Complications of liver failure and liver transplantation

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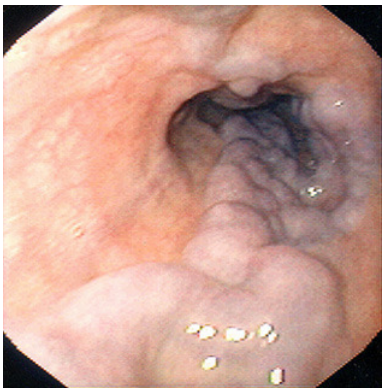
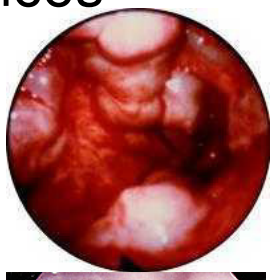
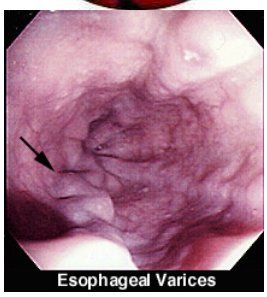
Complications of liver failure

- Variceal bleeding
- Hepatorenal syndrome
- Hepatic encephalopathy & cerebral edema
- Ascites & spontaneous Bacterial Peritonitis
- Hepatopulmonary syndrome
- Portopulmonary hypertension

Esophageal varices



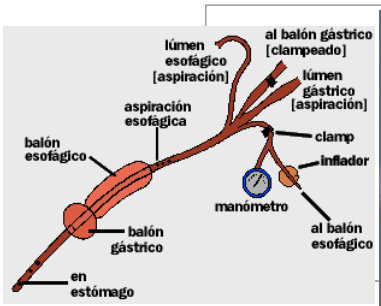


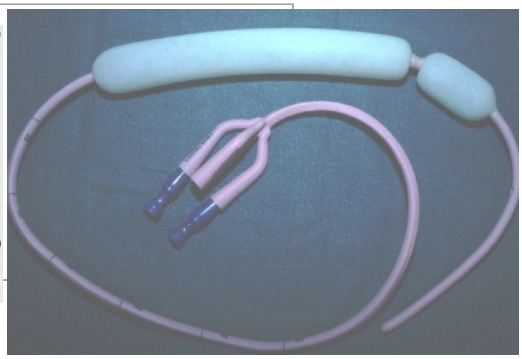


Sengstaken tube

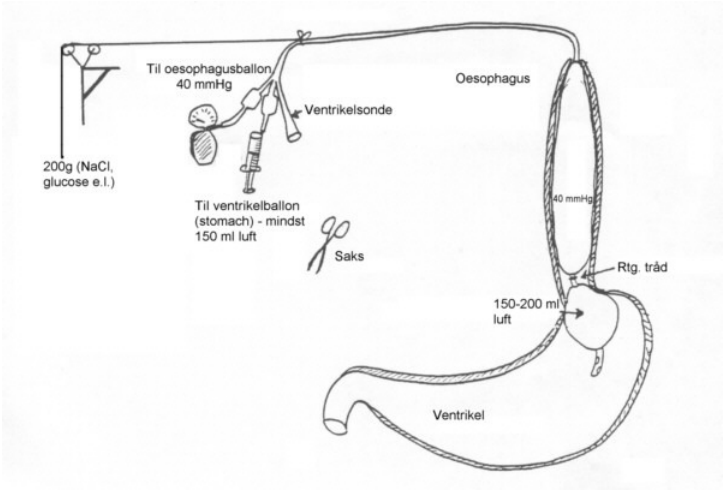
- There are three channels
  - 1: to aspirate blood from the patient's stomach.
  - 2: to inflate a balloon in his stomach to anchor the tube.
  - 3: to inflate another balloon in his oesophagus to compress his varices.
- Minnesota tube has a fourth lumen which allows intermittent suctioning above the oesophageal balloon
- usually deflated in about 24 hours

Sengstaken tube





Sengstaken tube application



Variceal bleeding: balloon tamponade

- Complications
  - Pressure necrosis
  - Migration into pharynx with airway obstruction
  - Rupture of the oesophagus
  - Mediastinitus
  - Pulmonary aspiration
  - Damage to esophageal mucosa and stricture
- Balloons should be inflated by gas because water has weight and changes the shape leading to malfunction

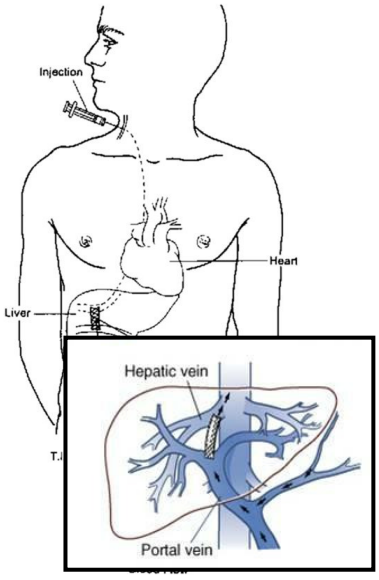
Variceal bleeding: endoscopic intervention

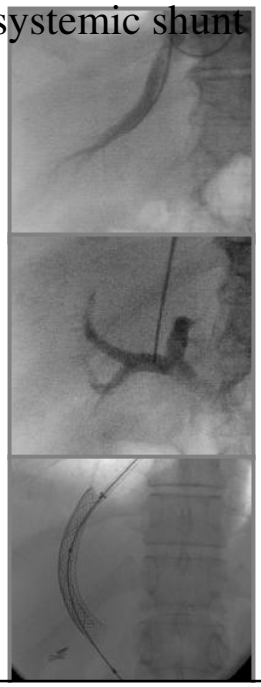
- Band ligation
- Sclerotherapy
- Tissue adhesive (cyanoacrylate)
- Endoloop, argon laser

Other treatments

- Prophylactic antibiotics
- Hemoactive drugs: octreotide, terlipressin
- Recombinant factor VII
- TIPS
- Shunt surgery

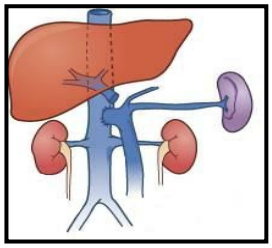
■transjugular intrahepatic portosystemic shunt



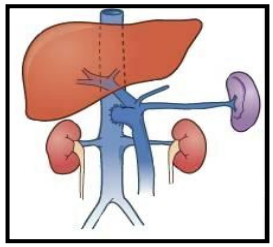


PortocavalTotal Shunts

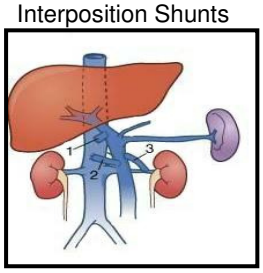
End to Side Portocaval



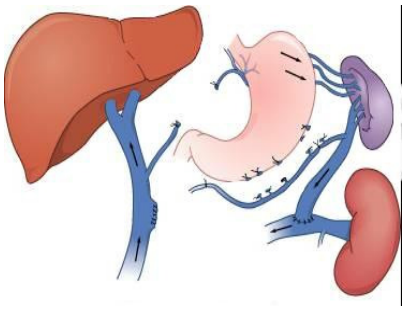
Side to Side Portocaval



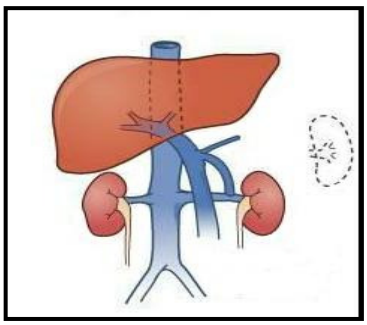
Interposition Shunts



Renoportal (selective) shunts



Distal Splenorenal Shunt



Central Splenorenal Shunt

HRS: definition

- *Type 1 hepatorenal syndrome* is an acute form of HRS in which renal failure occurs spontaneously in patients with severe liver disease and is rapidly progressive. Predicted mortality of more than 80% in 2 weeks.
- *Type 2 hepatorenal syndrome* usually occurs in patients with diuretic resistant ascites. Renal failure has a slow course, in which it may deteriorate over months.

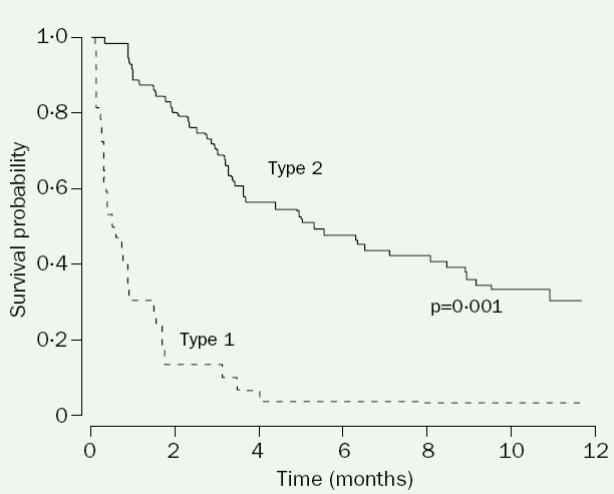


Figure 2: **Survival of patients with cirrhosis after the diagnosis of type 1 or type 2 HRS**

HRS: pathophysiology

- marked reduction in renal blood flow that is caused by the intense vasoconstriction of the renal circulation counteracting the pathologic vasodilatation of the splanchnic circulation.
- The kidneys are structurally normal

HRS: definition

Table. Definition of hepatorenal syndrome type 1 [4]

Major criteria	Minor criteria
1. Chronic or acute hepatic disease and liver failure with portal hypertension 2. Serum creatinine level > 1.5 mg/dL (133 μM/L) or 24-hour creatinine clearance < 40 mL/min (0.67 mL/s) 3. Absence of shock, ongoing bacterial infection, recent use of nephrotoxic drugs, excessive fluid or blood loss 4. No sustained improvement in renal function after volume expansion with 1.5 L isotonic saline solution 5. No clinical evidence of proteinuria, obstructive uropathy or renal parenchymal disease	1. Urine volume < 500 mL/day 2. Urine sodium < 10 mmol/L 3. Urine osmolality > plasma osmolality 4. Urine red blood cell count < 50 per high-power field 5. Serum sodium < 130 mmol/L

Arroyo V, Gines P, Gerbes AL, et al. Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. International Ascites Club. Hepatology 1996;23(1):164-76

HRS: ppt factors

- Infection: SBP
- Hypovolemia
  - large volume paracentesis without plasma expansion
  - Variceal bleed / GI bleeding
- Diuretics
- Nephrotoxic drugs

HRS: treatment options

- Terlipressin and albumin
- Midodrine and octreotide
- Misoprostol
- N-acetyl cysteine
- TIPS
- Renal replacement therapy
- MARS
- OLT

Hepatic encephalopathy: pathogenesis

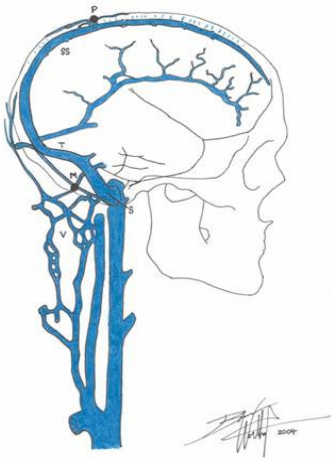
- Alteration of blood brain barrier
  - Provides mechanism where other factors of HE operate
- Gut derived factors
  - Ammonia, mercaptans, phemols, aromatic amino acids (false neurotransmitter)
- Changes in neurocerebral transmission
  - cerebral glutamate
  - γ-Aminobutyric acid (GABA)
  - Endogenous benzodiazepine

TABLE 1. A GRADING SYSTEM FOR HEPATIC ENCEPHALOPATHY.*

GRADE	LEVEL OF CONSCIOUSNESS	PERSONALITY AND INTELLECT	NEUROLOGIC SIGNS	ELECTROENCEPHALOGRAPHIC ABNORMALITIES
0	Normal	Normal	None	None
Subclinical	Normal	Normal	Abnormalities only on psychometric analysis	None
1	Inverted sleep pattern, restlessness	Forgetfulness, mild confusion, agitation, irritability	Tremor, apraxia, incoordination, impaired handwriting	Triphasic waves (5 cycles/sec)
2	Lethargy, slow responses	Disorientation as regards time, amnesia, decreased inhibitions, inappropriate behavior	Asterixis, dysarthria, ataxia, hypoactive reflexes	Triphasic waves (5 cycles/sec)
3	Somnolence but rousability, confusion	Disorientation as regards place, aggressive behavior	Asterixis, hyperactive reflexes, Babinski signs, muscle rigidity	Triphasic waves (5 cycles/sec)
4	Coma	None	Decerebration	Delta activity

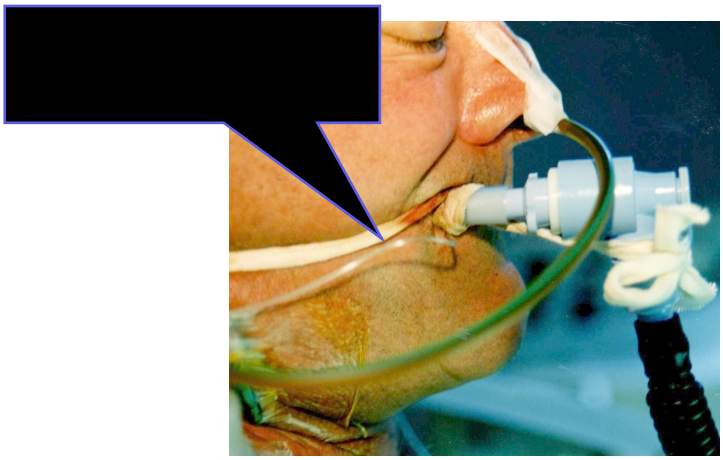
*The system is based on clinical and electroencephalographic features suggested by Gitlin.[1]

Cerebral venous drainage

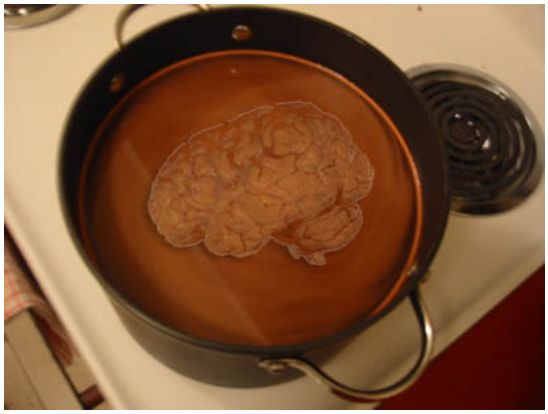


- Avoid jugular venous compression
- Head tilt no more than 30 degrees
- Endotracheal tube fixation by tapes and not string

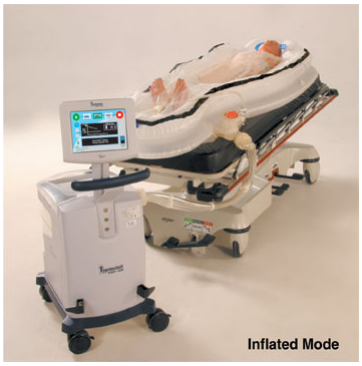
Endotracheal tube fixation



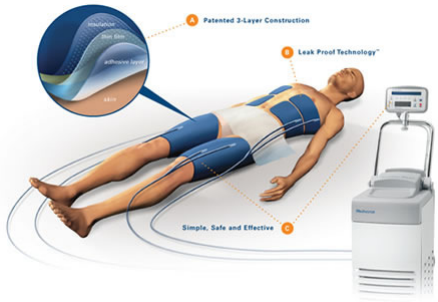
Hot brain is not a happy brain!



Systemic cooling



Thermosuit



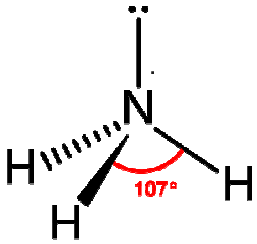
Arctic-Sun

Hypothermia vs normothermia

- Aggressively lowering body temperature is difficult and technology dependent
- Should at least allow normothermia and not artificially raise body temperature
- Need to explain to families

Ammonia

Amen – Egyptian Mythical God



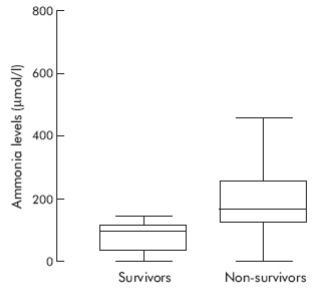


Figure 1 Comparison of arterial ammonia levels at admission between survivors and non- survivors among acute liver failure patients.

Bhatia et al. Gut.2006; 55: 98-104

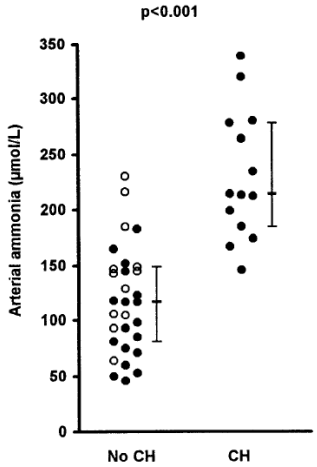
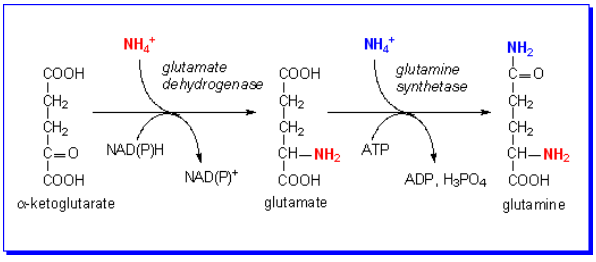


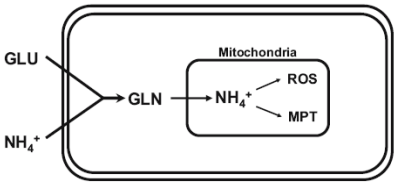
FIG. 1. Arterial plasma ammonia concentration in 30 patients who did not develop cerebral herniation (No CH) and 14 patients who died from cerebral herniation (CH). The *error bars* to the *left* of each group are median, 25th, and 75th percentiles. (○), Patients who underwent liver transplantation (n = 7); (●) patients who died from other reasons (n = 5).

Clemmesen JO, etal. Hepatology. 1999 Mar;29(3):648-53.

Ammonia, glutamine and cerebral edema



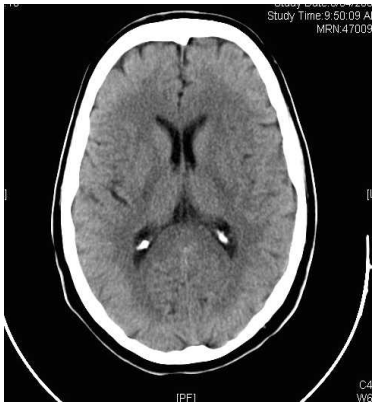
Ammonia, glutamine and cerebral edema:Trojan Horse Theory

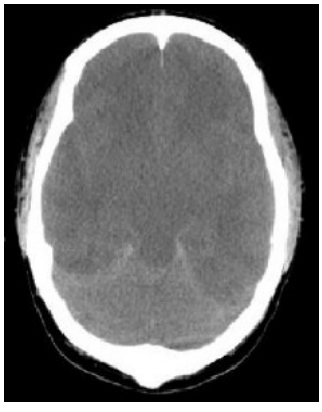


reactive oxygen species (ROS)
mitochondrial permeability transition (MPT)

Norenberg MD, etal. Metab Brain Dis. 2007 Dec;22(3-4):219-34.

Cerebral edema



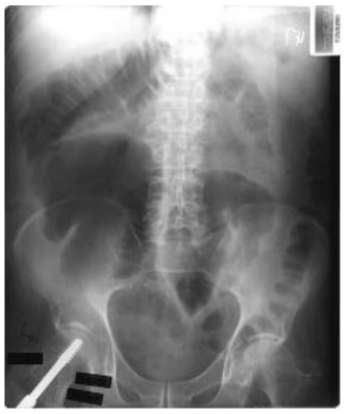


Oral lactulose

- Cathartic effect:
  - two to four soft, acidic (pH less than 6) stools daily.
  - For most patients the daily dose is between 30 and 60 g.
- Acidic effect:
  - creates hostile environment to urease-producing intestinal bacteria and promote the growth of non–urease-producing lactobacilli, resulting in reduced production of ammonia in the colonic lumen.
  - net movement of ammonia from the blood into the bowel lumen.

Side effects of lactulose

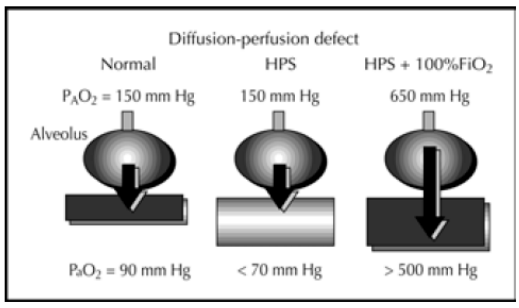
- Over diarrhea
- Gas forming: abdominal distension, respiratory embarrassment



Hepatopulmonary syndrome: clinical triad

- liver disease: usually chronic
- abnormal pulmonary gas exchange
  - Hypoxia (increased alveolar-arterial oxygen gradient (>20 mm Hg)) or
  - hypoxemia with PaO2 <70 mm Hg
- intrapulmonary vascular dilatations
  - a combination of high-flow perfusion and increased depth for diffusion

Figure 1. Capillary dilatations result in diffusion-perfusion abnormalities



In these abnormalities, unsaturated venous blood passes through dilated vessels and is inadequately saturated with oxygen because of a combination of high-flow perfusion and increased depth for diffusion. The hypoxia observed under these circumstances is readily reversed while breathing 100% FiO_2. HPS, hepatopulmonary syndrome; PAO_2, alveolar oxygen; PaO_2, arterial oxygen.

Hepatopulmonary Syndrome

- Platypnea: defined as dyspnea induced by the upright position and relieved by recumbency
- Orthodeoxia: arterial deoxygenation accentuated in the upright position and relieved by recumbency

Hepatopulmonary syndrome: investigation

- contrast-enhanced echocardiography
  - Direct arteriovenous communication allows the microbubbles to pass through the lung, the bubbles are observed in the left atrium
- lung perfusion scanning with technetium-labeled macroaggregated albumin.
  - Macroaggregated albumin that passes through the lung emerges on the left side is quantified by imaging over the brain.
- Pulmonary angiography
  - Insensitive, only for large AV malformations

Hepatopulmonary syndrome: treatment

Table 3. Pharmacologic interventions in hepatopulmonary syndrome

Agent	Effect
β-adrenergic	Increase pulmonary vascular tone
Almitrine bismesylate	Improve V/Q mismatch
Chemotherapy/corticosteroids	Treat underlying liver disease, *eg,* with autoimmune disease
Others	
Methylene blue	
Allium sativum (garlic)	
Plasma exchange	
Sympathomimetics	

Hepatopulmonary syndrome: treatment

- PEEP
  - Paradoxical worsening
- ECMO
- Methylene blue is an oxidizing agent that blocks the stimulation of soluble guanylate cyclase by nitric oxide and therefore its vasodilative effect
- One patient report in NEJM (Oct 1994)!

Donor factors leading to graft dysfunction

- Age of donor
- Size of liver: small for size syndrome
- Donor liver function
- ABO compatibility
- use of vasopressors
- Hypernatremia
- cardiopulmonary arrest
- Prolonged cold ischemic time

Technical complications leading to allograft dysfunction

- Abdominal bleeding
  - Anastomosis bleeding
  - Hematoma formation
- Vascular complications
  - Hepatic artery thrombosis
  - Portal vein thrombosis
- Biliary complications
  - Biliary leakage
  - Biliary stricture
- Prolonged warm ischemic time

Recipient factors leading to graft dysfunction

- Child Pugh score
- Preoperative gastrointestinal bleeding
- Mechanical ventilation
- Pretransplant renal failure
- Use of inotropes
- sepsis

PTLF: Treatment principles

- Amend reversible causes
  - Surgically correct anastomotic leakage
  - Hematoma evacuation
  - Control sepsis
- Supportive measures
  - Correct renal failure
  - Nutritional support
  - Correct coagulopathy
  - Maintain hemodynamic stability
- Retransplantation

Onset of graft dysfunction

Post transplantation liver failure (PTLF)

❑ Early (0-7 days)

- Acute rejection
- Small for size syndrome
- Primary non-function
- Preservation or reperfusion injury
- Hepatic artery thrombosis

❑ Delayed (1 wk to 2 mths)

- Cellular rejection
- Infection
- post-transplant lymphoproliferative disorder (PTLD)

❑ Late (>2 mths)

- Rejection
- Vascular occlusion
- Biliary complications
- Recurrent disease
- Drug hepatotoxicity
- Neoplasm

Early allograft dysfunction (EAD)

- defined by the presence of at least one of the following between 2 and 7 days after liver transplantation:
  1. serum bilirubin >10 mg/dl (170umol/L)
  2. prothrombin time (PT) > or =17 sec
  3. hepatic encephalopathy

National Institute of Diabetes and Digestive and Kidney Diseases Liver Transplantation Database

Early allograft dysfunction

- Primary non function
- Primary dysfunction
- Primary poor function
- Delayed graft function

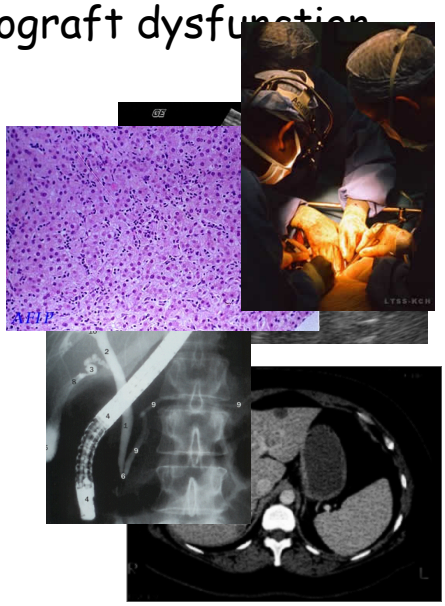
EAD

- 161 out of 710 (23%) liver transplant recipients developed EAD
- Median hospital stay was 22 days for patients with EAD and 15 days for patients without (p=0.0001)
- graft survival with EAD was 61% vs 79% in patients without (p<0.0001)
- 3 year patient survival for patients with EAD was 68% vs 83% in patients without (p<0.0001)

Deschenes M et al. Transplantation. 1998 Aug 15;66(3):302-10

Investigation for allograft dysfunction

- Doppler ultrasound
- Computed tomography
- ERCP
- Liver biopsy
- Explorative laparotomy



Treatment principles

- Amend reversible causes
  - Surgically correct anastomotic leakage
  - Hematoma evacuation
  - Control sepsis
- Maintain stable internal milieu
  - Correct renal failure
  - Nutritional support
  - Correct coagulopathy
  - Maintain hemodynamic stability

MARS

Molecular Adsorbent Recirculation System

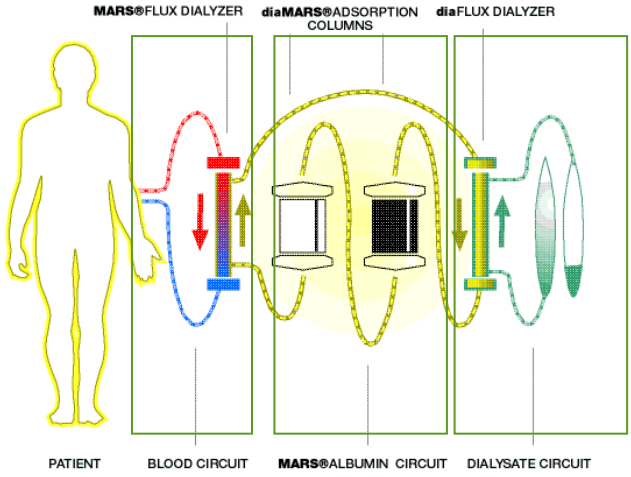
Artificial albumin dialysis that can remove both albumin-bound and water soluble putative toxins

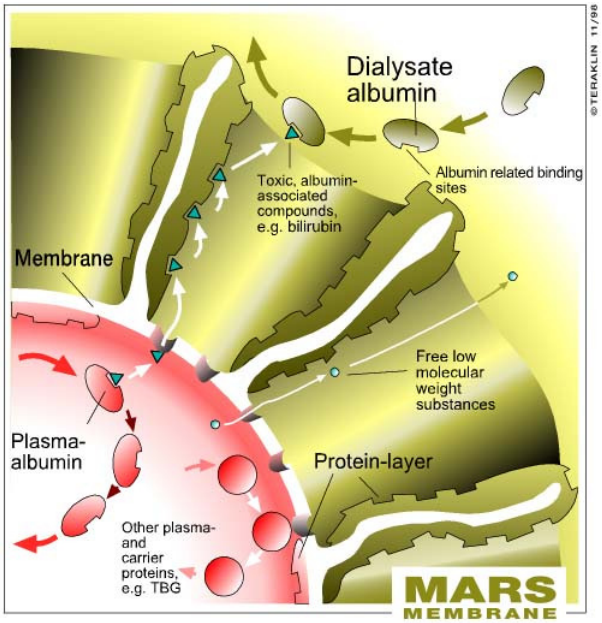
Developed by Mitzner and Stange, at Rostock, Germany in 1993

World wide clinical application begins 2000

Introduced to Queen Mary Hospital at 2002

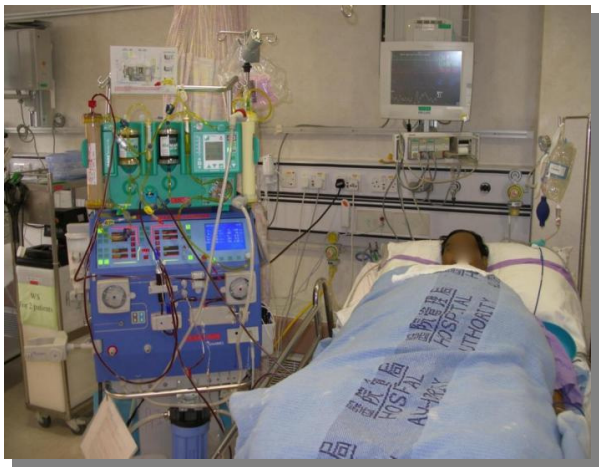
MARS circuit





ELIMINATION OF TOXINS

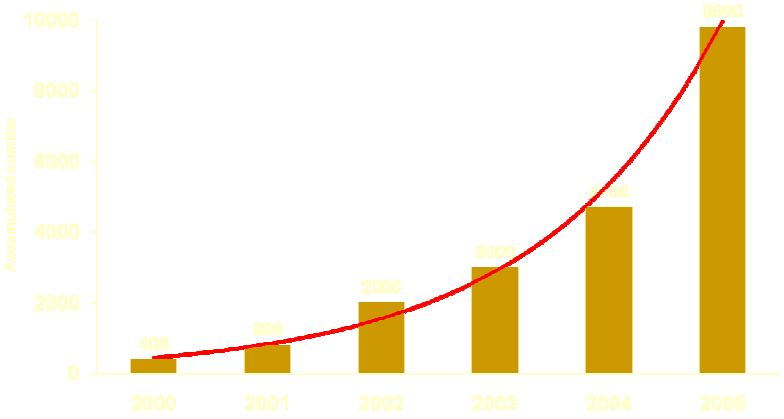
MARS membrane, Magnified view



before treatment

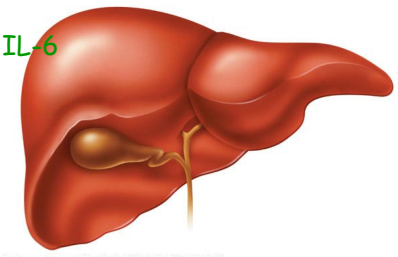
after treatment

MARS: World statistics



International MARS Registry
Annual Report 2005

Bilirubin
Bile acids
Cytokines: TNF-alpha, IL-6
Aromatic amino acid
GABA like substance
Maganese, Copper
Nitric oxide
Short and middle chain fatty acid



Ammonia
Urea, creatinine

(1) Sorkine. Crit Care Med 2001;29
(2) Awad. Surgery 2001;130
(3) Novelli. Transpl Proc 2001;33
(4) Mitzner. J Am Soc Nephr 2001;12
(5) Stange. Liver Transpl 2000;6
(6) Sorkine. Transpl Proc 2001;33
(7) Schmidt. Liver transpl 2001;7

	Before MARS	Std. Deviation	After MARS	Std. Deviation	p value
Platelet	86.13	43.424	85.45	39.013	0.785
Urea	18.835	9.9103	9.41	4.723	**<0.001**
Creatinine	273.40	127.043	155.95	74.775	**<0.001**
Bilirubin	596.00	264.985	474.58	201.206	**<0.001**
PT	20.68	7.729	19.412	7.542	**0.005**
Albumin	33.10	4.623	36.32	5.507	**<0.001**
AST	264.55	533.143	234.25	442.956	0.094
ALT	232.88	536.786	225.13	531.596	0.373
NH3	80.87	72.553	51.20	49.233	**<0.001**
Bile acid	134.473	85.4899	72.921	54.6508	**<0.001**
IL-6	79.194	96.6851	126.819	143.1005	**0.007**
TNF	19.545	7.8594	18.343	6.8922	0.108

Denotes statistical significance with Wilcoxon Signed-Rank Test

Physiological benefits of MARS

- Improvement of intracranial pressure
  - Pugliese F, et al. Transplant Proc. 2007 Jul-Aug;39(6):2042-4.
  - Sen S etal. Crit Care Med, Volume 34(1).January 2006.158-164
- Reduces portal pressure
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  - Donati G etal. Aliment Pharmacol Ther. 2007 Sep 1;26(5):717-26.
- Improves hemodynamic parameters
  - Catalina MV etal. Liver Int. 2003;23 Suppl 3:39-43
  - Lai WK etal. Intensive Care Med. 2005 Nov;31(11):1544-9.
  - Stefoni S, etal. Int J Artif Organs. 2006 Feb;29(2):207-18.

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