

# Hepatorenal Syndrome

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# Objectives

- Definition and Diagnosis
- Pathogenesis
- Treatment Options and Data

# History

- 1863: Absence of histologic changes to the kidney in some cirrhotics with renal failure
- 1956: 1<sup>st</sup> detailed description of the syndrome by Hecker and Sherlock
- 1960s: Reversal of renal failure with kidney transplant to patients with CKD
- 1970s: Reversal of HRS with liver transplantation

# Definition of HRS

- Functional renal failure
  - Absence of histologic changes
- Occurs in patients with chronic liver disease
- Progressive liver failure and ascites
- Can occur acutely in certain settings
  - Spontaneous bacterial peritonitis
  - Large-volume paracentesis without albumin
- Marked renal vasoconstriction
- Reduced GFR

# Clinical Types of HRS

- Type 1
  - Rapid decline in renal function
  - Doubling of serum Cr to  $>2.5\text{mg/dL}$  OR
  - 50% reduction in 24h CrCl to  $<20\text{ml/min}$
  - Less than 2 weeks
  - Spontaneous
  - Associated with SBP (20%) or large volume paracentesis w/o albumin (15%)

# Clinical Types of HRS

- Type 2
  - Slower decline in renal function
  - Serum Cr > 1.5mg/dL
  - Criteria for type 1 HRS not met
  - Development of diuretic-resistant or refractory ascites

# Epidemiology

- Incidence
  - 7-10% in hospitalized cirrhotics with ascites
  - 20% at 1 year, 40% at 5 years
- Risk Factors
  - Advanced ascites (diuretic-resistant)
  - SBP (20%)
  - Large-volume paracentesis w/o albumin (15%)
- Prognosis
  - Worst prognosis of all complications of cirrhosis
  - Type 1 median survival: <2 weeks
  - Type 2 median survival: ~6 months

# Diagnosis

- Lack of specific testing
- Diagnosis of exclusion
- DDX of renal failure in cirrhosis
  - Hypovolemia (GI hemorrhage, shock)
  - Nephrotoxins (drugs, contrast)
  - Glomerulonephritis (Hep B and C)
  - Acute Tubular Necrosis
  - Obstruction

# Diagnostic Criteria

## ■ Major Criteria

- Chronic or acute liver disease with advanced liver failure or portal HTN
- Low GFR (Cr > 1.5mg/dL OR CrCl < 40mL/min)
- Exclusion of shock, ongoing bacterial infection, volume depletion, and use of nephrotoxic drugs
- No improvement in renal function despite stopping diuretics and volume repletion with 1.5L of saline
- No proteinuria or ultrasonographic evidence of obstruction or parenchymal renal disease

# Diagnostic Criteria

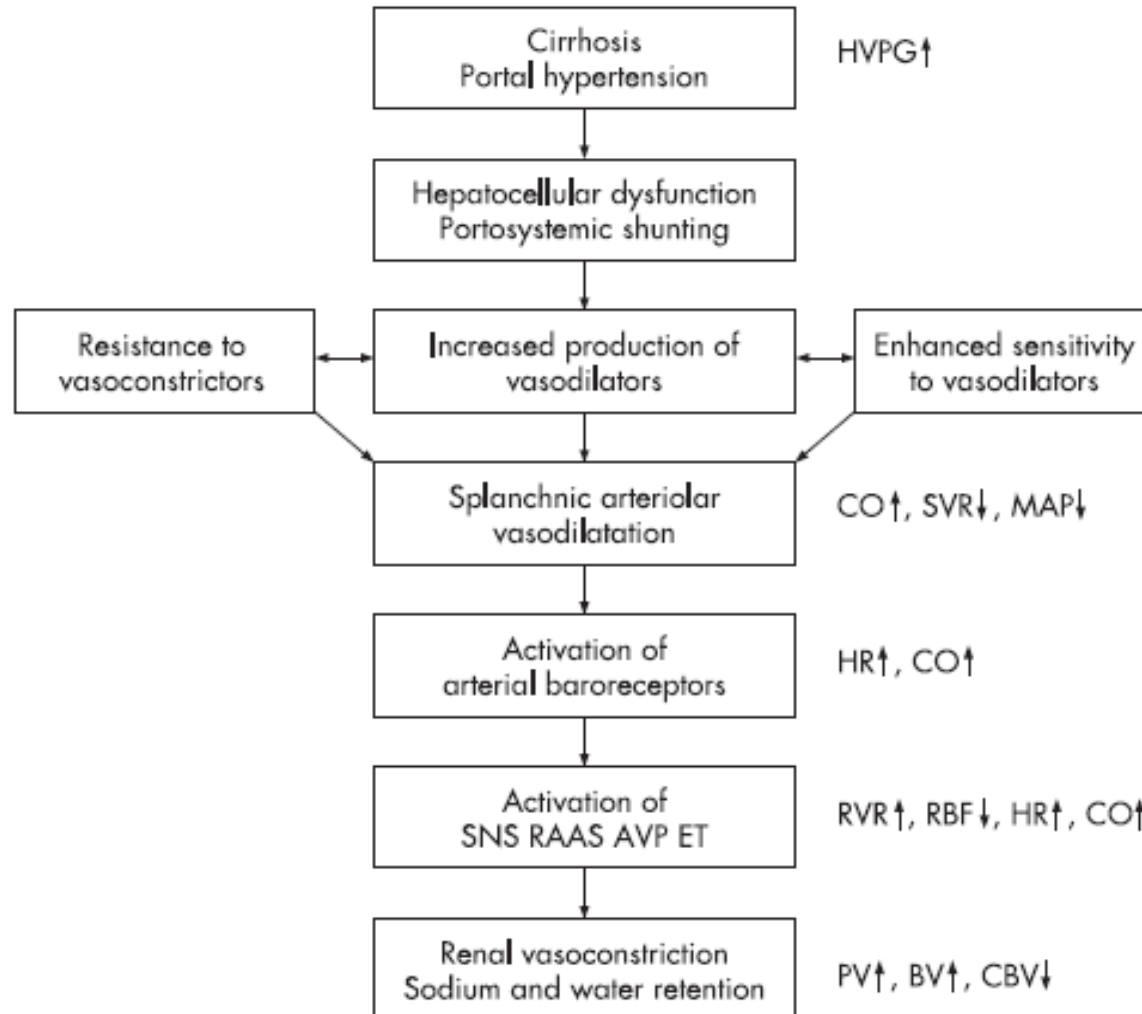
## ■ Minor Criteria

- Urine volume < 500mL/day
- Urine sodium < 10mEq/L
- Urine osmolality > plasma osmolality
- Urine RBCs < 50 per hpf
- Serum sodium < 130mEq/L

# Pathophysiology

- Severe renal vasoconstriction
- Advanced cirrhosis and portal HTN
- Splanchnic arteriolar vasodilatation
- Hyperdynamic circulation
- "Cirrhotic cardiomyopathy"

# Pathophysiology



# Pathophysiology

- Splanchnic arteriolar vasodilatation
  - Progressive portal hypertension
  - Portosystemic shunting
  - Arteriovenous communications
  - Local vasodilator production (NO, glucagon, VIP)
  - ↑ portal pressures »»»» ↑ nitric oxide synthase

# Pathophysiology

- Mechanisms for vasodilatation
  - Overproduction of NO
  - Decreased NO clearance by cirrhotic liver
  - Bypass degradation via portosystemic shunting
  - Increased splanchnic sensitivity to NO
  - Decreased splanchnic sensitivity to vasoconstrictors (Angiotensin II)

# Pathophysiology

- Splanchnic arteriolar vasodilatation
  - Decreased effective arterial volume (EAV)
  - Decreased systemic vascular resistance
  - Hypotension
  - Activation of vasoconstrictor systems
    - Renin-Angiotensin-Aldosterone-System
    - Sympathetic Nervous System
    - Anti-Diuretic Hormone

# Pathophysiology

- Hyperdynamic circulation
  - Hypotension from decreased EAV
  - Low systemic vascular resistance (SVR)
  - Baroreceptor activation
  - SNS activation → increased contractility
  - Increased cardiac output
  - Patients still remain hypotensive

# Why Does Hypotension Persist?

- Progressive portal HTN
  - Increased NO production
- Progressive cirrhosis/liver dysfunction
  - Decreased NO clearance
- Cardiac dysfunction

# Cardiac Dysfunction in HRS

- Reduced cardiac output may contribute to effective hypovolemia and renal hypoperfusion »»» HRS
- First suggested by Tristani, et al. in 1967
- Few studies have assessed cardiovascular function in advanced cirrhosis
- Several studies have shown impaired cardiac function in patients with HRS

# Cardiac Dysfunction in HRS

- 2005: Ruiz-del-Arbol, et al.
- Longitudinal study
- N = 66 non-azotemic cirrhotics with ascites
- Measures of circulatory function
  - Systemic hemodynamics (Swan-Ganz catheter)
  - Plasma levels of vasoactive systems
- Repeat measurements made in those who developed HRS (n = 27)

**Table 1. Baseline Measurements in Patients Who Did Not Develop Hepatorenal Syndrome (Group A) and Baseline and Follow-up Measurements in Patients Who Presented With Hepatorenal Syndrome (Group B)**

|                                     | Group A (n = 39)      |  | Group B (n = 27)      |                        |
|-------------------------------------|-----------------------|--|-----------------------|------------------------|
|                                     | Baseline Measurements |  | Baseline Measurements | Follow-up Measurements |
| Serum bilirubin (mg/dL)             | 2.7 ± 1.9             |  | 3.8 ± 3.9             | 4.3 ± 3.9              |
| Serum albumin (g/L)                 | 24 ± 4                |  | 24 ± 5                | 24 ± 4                 |
| Prothrombin index (%)               | 64 ± 14               |  | 59 ± 14               | 51 ± 13††††            |
| Child-Turcotte-Pugh score (points)  | 9.7 ± 1.3             |  | 9.9 ± 1.3             | 10.8 ± 2.1†            |
| MELD score (points)                 | 13.7 ± 4.0            |  | 15.8 ± 4.6            | 25.7 ± 6.8††††         |
| Serum creatinine (mg/dL)            | 0.85 ± 0.18           |  | 1.05 ± 0.26***        | 3.03 ± 1.49†††††       |
| Serum sodium (mmol/L)               | 134.5 ± 4.8           |  | 132.6 ± 4.6           | 127.0 ± 5.1††††        |
| Urinary sodium (mmol/L)             | 17.4 ± 18.9           |  | 7.0 ± 6.1***          | 4.0 ± 4.5†             |
| MAP (mmHg)                          | 88 ± 9                |  | 83 ± 9*               | 75 ± 7††††             |
| HR (bpm)                            | 87 ± 15               |  | 85 ± 13               | 82 ± 14                |
| RAP (mmHg)                          | 6.7 ± 2.5             |  | 6.9 ± 2.6             | 5.7 ± 2.2†             |
| PAP (mmHg)                          | 15.2 ± 3.8            |  | 14.3 ± 4.3            | 12.8 ± 2.8††           |
| PCWP (mmHg)                         | 9.2 ± 3.2             |  | 9.2 ± 2.6             | 7.5 ± 2.6††††          |
| CO (L/min)                          | 7.2 ± 1.8             |  | 6.0 ± 1.2**           | 5.4 ± 1.5†††           |
| SVR (dyne · s/cm <sup>-5</sup> )    | 962.0 ± 236.4         |  | 1,058.6 ± 265.6       | 1,096.1 ± 327.6        |
| Stroke volume (mL/beat)             | 85.2 ± 17.0           |  | 73.2 ± 18.9*          | 65.3 ± 18.8†           |
| Stroke work (gm-m)                  | 91.3 ± 17.9           |  | 75.3 ± 22.9**         | 62.7 ± 21.3††††        |
| Left ventricular stroke work (gm-m) | 140.0 ± 32.6          |  | 114.2 ± 43.5*         | 88.5 ± 32.3††††        |
| Plasma renin activity (ng/mL · hr)  | 3.1 ± 2.3             |  | 9.9 ± 5.2****         | 17.5 ± 11.4††††        |
| Plasma aldosterone (ng/dL)          | 32.0 ± 30.7           |  | 130.5 ± 69.4***       | 202.5 ± 130.0††††      |
| Plasma norepinephrine (pg/mL)       | 221.6 ± 68.2          |  | 571.1 ± 241.1****     | 965.0 ± 502.5††††      |
| WHVP (mmHg)                         | 28.0 ± 4.0            |  | 30.5 ± 4.0*           | 29.5 ± 5.0             |
| FHVP (mmHg)                         | 11.5 ± 3.0            |  | 11.0 ± 4.0            | 8.5 ± 3.5††            |
| HVPG (mmHg)                         | 16.5 ± 3.0            |  | 19.5 ± 3.0***         | 21.0 ± 4.0††           |
| HBV (mL/min)‡                       | 1,123 ± 328.0         |  | 948 ± 221.1           | 713 ± 188.4††††        |

NOTE. Data are presented as mean ± SD.

Abbreviations: MELD, Model for End-Stage Liver Disease; MAP, mean arterial pressure; HR, heart rate; RAP, right atrial pressure; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedged pressure; CO, cardiac output; SVR, systemic vascular resistance; WHVP, wedged hepatic venous pressure; FHVP, free hepatic venous pressure; HVPG, hepatic venous pressure gradient; HBF, hepatic blood flow.

\* $P < .05$ ; \*\* $P < .01$ ; \*\*\* $P < .005$ ; \*\*\*\* $P < .001$  with respect to baseline values of group A.

† $P < .05$ ; †† $P < .01$ ; ††† $P < .005$ ; †††† $P < .001$  with respect to baseline values of group B.

‡A hepatic extraction greater than 10% was required for the calculation of hepatic blood flow in 15 patients of group A and 19 patients of group B.

# Cardiac dysfunction in HRS

## ■ Results

- No differences in SVR or HR between groups
- 10 variables with significant differences between both groups (including CO)
- Only 2 variables independently associated with development of HRS
  - Cardiac output (RR: 5.8; 95% CI: 6.5-150.3;  $p < .05$ )
  - Plasma renin activity (RR: 31.3; 95% CI 1.3-25.2;  $p < .05$ )

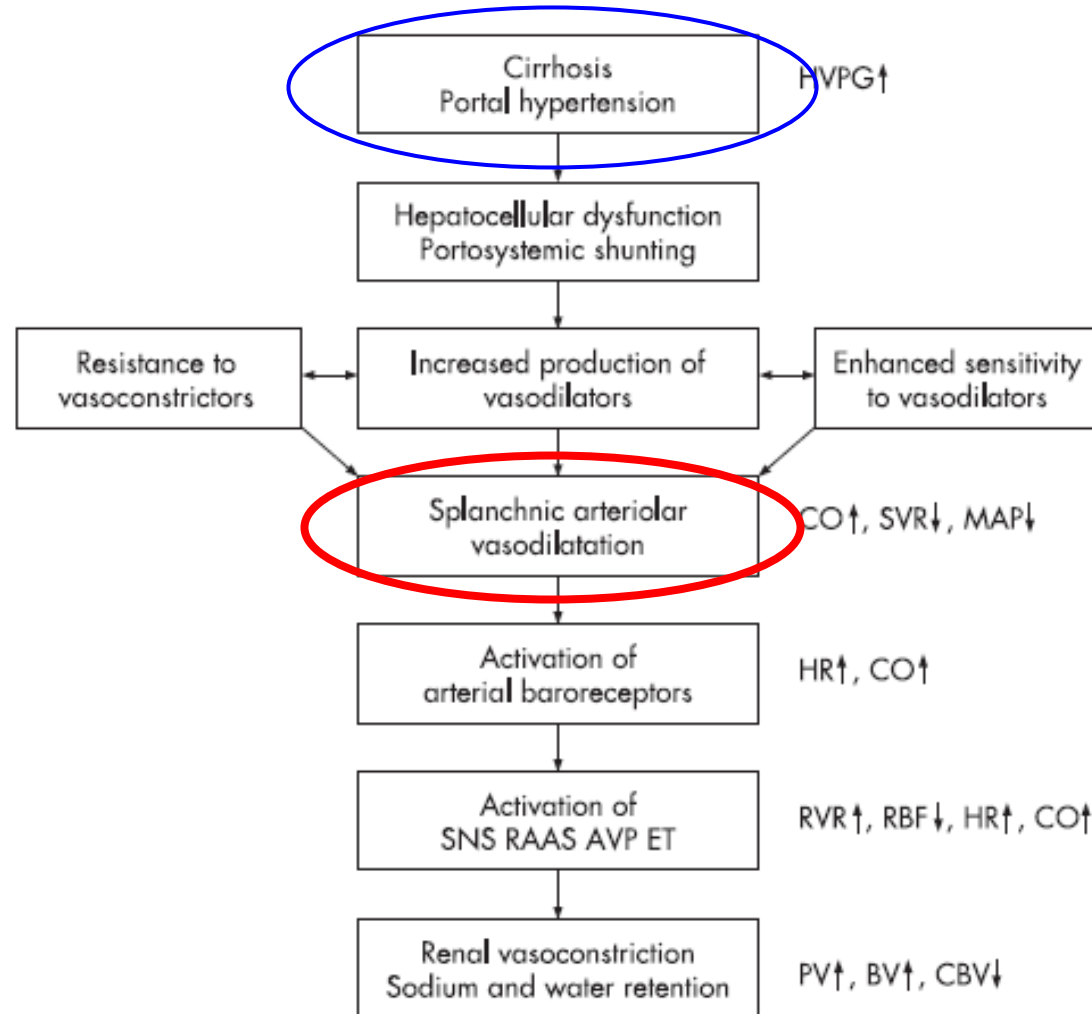
# Cardiac dysfunction in HRS

- Impaired chronotropic response?
  - No difference in HR between groups
  - Marked differences in SNS activation
- Alcoholic cardiomyopathy?
  - 35/66 patients with cirrhosis from EtOH
- Intrinsic LV dysfunction?

# Cirrhotic Cardiomyopathy

- Mechanisms not entirely clear
- Distinct from alcoholic heart muscle disease
- Blunted contractile response to stresses
  - Negative inotropic effects of NO and bile acids
  - Defective or decreased number of  $\beta$ -receptors
- Diastolic dysfunction (echo, autopsy)
- Systolic dysfunction unmasked by physical or pharmacological stress?
  - TIPS (rapid increase in preload w/portal decompression)
  - Normalizes with time

# Treatment of HRS



# Treatment of HRS

- Vasoconstrictors
  - Often combined with albumin
  - Vasopressin analogues (Terlipressin)
  - Midodrine and Octreotide
- TIPS
- MARS (“Liver dialysis”)
- Liver Transplantation

# Treatment of HRS

- Limited data
  - < 20 clinical studies with Terlipressin
  - Very few RCTs
  - Most only assess response to therapy
  - Limited data on survival
- Variability between studies
  - Study design
  - Dose titration and schedule
  - Duration of therapy

# Terlipressin

- Synthetic vasopressin analogue
- Most studied drug for treatment of HRS
- Mechanism: V-1 receptor agonist
- Splanchnic vasoconstriction
- Adverse events (arrhythmia, ischemia) <5%
- IV bolus dosing
- **NOT AVAILABLE IN THE UNITED STATES**

# Meta-analysis on Terlipressin in HRS

- Fabrizi, et al. 2006
- 10 clinical trials (n = 154)
  - 5 prospective (2 RCTs)
- Outcome measures
  - Primary: Rate of responders (reversal of HRS)
  - Secondary: Recurrence of HRS after therapy
  - Drop-out rate (0%)
- 6/11 studies with data on recurrence
- No predictive factors of response to therapy found

Table 6. Design of clinical trials

| Authors                                 | Terlipressin dose, mg/day | Terlipressin duration (days) | Concomitant plasma-expander therapy |
|---|---------------------------|------------------------------|-------------------------------------|
| Hadengue <i>et al.</i> <sup>17</sup>    | 2.0                       | 2.0                          | No                                  |
| Duhamel <i>et al.</i> <sup>18</sup>     | 1.0–2.0                   | 6.3+                         | No                                  |
| Mulkay <i>et al.</i> <sup>19</sup>      | 2.0                       | 26.0 (8–68)                  | 12 (100%)                           |
| Alessandria <i>et al.</i> <sup>20</sup> | 6.0                       | 7                            | 7 (100%)                            |
| Colle <i>et al.</i> <sup>23</sup>       | 2.0–4.0                   | 9.1 ± 1.3                    | 13 (72.2%)                          |
| Halimi <i>et al.</i> <sup>21</sup>      | 4.0 (1.5–12)              | 7.0 (2–16)                   | No                                  |
| Ortega <i>et al.</i> <sup>22</sup> (2)  | 5.0 ± 0.6                 | 8.5 ± 1                      | 13 (100%)                           |
| Ortega <i>et al.</i> <sup>22</sup> (2)  | 4.7 ± 0.5                 | 7.4 ± 1                      | No                                  |
| Solanki <i>et al.</i> <sup>24</sup>     | 2.0                       | 15.0                         | 11 (91.7%)                          |
| Danalioglu <i>et al.</i> <sup>25</sup>  | 2–4                       | 6 (3–14)                     | 7 (100%)                            |
| Saner <i>et al.</i> <sup>26</sup>       | 6.0                       | 6.0                          | 7 (100%)                            |

Review: Terlipressin in HSR  
 Comparison: 01 Creatinine reversal after terlipressin  
 Outcome: 09 HRS reversal after terlipressin therapy

| Study or sub-category   | HRS reversal (SE) | Weight % | HRS reversal (random) 95% CI | Year |
|---|-------------------|----------|------------------------------|------|
| Hacengue  | 0.6666 (0.1571)   | 7.72     | 0.67 [0.36 - 0.97]           | 1998 |
| Duhamel   | 0.5000 (0.1443)   | 8.81     | 0.50 [0.22 - 0.78]           | 2000 |
| Mulkay  | 0.4166 (0.1423)   | 9.00     | 0.42 [0.14 - 0.70]           | 2001 |
| Alessandria   | 0.6363 (0.1450)   | 8.75     | 0.64 [0.35 - 0.92]           | 2002 |
| Cole  | 0.6111 (0.1149)   | 12.23    | 0.61 [0.39 - 0.84]           | 2002 |
| Halmi   | 0.4444 (0.1171)   | 11.92    | 0.44 [0.21 - 0.67]           | 2002 |
| Ortega  | 0.7692 (0.1168)   | 11.97    | 0.77 [0.54 - 1.00]           | 2002 |
| Ortega (B)  | 0.2500 (0.1530)   | 8.05     | 0.25 [-0.05 - 0.55]          | 2002 |
| Daneloglu   | 0.2857 (0.1707)   | 6.75     | 0.29 [-0.05 - 0.62]          | 2003 |
| Solanki   | 0.4166 (0.1423)   | 9.00     | 0.42 [0.14 - 0.70]           | 2003 |
| Saner   | 0.5714 (0.1870)   | 5.90     | 0.57 [0.20 - 0.94]           | 2004 |
| Total (95% CI)  |                   | 100.00   | 0.52 [0.42 - 0.61]           |      |
| Test for heterogeneity: $\chi^2=13.25$ , $df=10$ ( $P=0.21$ ), $I^2=24.6\%$ |                   |          |                              |      |
| Test for overall effect: $Z=10.59$ ( $P<0.00001$ )                          |                   |          |                              |      |

Review: Terlipressin in HSR  
 Comparison: 01 Creatinine reversal after terlipressin  
 Outcome: 10 HRS recurrence after terlipressin withdrawal in responders

| Study or sub-category   | HRS recurrence (SE) | Weight % | HRS recurrence (random) 95% CI | Year |
|---|---------------------|----------|--------------------------------|------|
| Duhamel   | 0.5000 (0.1443)     | 15.44    | 0.50 [0.22 - 0.78]             | 2000 |
| Mulkay  | 0.4166 (0.1423)     | 15.70    | 0.42 [0.14 - 0.70]             | 2001 |
| Alessandria   | 0.6363 (0.1450)     | 15.35    | 0.64 [0.35 - 0.92]             | 2002 |
| Cole  | 0.6111 (0.1149)     | 19.72    | 0.61 [0.39 - 0.84]             | 2002 |
| Ortega  | 0.7692 (0.1168)     | 19.41    | 0.77 [0.54 - 1.00]             | 2002 |
| Ortega (B)  | 0.2500 (0.1530)     | 14.38    | 0.25 [-0.05 - 0.55]            | 2002 |
| Total (95% CI)  |                     | 100.00   | 0.55 [0.40 - 0.69]             |      |
| Test for heterogeneity: $\chi^2=8.98$ , $df=5$ ( $P=0.11$ ), $I^2=44.3\%$ |                     |          |                                |      |
| Test for overall effect: $Z=7.41$ ( $P<0.00001$ )                         |                     |          |                                |      |

# Midodrine and Octreotide

- Alpha-1 agonist
- Splanchnic vasoconstrictor
- Oral dosing
- Side effects
  - Hypertension
  - Urinary retention
- Somatostatin analogue
- Inhibits glucagon and VIP activity
- Subcutaneous dosing
- Side effects
  - Hypoglycemia

# Midodrine and Octreotide

- Esralian, et al. 2007
- Survival and sustained response to therapy
  - 30 day mortality
  - Serum Cr < 1.5 at day 30
- Retrospective case-control study
  - 60 cases of Type 1 HRS treated
  - 21 matched controls not treated
  - Dx of HRS by IAC criteria
  - Albumin NOT used in treatment of HRS
- Follow up: 1, 3, and 6 months

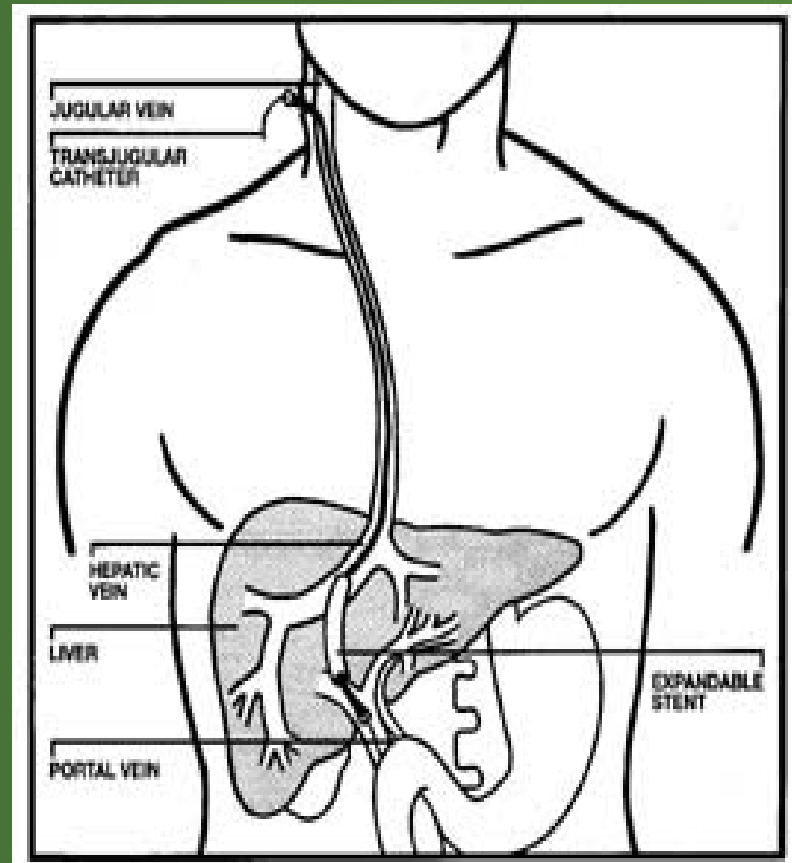
# Midodrine and Octreotide

| 30 Day Outcomes         | Treatment Group | Control Group  | <i>P</i> value |
|-------------------------|-----------------|----------------|----------------|
| Reduction in Creatinine | 24/60<br>(40%)  | 2/21<br>(9.5%) | 0.01           |
| Mortality               | 26/60<br>(43%)  | 15/21<br>(71%) | 0.03           |


- High rate of loss to follow up at 3 and 6 months
- 7/10 patients had sustained response at 3 months
- 72% of treatment group alive at 3 months ( $P = 0.03$ )

# TIPS

- Reduce portal HTN
- Increase EAV
- Reverse splanchnic vasodilatation
- Complications
  - Encephalopathy
  - Shunt stenosis
  - Hemolysis
  - Hyperbilirubinemia



# TIPS

- Small pilot studies
- Improvements in GFR and serum Cr shown
- Many patients ineligible or excluded
  - Childs-Pugh score ( $> 11$  in most series)
  - Severe encephalopathy
- Combining modalities for treatment?
  - Midodrine/Octreotide  TIPS
  - Further improved GFR in responders post-TIPS

# Liver Transplantation

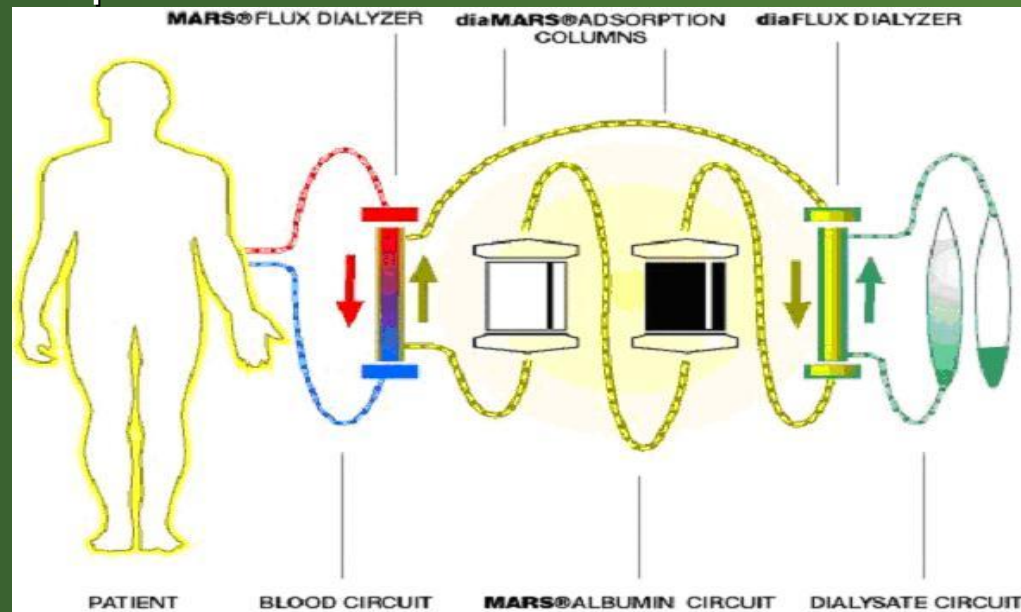
- Treatment of choice for HRS
- Limited by organ availability and mortality of HRS
- Higher rate of complications:
  - Higher post-operative mortality
  - More days in the ICU
  - Increased need for post-op RRT (35% vs. 5% w/o HRS)
- Improvement in renal function
  - Increased GFR post-op vs. decline in non-HRS pts
  - Lower overall GFR compared to non-HRS pts

# Survival after Transplant

- Pre-transplant renal function
- UNOS: 50% at 5 years w/baseline Cr > 2.0
- Single center studies
  - 60% at 3 years vs. 70-80% without HRS
  - 7-10% incidence of ESRD
- Treatment of HRS may improve outcomes

# MARS

- Molecular Adsorbent Recirculating System
- Removes albumin-bound particles (bile acids, cytokines, etc.)
- Developed in Germany; available in the US since 2005
- FDA approval for drug overdoses and poisonings
- Limited experience in US centers



# MARS

- Use in acute on chronic liver failure
- Studies in type 1 HRS
  - Decreased serum Cr (filtration effect?)
  - Few measured hemodynamics
- Experimental therapy
- Role as a bridge to transplant?

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