- Primary kidney failure
- Portal hypertension
- Creatinine clearance <40 mL/min

Which is true regarding prognosis in hepatorenal syndrome?

Answers | Teaching Points

Click Your Answer Below

- A complete cure is likely in most patients
- Liver transplant can cure most patients
- Dialysis is not usually a long-term option for most patients
- The prognosis is highly dependent on the cause of liver failure

Which is an inappropriate action in the treatment of the patient with hepatorenal syndrome?

Answers | Teaching Points

Click Your Answer Below

- Correct hyperkalemia, electrolyte imbalance, and severe acidosis resulting from renal failure
- Monitor volume status, use albumin and normal saline to correct hypovolemia
- Treat spontaneous bacterial peritonitis (SBP) with antibiotics
- Use NSAIDs rather than opioids for pain control

65-year-old female patient with nonalcoholic steatohepatitis (NASH) cirrhosis is admitted with hepatorenal syndrome and is clinically significant ascites. She has a background of severe COPD with mild cor pulmonale. Which of the following is not appropriate for management?

Answers | Teaching Points

Click Your Answer Below

- Liver transplant
- Paracentesis with intravascular albumin replacement
- Transjugular intrahepatic portosystemic shunt (TIPS)
- Noradrenaline with albumin

Which of the following is not seen in hepatorenal syndrome?

Answers | Teaching Points

Click Your Answer Below

- Oliguria
- Hyponatremia
- Creatinine elevation of more than 1.5 mg/dL
- Hypernatremia