HEPATORENAL SYNDROME

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HEPATORENAL SYNDROME (HRS)

- A unique form of functional renal failure due to diminished renal blood flow, which occurs typically in histologically normal kidneys.
- Potentially reversible but involves highly complex pathogenetic mechanisms and equally complex clinical and therapeutic management.
- Once HRS has developed, it has a very poor prognosis.

EPIDEMIOLOGY

- **Incidence:**
  - In 1993 : 18% at one year and 39% at five years in patients with cirrhosis and ascites.
  - In 2010 : A study showed 263 consecutive cirrhotic patients with ascites, 49% of patients developed functional renal impairment during follow-up.
  - The annual incidence of HRS was 7.6%.

- **Prevalence:** Ranges from 13 to 45.8%.

Age	Sixth or seventh decade
Sex	Male preponderance

Pathogenesis of HRS

Portal hypertension

↓

Splanchnic vasodilation

↓

Decreased effective circulatory volume

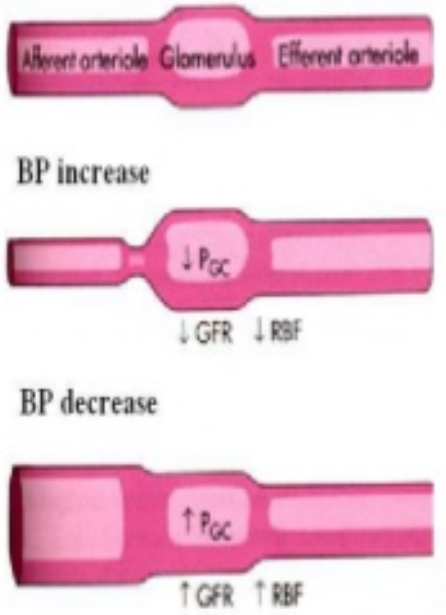
↓

Renal vasoconstriction

↓

HEPATORENAL SYNDROME

+ Loss of renal autoregulation



NephroTube

Diagnostic Criteria for Hepatorenal Syndrome By International Ascites Club (IAC)

- Cirrhosis with ascites
- Serum creatinine > 1.5 mg/dL
- Absence of shock
- No improvement of serum creatinine (decrease to a level of 1.5 mg/dL or less) after at least 2 d of diuretic withdraw 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)
- No current o recent exposure to nephrotoxic drugs
- Absence of parenchymal disease as indicated by proteinuria > 500 mg/day, microscopic hematuria (50 red blood cells per high power field) and abnormal renal ultrasonography

TYPES OF HRS

Type I	Type II
A rapid progressive renal impairment defined by doubling of the serum creatinine to a level > 2.5mg/dL or >226 μmol/L in less than two weeks	A moderate renal impairment (serum creatinine > 1.5 and up to 2.5mg/dL or > 133 and up to 226 μmol/L) with a steady progressive course that evolves over weeks to months
Acute deterioration in circulatory, renal and hepatic function is characteristic.	Acute deterioration develops more gradually than Type I
Often associated with a precipitating factor	Typically develops de novo in patients with refractory ascites, rarely may progress to Type I
Prognosis is poor (weeks)	Prognosis is poor (months)

RISK FACTORS FOR THE ONSET OF HEPATORENAL SYNDROME

- Spontaneous bacterial peritonitis
- Large volume paracentesis (> 5 L) with inadequate albumin substitution
- NSAID and other nephrotoxic drugs, iv contrast
- Bleeding from esophageal varices
- Post TIPS syndrome
- Diuretic treatment

LABORATORY FINDINGS

- Elevated plasma renin activity
- Elevated plasma nor-adrenaline activity
- Hyponatraemia, hyperkalaemia & elevated blood urea nitrogen
- Decreased plasma osmolality
- Elevated urinary osmolality
- Decreased urinary sodium excretion
- Serum abnormalities of liver disease include:
  - Hyperbilirubinemia
  - Hypoalbuminemia
  - Prolonged prothrombin time

MANAGMENT

- The current therapeutic option includes:
  - Drugs with specific vasoconstrictive effects on the splanchnic circulation.
  - Renal and liver replacement therapies which can be artificial or natural.

MEDICAL MANAGEMENT

- **TERIPRESSIN:**

- V1 receptor agonist that causes vasocostriction in both systemic and splanchnic circulation.

- 0.5 mg every 4-6 hour as a continuous infusion (2 mg/d).

- The dosage can be doubled after three days of treatment if shows no improvement in serum creatinine.

- The total daily dose should not exceed 2 mg IV bolus every 4-6 h or 12 mg/d in continuous infusion.

TERLIPRESSIN

- Terlipressin should be associated with albumin (at a dose of 1 g/kg per day on the first day, without exceeding 100 g/d, followed by 20-40 g/d)

- Two randomized controlled trials have shown efficacy in reversing type 1 HRS in approximately 34–43% of patients, but SURVIVAL WAS NOT IMPROVED.

A Randomized, Prospective, Double-Blind, Placebo-Controlled Trial of Terlipressin for Type 1 Hepatorenal Syndrome

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Terlipressin and Albumin vs Albumin in Patients With Cirrhosis and Hepatorenal Syndrome: A Randomized Study

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NOREPINEPHRINE

1
- Norepinephrine continuous infusion at 0.5 mg/hour
- Albumin 20-40 g/day

2
- ↑ Norepinephrine dose by 0.5 mg/hours until MAP is increased by 10 mmHg
- Albumin 20-40 g/day

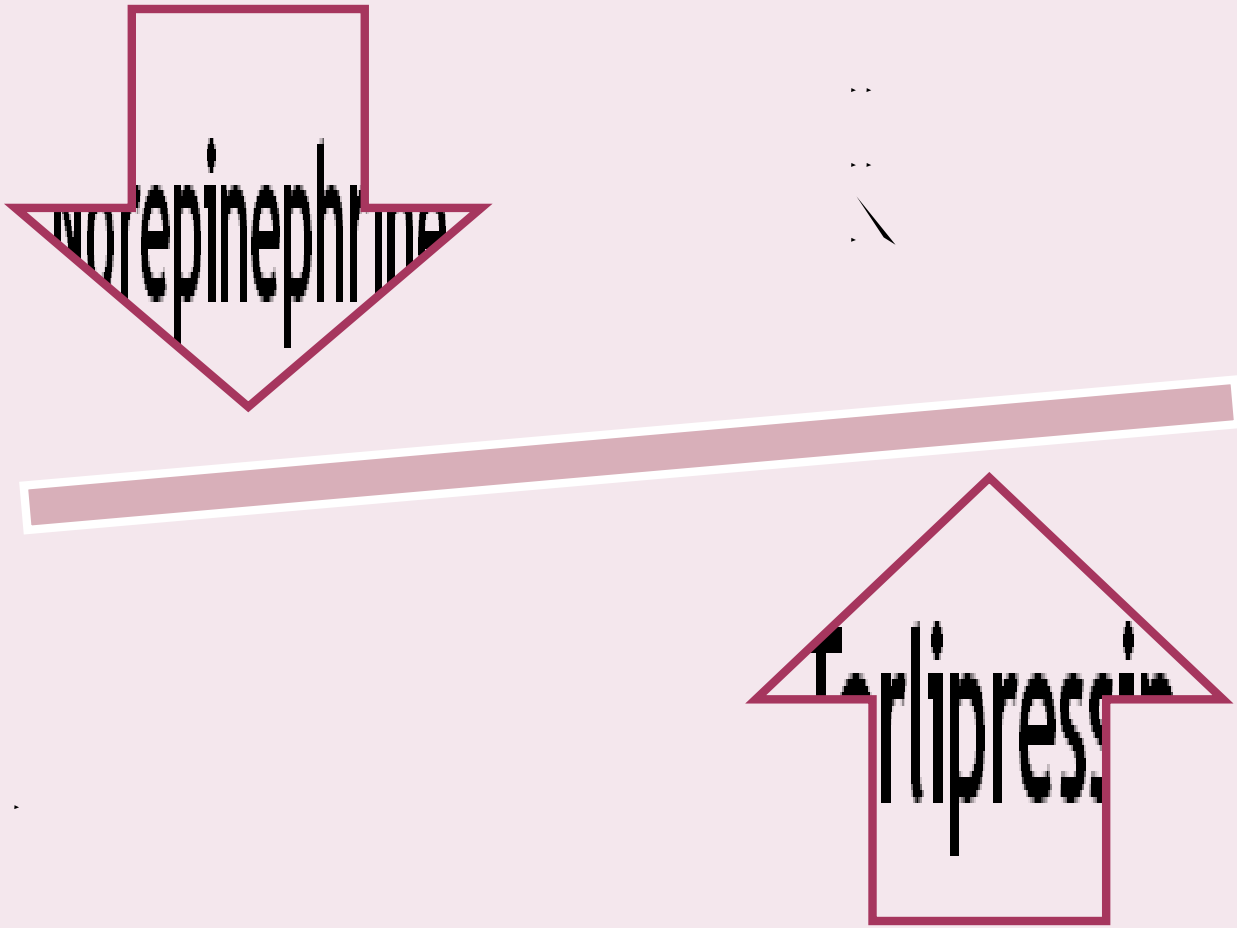
3
- Maximum dose = 3 mg/hr
- Maximum duration =15 days

NOREPINEPHRINE

- To date, three randomized controlled trials comparing the safety and efficacy of norepinephrine with terlipressin in reversing type 1 HRS showed similar results with an improvement in mean arterial pressure and renal function when compared with the terlipressin groups.

- Side-effect profiles and cumulative survival were also comparable between the two drugs.

NOREPINEPHRINE VS TERLIPRESSION



ALBUMIN

- NOT been established as a stand-alone treatment for type 1 HRS, especially as recent studies have not shown albumin alone to be able to reverse type 1 HRS.

- The International Ascites Club recommends

  the use of **20–40 g/day albumin in combination with vasoconstrictors, after the initial dose of 1 g/kg of body weight on initial 2 days**.

- **MIDODRINE:**

  Administered orally (initial dose 7.5 mg every 8 hour up to a maximum of 12.5 mg three times daily).

- **OCTREOTIDE:**

  Given by continuous infusion (50 mcg/h) or subcutaneously (from 100 to 200 mcg 12.5 mg three times daily)

OTHER MANAGEMENT OPTIONS

- **Transjugular Intrahepatic Portosystemic Shunt (TIPS):**

- Effective for the treatment of diuretic-resistant ascites, a precursor to type II HRS.

- In case of type I HRS, the use of vasoconstrictor therapy has reduced the usage of TIPS .

- Latest reviews suggest that TIPS should be considered in those patients whose liver function is relatively preserved such as abstinent alcoholics, and/or possible candidates for liver transplantation.

CONTED……

- **Renal Replacement Therapy (RRT):**
  - Continuous renal replacement therapy (CRRT) is usually preferred to intermittent dialysis due to its greater hemodynamic stability.
  - Peritoneal dialysis is an option to resolve ascites and correct other complications of cirrhosis without exposing patients to the complications of hemodialysis.

CONTED……

- **Extracorporeal Artificial Liver Support Therapy:**
  - Designed to enhance and optimize to increase the removal of water soluble toxins and those linked to albumin.
- **Molecular Adsorbent Recirculating System (MARS):**
  - The results of one small randomized trial have supported the use of MARS to improve serum creatinine levels and survival rates in patients with HRS, although larger studies are needed to confirm these findings.
- **Fractionated plasma separation and absorption (Prometheus):**

CONTED……

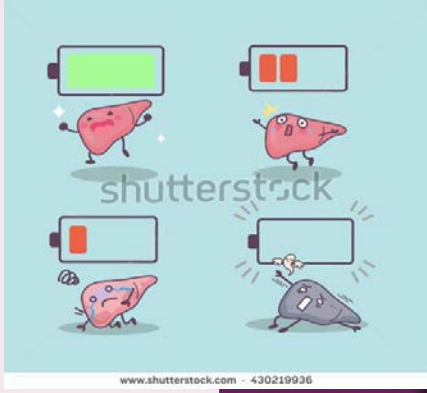
Liver Transplantation:

- Remains the treatment of choice in HRS patients despite its high mortality rate.

- Organ allocation is mainly based on the MELD score which is a system devised to stratify disease severity on the basis of laboratory parameters (serum creatinine, bilirubin and INR).

- RRT prior to liver transplant is an important predictive factor.

PROGNOSIS



- HRS is one of the most lethal complications of cirrhosis.
- Patients with type 1 HRS with a MELD score ≥ 20 had median survival of one month.
- In type II HRS, the median survival is 11 months for a MELD score < 20 and 3 months for a MELD score ≥ 20.

Prevention of HRS & General Management Strategies

- Avoid drugs that reduce renal perfusion or nephrotoxic substances
- Minimize exposure to organ-iodated contrast agents
- Intravenous albumin is recommended for volemic filling after large volume paracentesis (8 g of albumin for each liter of ascites removed)
- Diuretic therapy should be suspended
- Pentoxifylline as drug's anti-TNFα activity
- Antibiotic prophylaxis to prevent infections reducing intestinal bacterial translocation (norfloxacin 400 mg/d)
- Intravenous albumin administered in association with ceftriaxone in SBP
- Adrenal insufficiency should be identified and treated
- Drug dosages must be adjusted according to renal function


THANK YOU