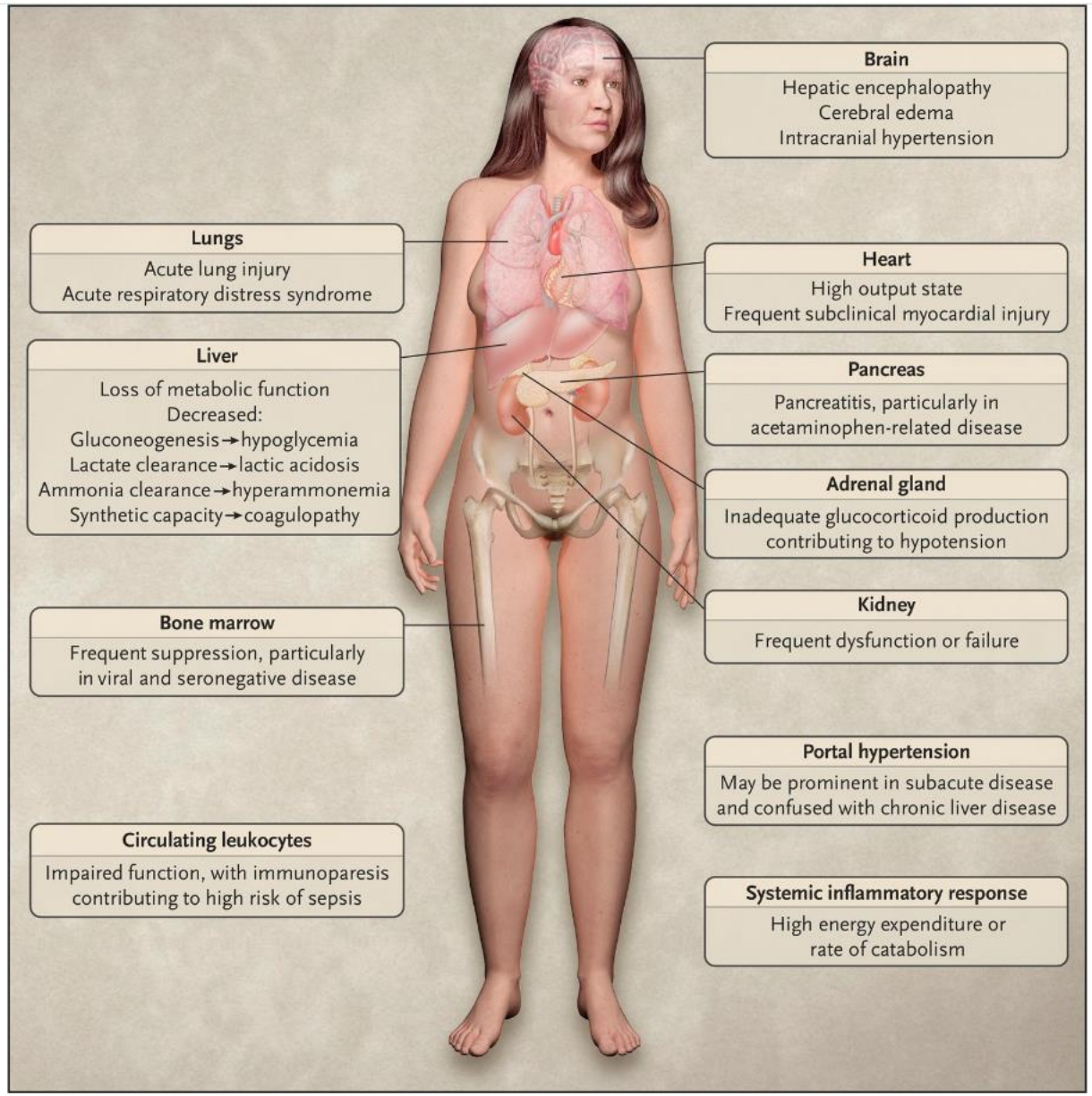
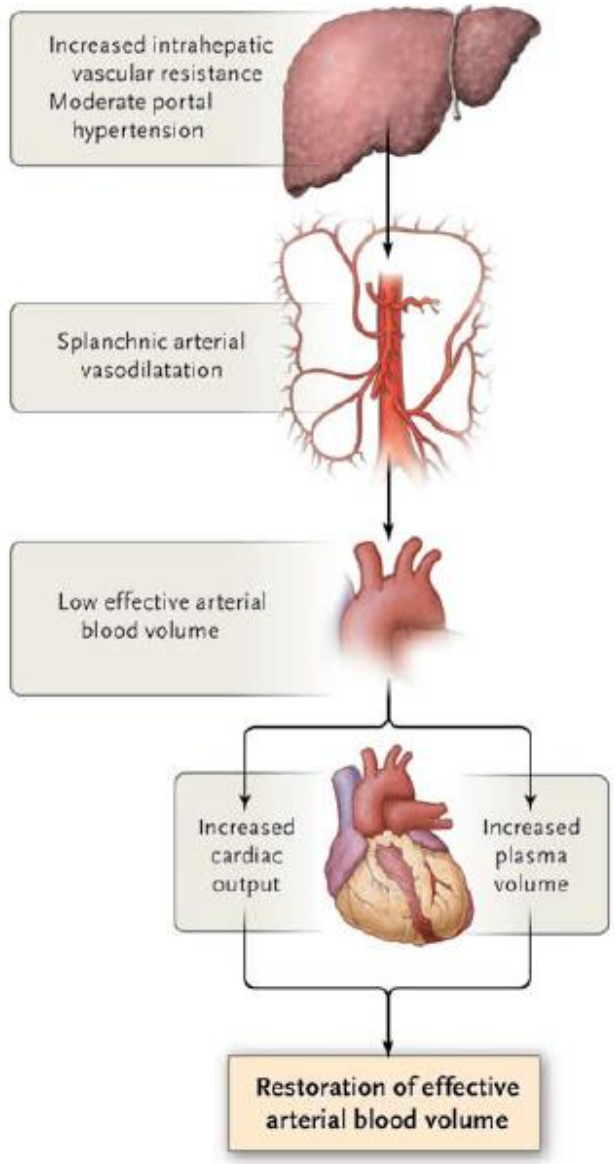
Acute-on-Chronic Liver Failure: A Multiorgan Failure Challenge For The Intensivist

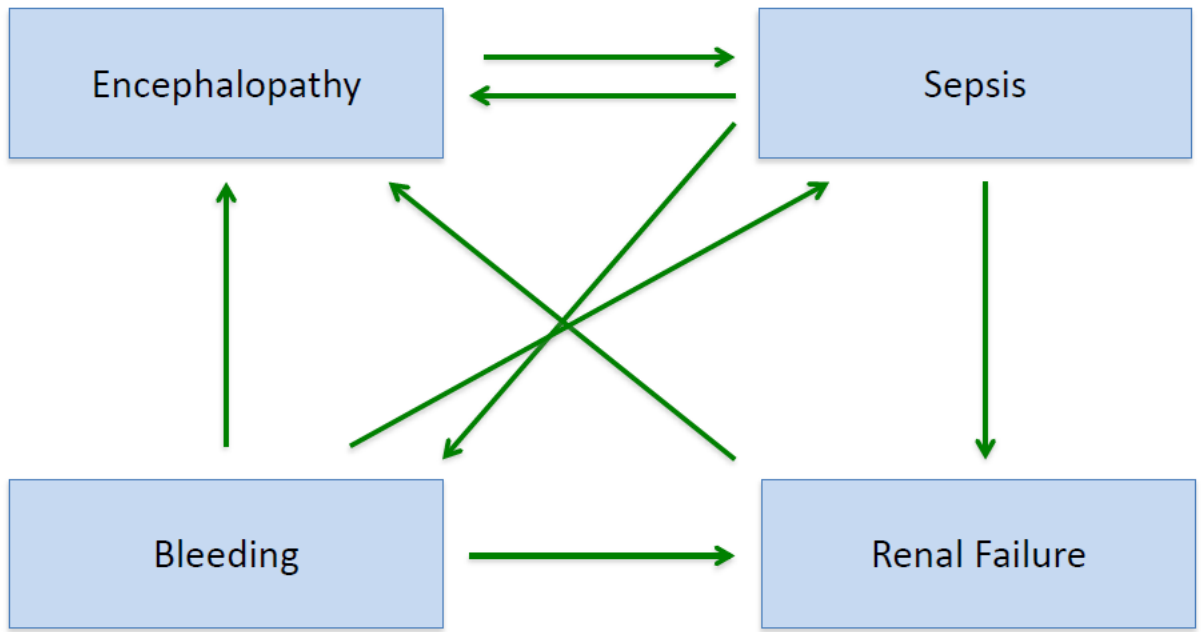
« Debates and consensus »

S. Redant MD, P.M. Honoré MD PhD


Brain
Hepatic encephalopathy
Cerebral edema
Intracranial hypertension
Lungs
Acute lung injury
Acute respiratory distress syndrome
Heart
High output state
Frequent subclinical myocardial injury
Liver
Loss of metabolic function
Decreased:
Gluconeogenesis→hypoglycemia
Lactate clearance→lactic acidosis
Ammonia clearance→hyperammonemia
Synthetic capacity→coagulopathy
Pancreas
Pancreatitis, particularly in acetaminophen-related disease
Adrenal gland
Inadequate glucocorticoid production contributing to hypotension
Bone marrow
Frequent suppression, particularly in viral and seronegative disease
Kidney
Frequent dysfunction or failure
Portal hypertension
May be prominent in subacute disease and confused with chronic liver disease
Circulating leukocytes
Impaired function, with immunoparesis contributing to high risk of sepsis
Systemic inflammatory response
High energy expenditure or rate of catabolism


Increased intrahepatic vascular resistance
Moderate portal hypertension
Splanchnic arterial vasodilatation
Low effective arterial blood volume
Increased cardiac output
Increased plasma volume
Restoration of effective arterial blood volume

The Loop



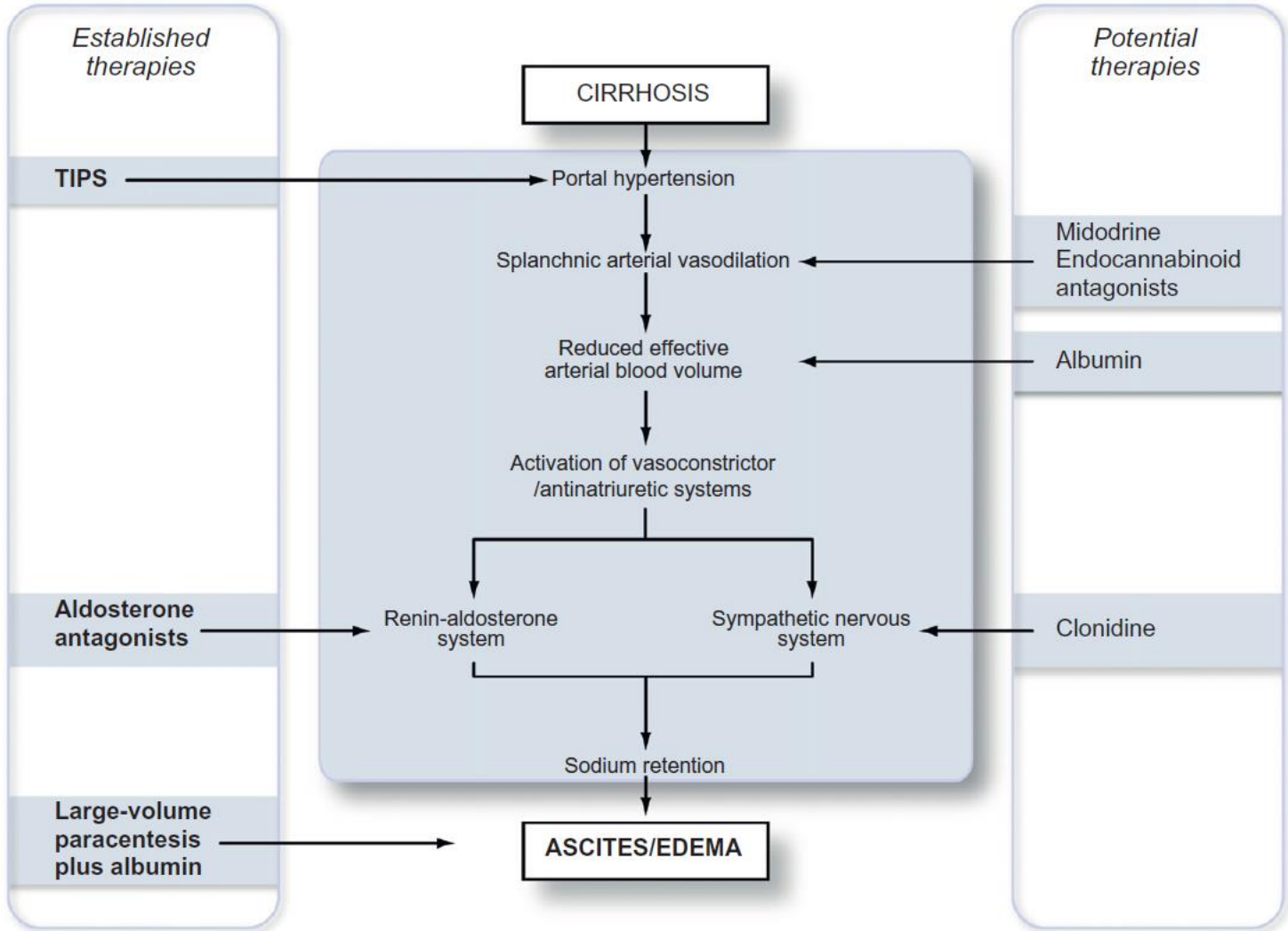


Fig. 1. Schematic representation of the proposed pathogenesis of ascites and edema formation in cirrhosis. Established therapies are given on the left side and potential new therapies on the right. TIPS, transjugular intrahepatic portosystemic shunt.

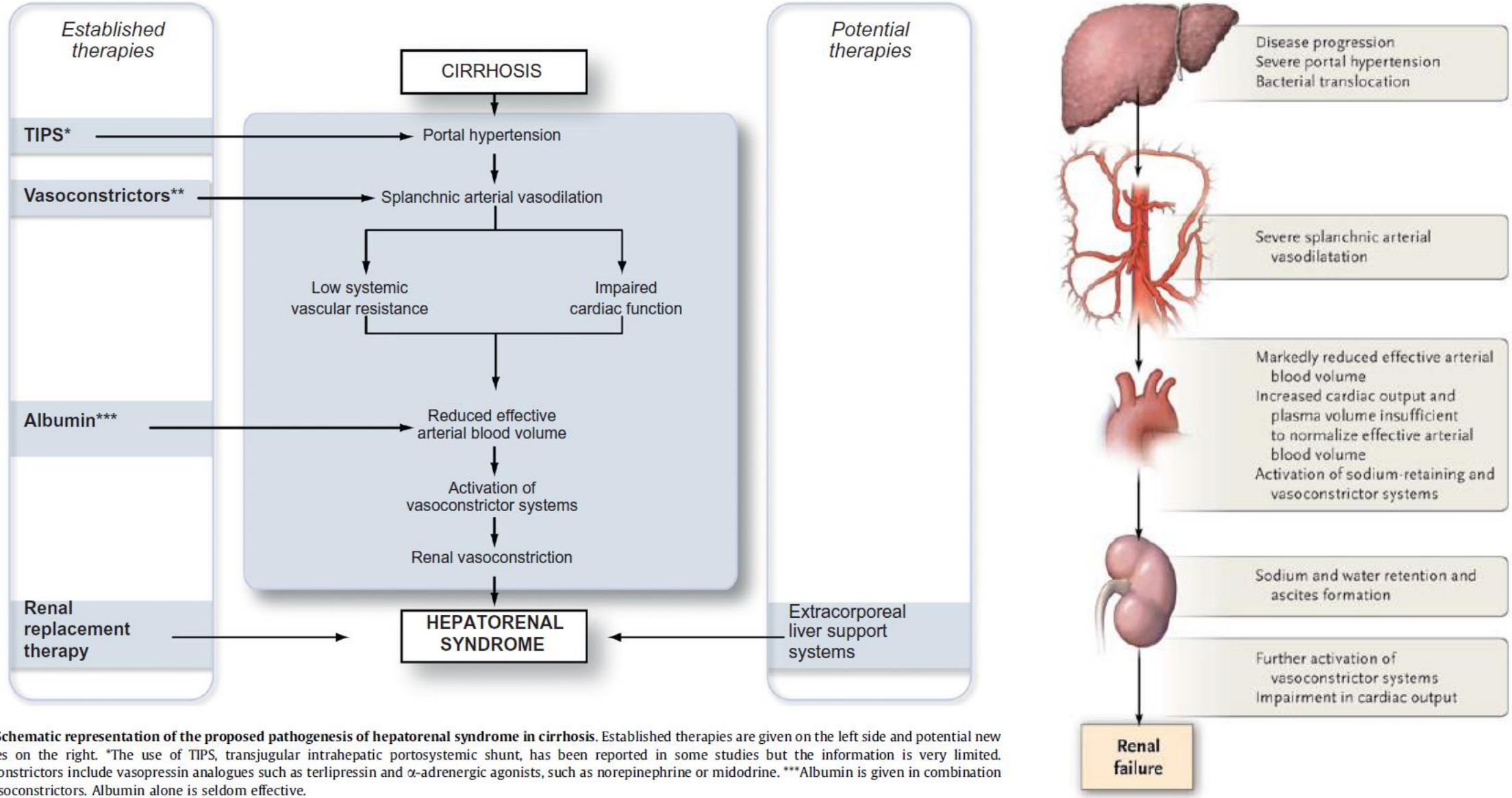


Fig. 3. Schematic representation of the proposed pathogenesis of hepatorenal syndrome in cirrhosis. Established therapies are given on the left side and potential new therapies on the right. *The use of TIPS, transjugular intrahepatic portosystemic shunt, has been reported in some studies but the information is very limited. **Vasoconstrictors include vasopressin analogues such as terlipressin and α-adrenergic agonists, such as norepinephrine or midodrine. ***Albumin is given in combination with vasoconstrictors. Albumin alone is seldom effective.

Table 2. Main Types of Renal Failure in Patients with Cirrhosis.

Disorder	Comments
Hepatorenal syndrome*	The hepatorenal syndrome is diagnosed on the basis of a serum creatinine concentration of more than 1.5 mg/dl (133 μmol/liter), which is not reduced (to <1.5 mg/dl) with the administration of albumin (1 g/kg of body weight) and after a minimum of 2 days off diuretics, along with the absence of current or recent treatment with potentially nephrotoxic drugs, the absence of shock, and the absence of findings suggestive of parenchymal renal disease (urinary excretion of >500 mg of protein/day, >50 red cells/high-power field, or abnormal kidneys on ultrasonography). The syndrome is classified into two types: type 1 is characterized by a doubling of the serum creatinine level to more than 2.5 mg/dl (221 μmol/liter) in less than 2 weeks; type 2 is characterized by a stable or less rapidly progressive course than in type 1.
Hypovolemia-induced renal failure	Hypovolemia is usually due to hemorrhage (in most cases gastrointestinal bleeding) or to fluid losses — either renal losses because of excessive diuretic therapy or gastrointestinal losses as a result of diarrhea from excessive lactulose administration or gastrointestinal infection. Renal failure occurs soon after the onset of hypovolemia.
Parenchymal renal disease	Parenchymal renal disease should be suspected as a cause of renal failure when proteinuria (>500 mg of protein/day), hematuria (>50 red cells/high-power field), or both are present and ideally should be confirmed by renal biopsy, if this procedure is not contraindicated. The differential diagnosis between acute tubular necrosis and the hepatorenal syndrome remains a difficult issue; the presence of renal tubular epithelial cells in the urine sediment favors the diagnosis of acute tubular necrosis.
Drug-induced renal failure	Current or recent treatment with nonsteroidal antiinflammatory drugs or aminoglycosides suggests drug-induced renal failure.

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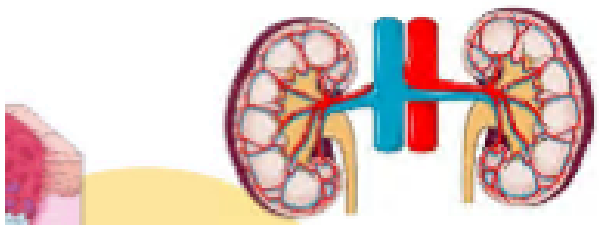
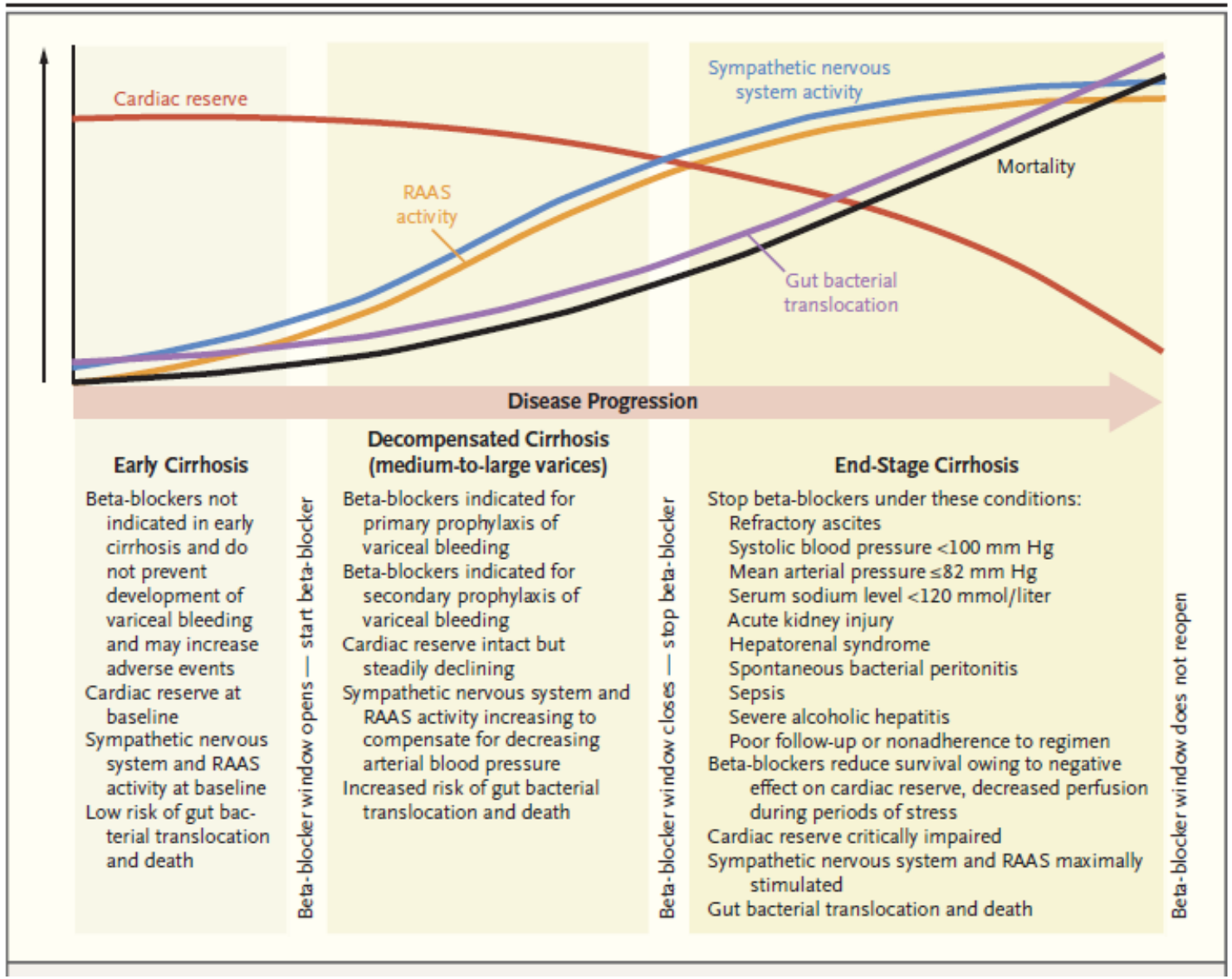
Acute kidney injury

- Treatment of the underlying cause (GIB, infection,…)
- Plasma volume expansion
  - Crystalloids for volume expansion
  - Blood preservation in GIB and hemoglobin < 7g/gL
  - Albumin in case of progressive AKI to exclude HRS (2 consecutive days 1g/kg -maximal dose 100g/day-)

HRS: Albumin (40g/day, maximal duration of therapy 7-14 days) plus vasopressor (terlipressin, alternatively norepinephrine)

- Extracopropreal therapies (define goal: bridging/LT)




Cardiac reserve
Sympathetic nervous system activity
RAAS activity
Mortality
Gut bacterial translocation
Disease Progression
Early Cirrhosis
Beta-blockers not indicated in early cirrhosis and do not prevent development of variceal bleeding and may increase adverse events
Cardiac reserve at baseline
Sympathetic nervous system and RAAS activity at baseline
Low risk of gut bacterial translocation and death
Beta-blocker window opens — start beta-blocker
Decompensated Cirrhosis (medium-to-large varices)
Beta-blockers indicated for primary prophylaxis of variceal bleeding
Beta-blockers indicated for secondary prophylaxis of variceal bleeding
Cardiac reserve intact but steadily declining
Sympathetic nervous system and RAAS activity increasing to compensate for decreasing arterial blood pressure
Increased risk of gut bacterial translocation and death
Beta-blocker window closes — stop beta-blocker
End-Stage Cirrhosis
Stop beta-blockers under these conditions:
Refractory ascites
Systolic blood pressure <100 mm Hg
Mean arterial pressure ≤82 mm Hg
Serum sodium level <120 mmol/liter
Acute kidney injury
Hepatorenal syndrome
Spontaneous bacterial peritonitis
Sepsis
Severe alcoholic hepatitis
Poor follow-up or nonadherence to regimen
Beta-blockers reduce survival owing to negative effect on cardiac reserve, decreased perfusion during periods of stress
Cardiac reserve critically impaired
Sympathetic nervous system and RAAS maximally stimulated
Gut bacterial translocation and death
Beta-blocker window does not reopen

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Coagulation

- Platelets and fibrinogen, not INR is predictive for new onset of major bleeding
- In case of active bleeding platelets > 50/µl and fibrinogen > 1,5 g/dL
- Point of care testing (ROTEM, TEG) may reduce number of administered blood products
- No correction of coagulatory abnormalities prior to routine procedures (i.e. CVC, paracentesis, etc)
- Thromboprophylaxis also in cirrhosis

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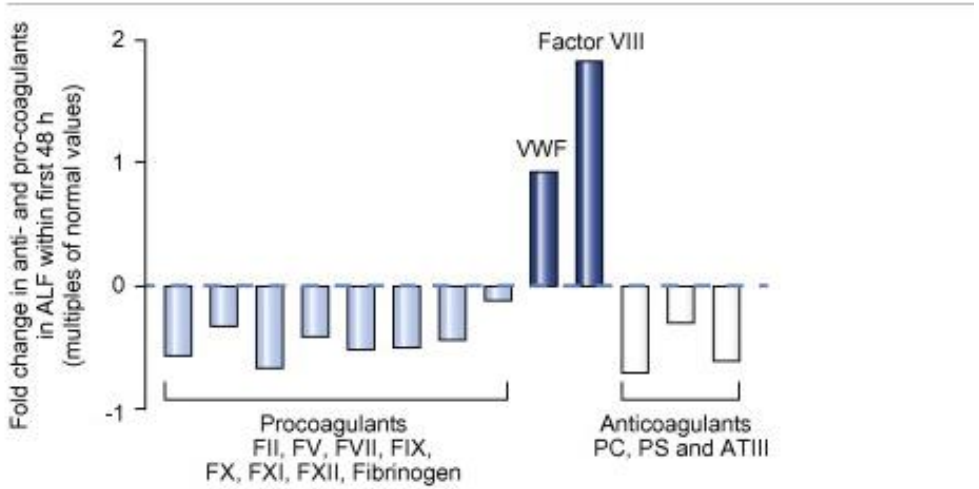
Table 2. Relative changes in pro and anticoagulant factor levels of ALF patients

	Normal range (NR)	Median (IQR)	% change from NR
Procoagulant activity			
Factor II	50-150 IU/dl	24 (17-37)	-59***
Factor VII	50-150 IU/dl	15 (8-29)	-66***
Factor IX	50-150 IU/dl	41 (30-67)	-42**
Factor X	50-150 IU/dl	34 (15-46)	-51***
Factor V	50-150 IU/dl	21 (12-44)	-34***
Factor XI	70-150 IU/dl	51 (38-60)	-50***
Factor XII	50-150 IU/dl	49 (32-69)	-44***
Fibrinogen	1.5-2.5 g/L	1.6 (1.1-2.1)	-1
Endothelial factors			
Factor VIII	70-175 IU/dl	194 (174-248)	94**
VWF:Ag	45-175 IU/dl	288 (240-356)	184***
Anticoagulant activity			
Protein C	70-140 IU/dl	14 (8-28)	-70***
Protein S	66-126 IU/dl	41 (24-66)	-30**
Antithrombin III	45-175 IU/dl	39 (28-50)	-61***

Data represent mean ± SEM, with negative numbers denoting inverse correlation.

**p <0.01, and ***p <0.001 indicate significant correlation.



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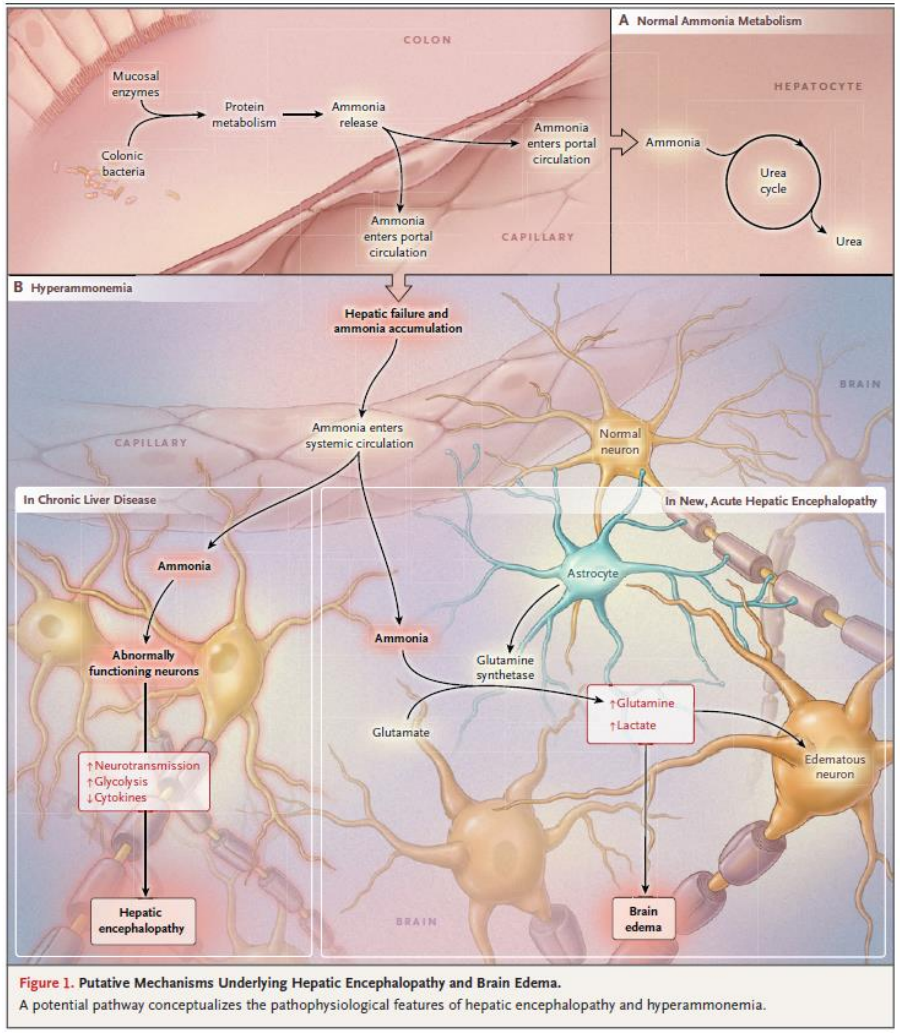
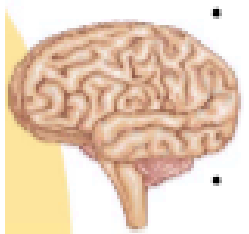
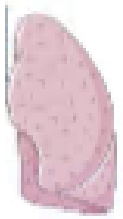


Figure 1. Putative Mechanisms Underlying Hepatic Encephalopathy and Brain Edema.
A potential pathway conceptualizes the pathophysiological features of hepatic encephalopathy and hyperammonemia.

Hepatic encephalopathy



- Treatment of the underlying cause (GIB, infection, hypovolemia,…)
- lactulose (20-30mL lactulose 2-3 times daily)
- Add on rifaximin (400mg tid or 550 mg bid)
- Endotracheal intubation in GCS < 8
- Avoid deep sedation
- Avoid benzodiazepines
- Extracorporeal therapies in refractory cases

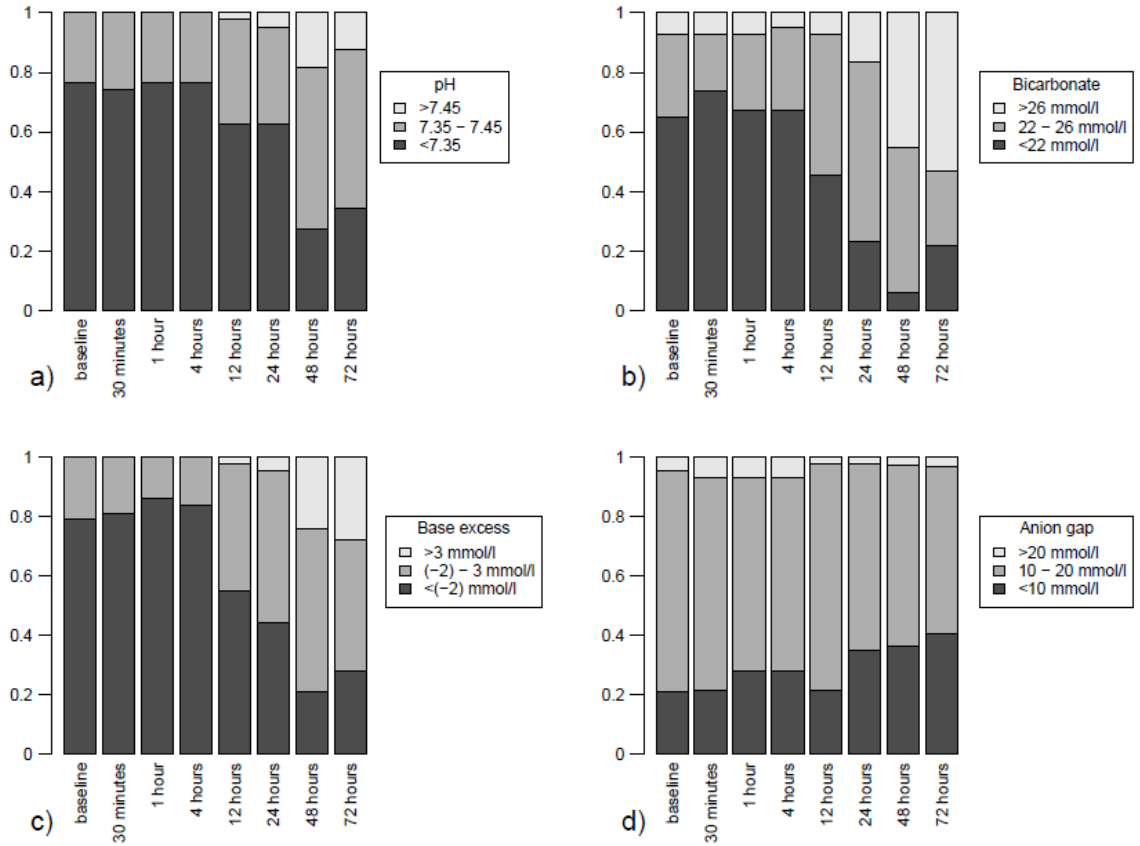


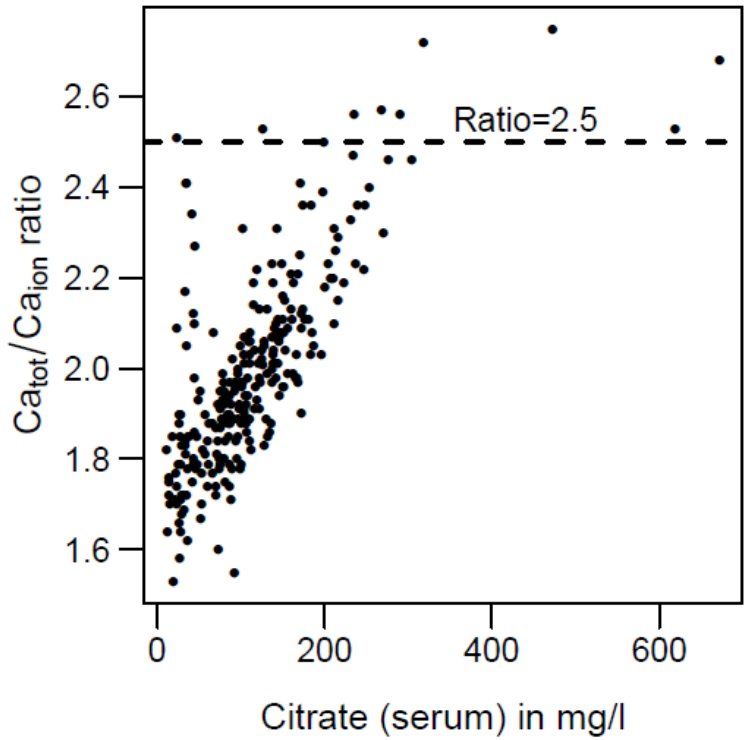
Schultheiß et al. Critical Care 2012, 16:R162
http://ccforum.com/content/16/4/R162

CRITICAL CARE

RESEARCH Open Access

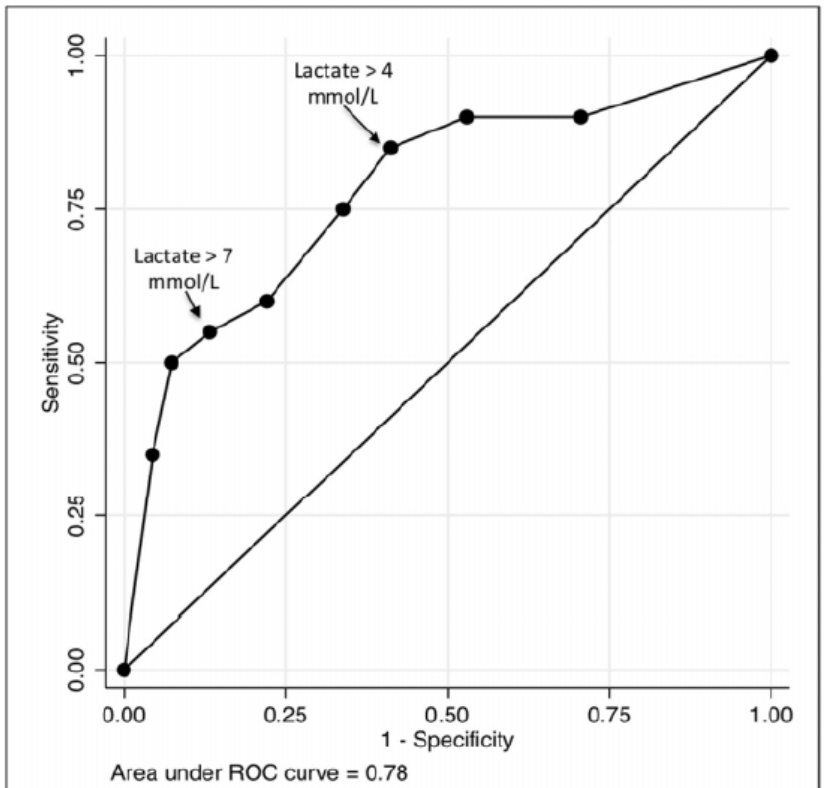
Continuous venovenous hemodialysis with regional citrate anticoagulation in patients with liver failure: a prospective observational study





Original Research

Hyperlactatemia Predicts Citrate Intolerance With Regional Citrate Anticoagulation During Continuous Renal Replacement Therapy



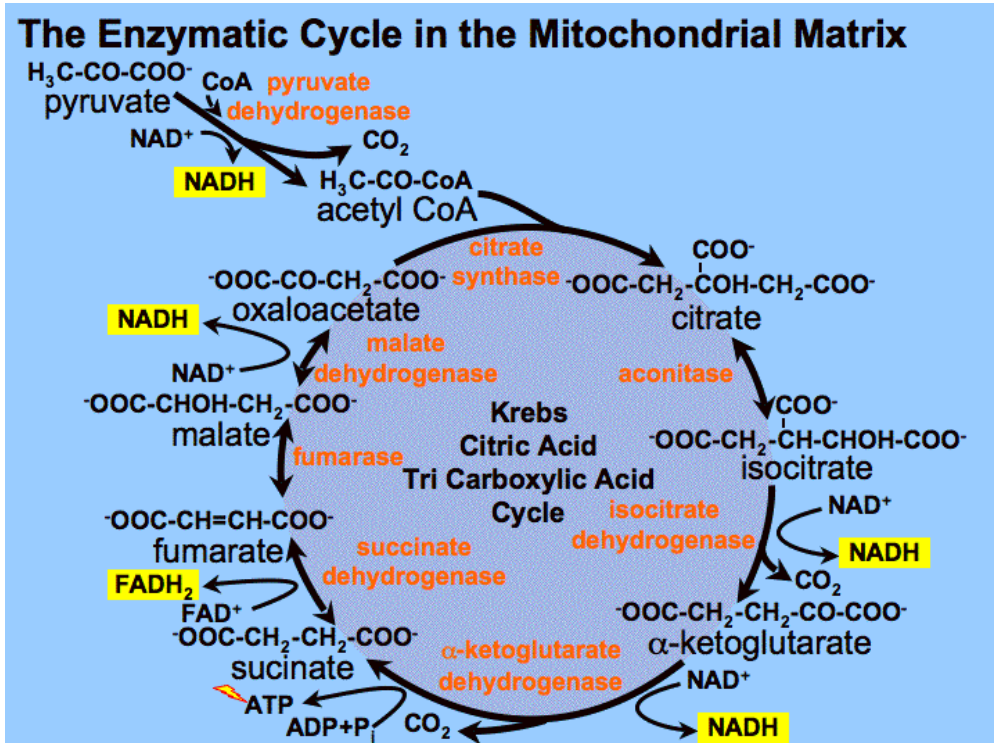
(mmol/L)	Sensitivity	Specificity	Positive PV	Negative PV
Lactate > 4	85%	59%	38%	93%
Lactate > 6	60%	78%	44%	87%
Lactate > 7	55%	87%	55%	87%

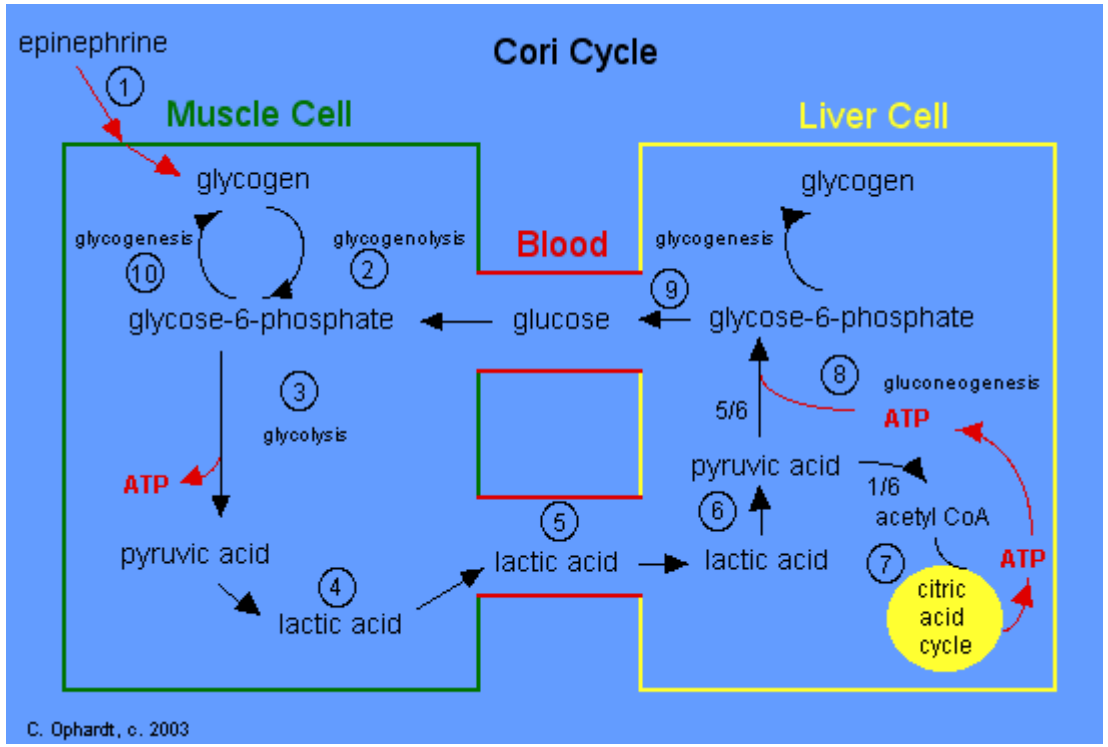
LEGEND: PV: predictive value; ROC: receiver operating characteristic.

REVIEW

Bench-to-bedside review: Citrate for continuous renal replacement therapy, from science to practice

Heleen M Oudemans-van Straaten[1,*] and Marlies Ostermann[2]





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Inflammation/Infection

- Culture surveillance
- Antibiotic prophylaxis following SBP
- Antimicrobial therapy in case of suspected infection
- Antibiotics in GIB (5-7 days)
- Steriods in severe alcoholic hepatitis (MELD >15 or discriminant function > 32); addition of N-acetylcysteine; pentoxifylline as

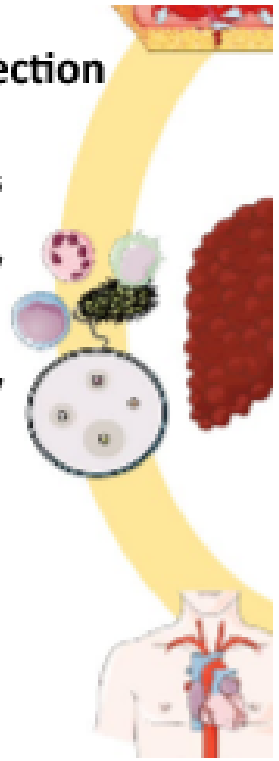

Table 1 Characteristics, details of interventions used and outcomes measured in randomized trials studying albumin treatment during spontaneous bacterial peritonitis, sepsis other than SBP in cirrhotic patients and general ICU population with sepsis

Trial	*N*	Age, *y*[a]	Experimental treatment	Control treatment	Mortality (albumin vs. control group; *p*)
Spontaneous bacterial peritonitis					
Sort et al. [8]	126	61.0 (7.9)	20% albumin	No vascular filling	Favors albumin (22% vs. 41%; $p=0.03$)[b]
Xue et al. [10]	112	22–70	20% albumin	No vascular filling	Favors albumin (10% vs. 34%; $p=0.002$)[c]
Fernandez et al. [14]	20	61.0 (9.5)	20% albumin	6% HES 200/0.5	NS (not significant) (0% vs. 20%; $p=0.47$)[c]
Chen et al. [11]	30	56.5 (11.5)	20% albumin	No vascular filling	NS (26.7% vs. 40%; $p=0.70$)[c]
Sepsis other than SBP in cirrhotic patients (no septic shock)					
Guevara et al. [15]	97	56 (11)	20% albumin	No vascular filling	NS (17% vs. 20%; $p=0.78$)[b]
Thévenot et al. [16]	193	55.3 (8.6)	20% albumin	No vascular filling	NS (30% vs. 22%; $p=0,16$)[b]
Sepsis and septic shock in general ICU population[d]					
SAFE study [2][e]	1218	60.5 (17.2)	4% albumin	NaCl 0.9%	NS (30.7% vs. 35.3%; $p=0.09$)[f]
ALBIOS study [3]	1810	69 [59–77]	20% albumin	Crystalloids	NS (20.9% vs. 21.1%; $p=0.87$)[f]

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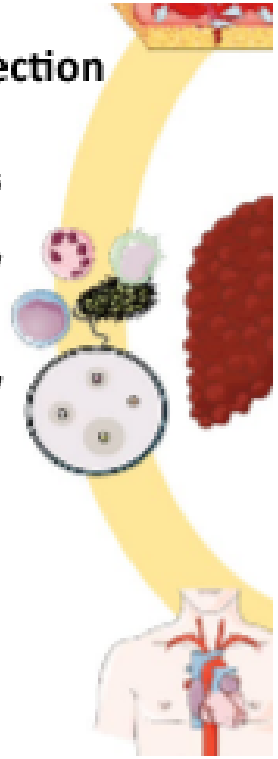

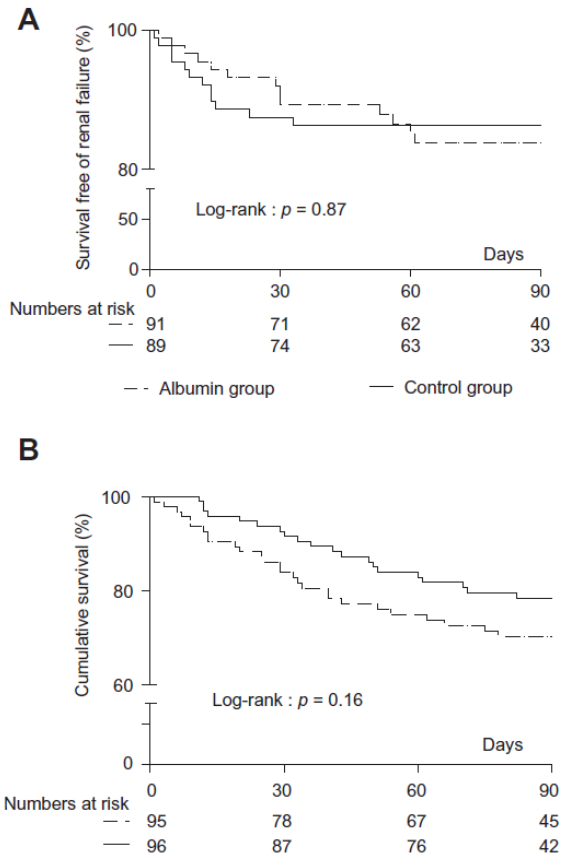

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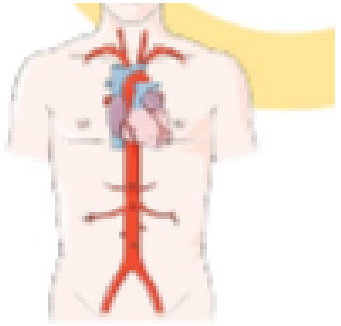
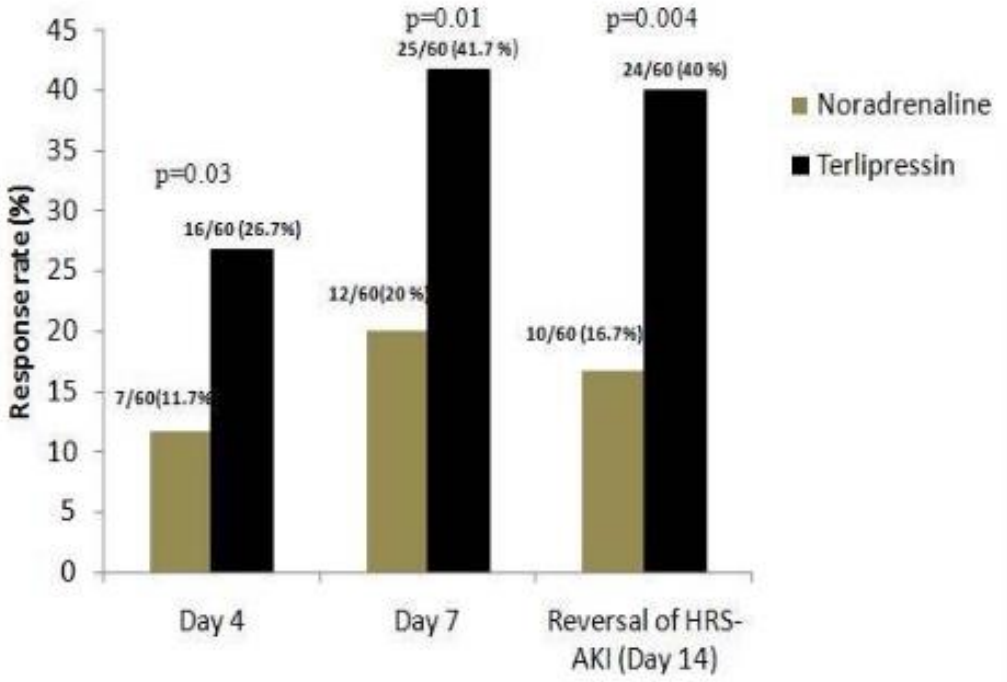


Circulation

- Mean arterial pressure > 60 mmHg
- Crystalloids for volume expansion
- Indications for albumin are:
  - SBP
  - HRS
  - Large volume paracentesis (> 5L)
- Norepinephrine as first line vasopressor
- Terlipressin is indicated in treatment of HRS and suspicion of/proven variceal hemorrhage
- Early paracentesis in case of ascites with albumin replacement



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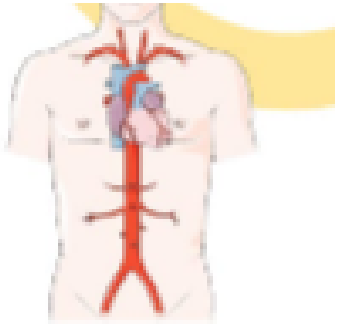

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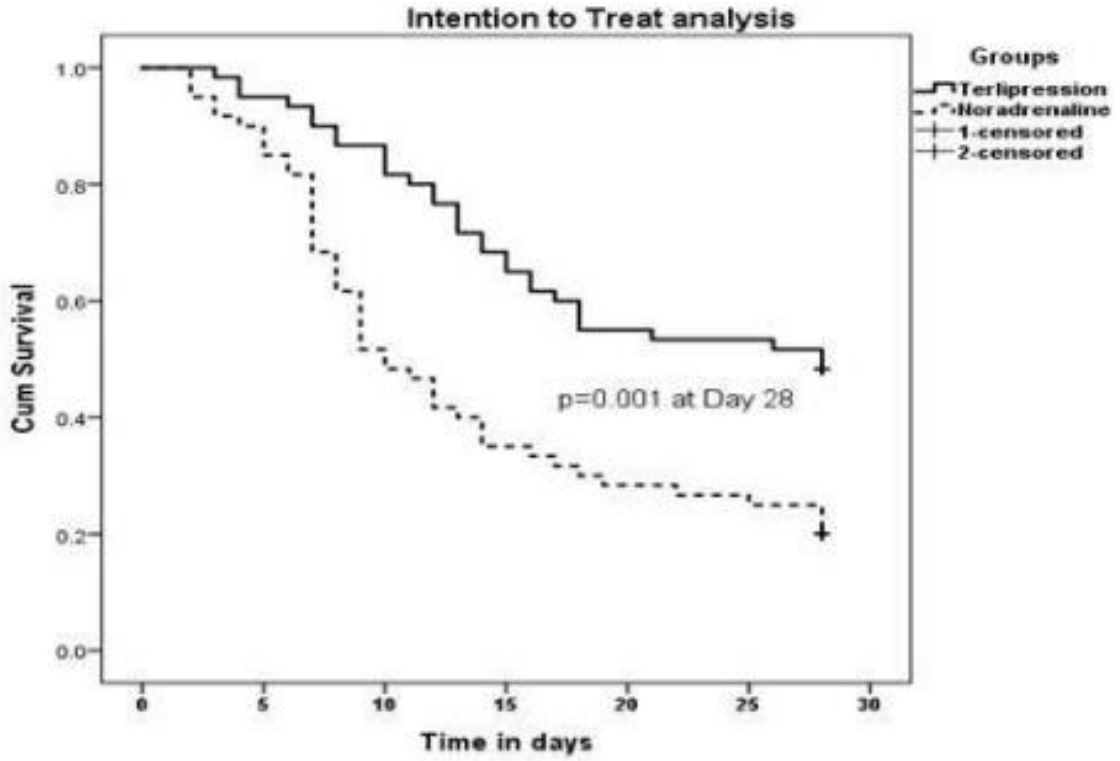

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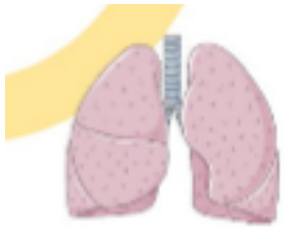

Lungs

- Endotracheal intubation if GCS <8 and individualized in presence of upper GIB
- Lung protective ventilation strategies
- Prone position possible
- Percutaneous tracheostomy may be appropriate and can be performed safely in liver failure
- Paracentesis in case of tense ascites
- TIPS may be appropriate for reduciton of portal pressures and refractory hepatic hydrothorax
- Consider hepatopulmonary syndrome (=intrapulmonary vasodilatation and hypoxemia in liver disease) as cause of severe hypoxemia

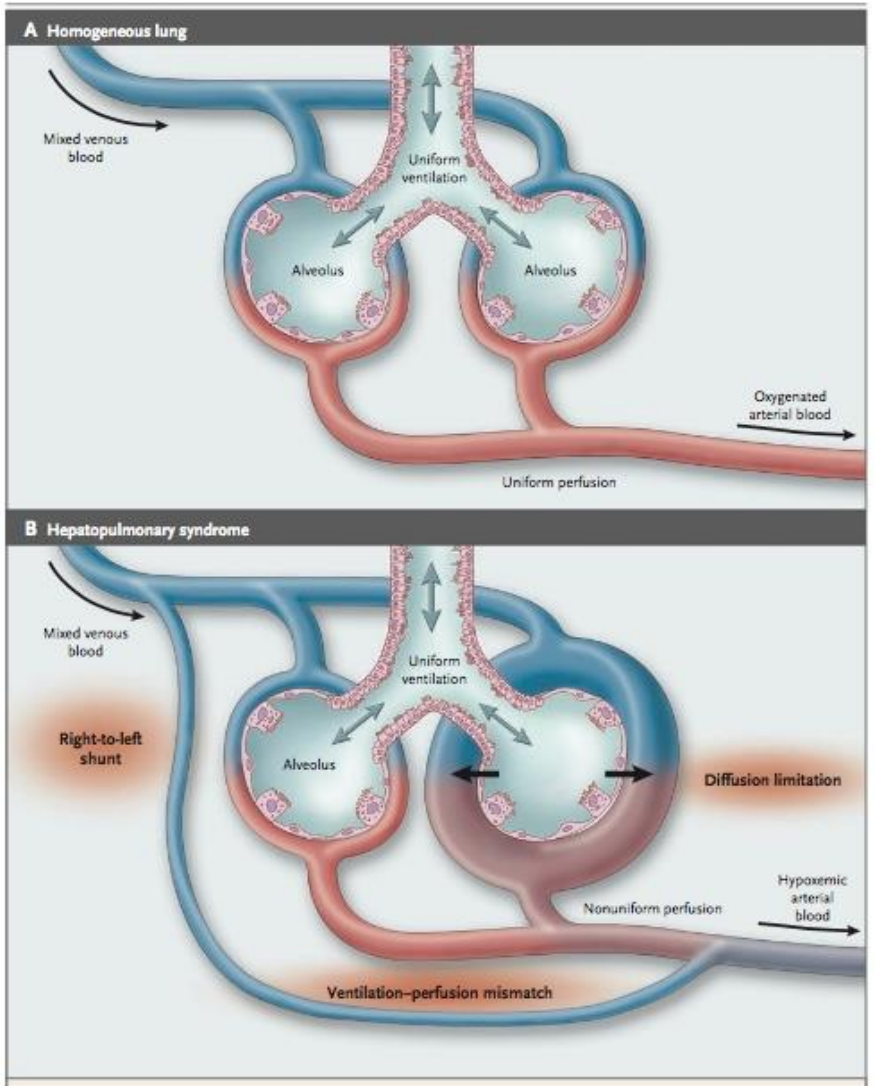

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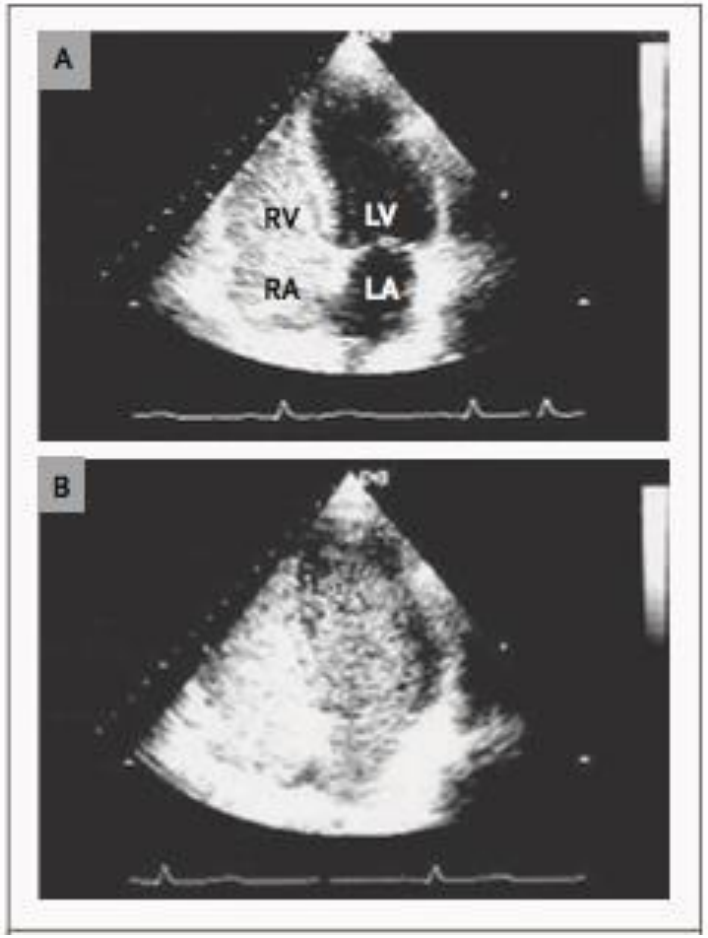
Table 1. Diagnostic Criteria for the Hepatopulmonary Syndrome.*

Variable	Criterion
Oxygenation defect	Partial pressure of oxygen <80 mm Hg or alveolar–arterial oxygen gradient ≥15 mm Hg while breathing ambient air
Pulmonary vascular dilatation	Positive findings on contrast-enhanced echocardiography or abnormal uptake in the brain (>6%) with radioactive lung-perfusion scanning
Liver disease	Portal hypertension (most common) with or without cirrhosis
Degree of severity†	
Mild	Alveolar–arterial oxygen gradient ≥15 mm Hg, partial pressure of oxygen ≥80 mm Hg
Moderate	Alveolar–arterial oxygen gradient ≥15 mm Hg, partial pressure of oxygen ≥60 to <80 mm Hg
Severe	Alveolar–arterial oxygen gradient ≥15 mm Hg, partial pressure of oxygen ≥50 to <60 mm Hg
Very severe	Alveolar–arterial oxygen gradient ≥15 mm Hg, partial pressure of oxygen <50 mm Hg (<300 mm Hg while the patient is breathing 100% oxygen)

* All criteria were determined by means of positive contrast-enhanced echocardiography (i.e., microbubble opacification of the left heart chambers three to six cycles after right atrial passage). The abbreviated formula for the alveolar–arterial gradient is as follows:

$$P_AO_2 - PaO_2 = (F_iO_2\,[P_{atm} - PH_2O] - [PaCO_2/0.8]) - PaO_2,$$



Early Use of TIPS in Patients with Cirrhosis and Variceal Bleeding

Juan Carlos García-Pagán, M.D., Karel Caca, M.D., Christophe Bureau, M.D., Wim Laleman, M.D., Beate Appenrodt, M.D., Angelo Luca, M.D., Juan G. Abraldes, M.D., Frederik Nevens, M.D., Jean Pierre Vinel, M.D., Joachim Mössner, M.D., and Jaime Bosch, M.D., for the Early TIPS (Transjugular Intrahepatic Portosystemic Shunt) Cooperative Study Group

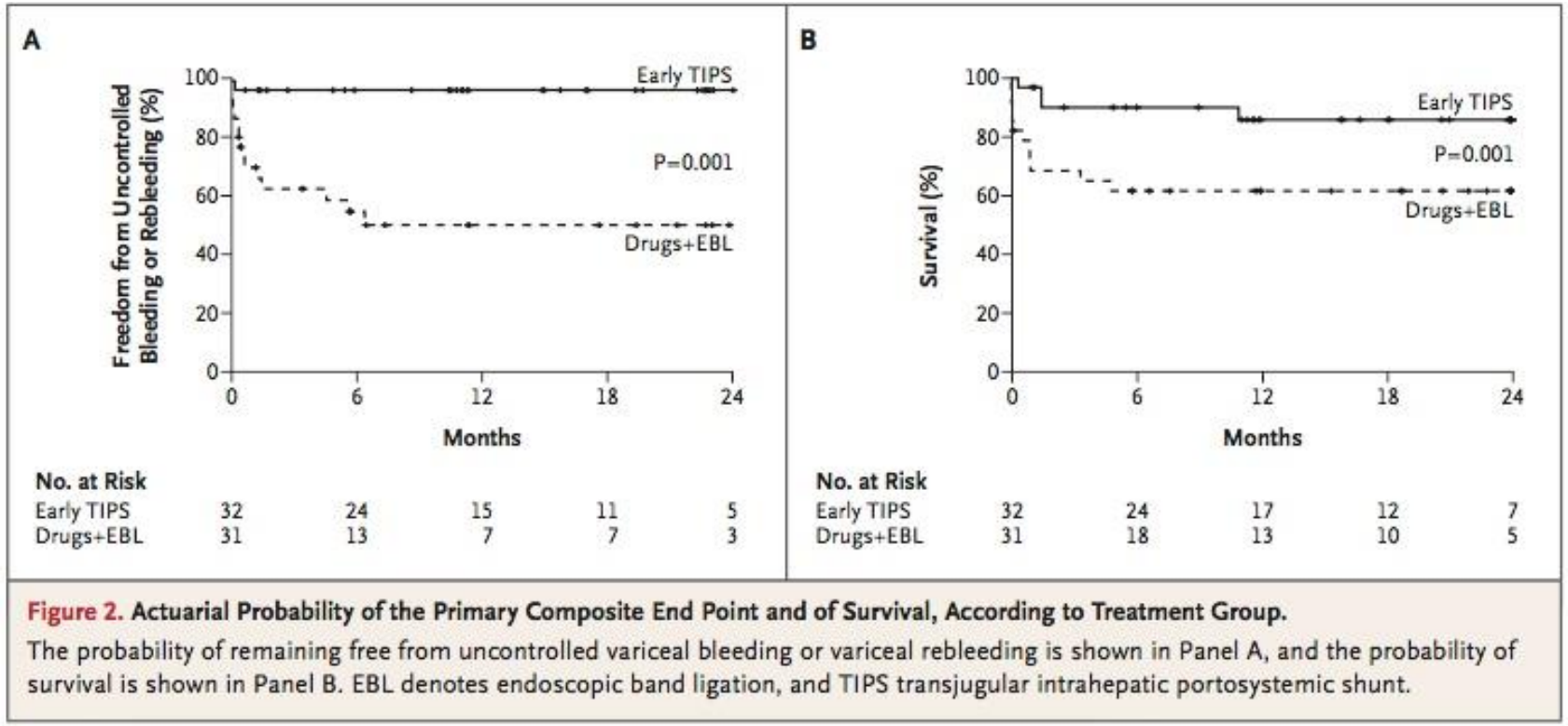


Figure 2. Actuarial Probability of the Primary Composite End Point and of Survival, According to Treatment Group.

The probability of remaining free from uncontrolled variceal bleeding or variceal rebleeding is shown in Panel A, and the probability of survival is shown in Panel B. EBL denotes endoscopic band ligation, and TIPS transjugular intrahepatic portosystemic shunt.