Intensive Care of Portal Hypertension for Patients with Acute on Chronic Liver Failure

Prevention and Management for the Gastrointestinal Specialist

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The Pathophysiology of Portal Hypertension

The sequence of events leading to the clinical manifestations of Portal Hypertension

Sequence

Intra-hepatic pressure rises

↓

Hepatic architectural distortion

↓

Rising portal pressure

↓

Splanchnic vasodilation

↓

Low effective blood volume

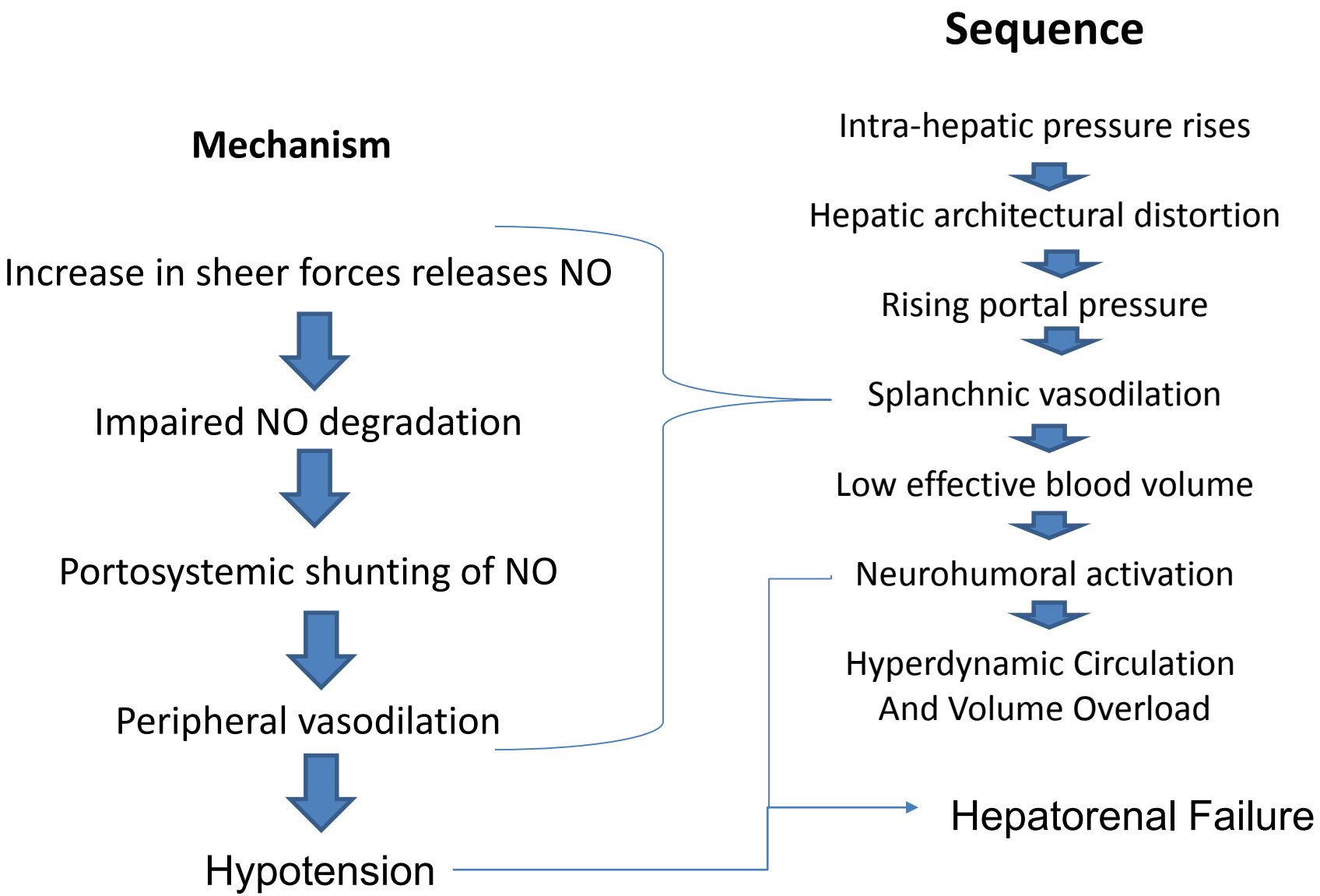
↓

Neurohumoral activation

↓

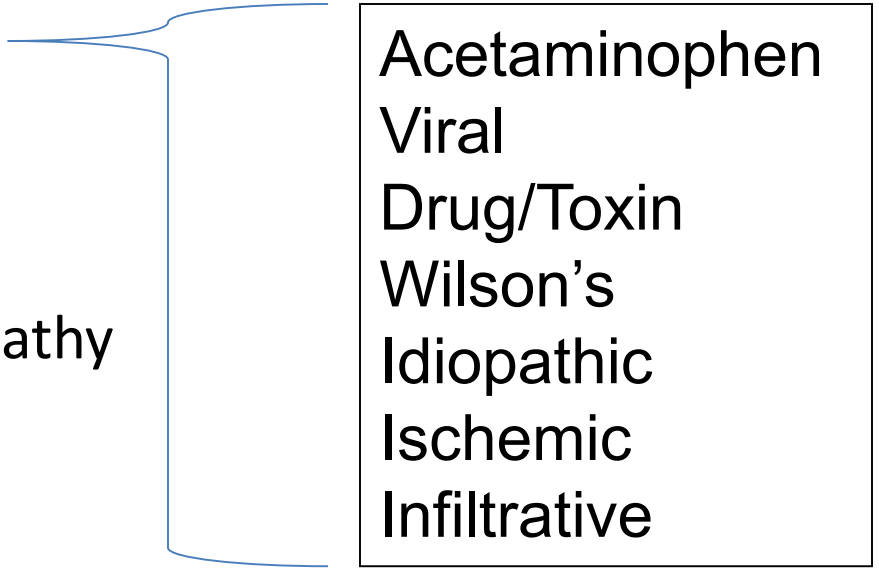
Hyperdynamic Circulation
And Volume Overload

The Pathophysiology of Portal Hypertension



Liver Failure

- Acute
  - Previously well
  - Within 8-26 weeks
    - Hepatic encephalopathy
    - Coagulopathy
    - Jaundice
- Acute Decompensation
- Acute on Chronic



Liver Failure

- Acute
- Acute Decompensation
- Acute on Chronic

Known cirrhosis
Ascites
Peritonitis
Encephalopathy
AKI/HRS
Variceal bleed

Liver Failure

- Acute
- Acute Decompensation
- Acute on Chronic

Underlying Liver disease (possibly cirrhosis) & extrahepatic organ failure; number and type of organ failures determine outcome

Acute on Chronic Liver Failure

- Type A - non-cirrhotic
- Type B - compensated cirrhosis
- Type C - decompensated cirrhosis

Acute on Chronic Liver Failure

APASL EASL/CLIF NACSELD

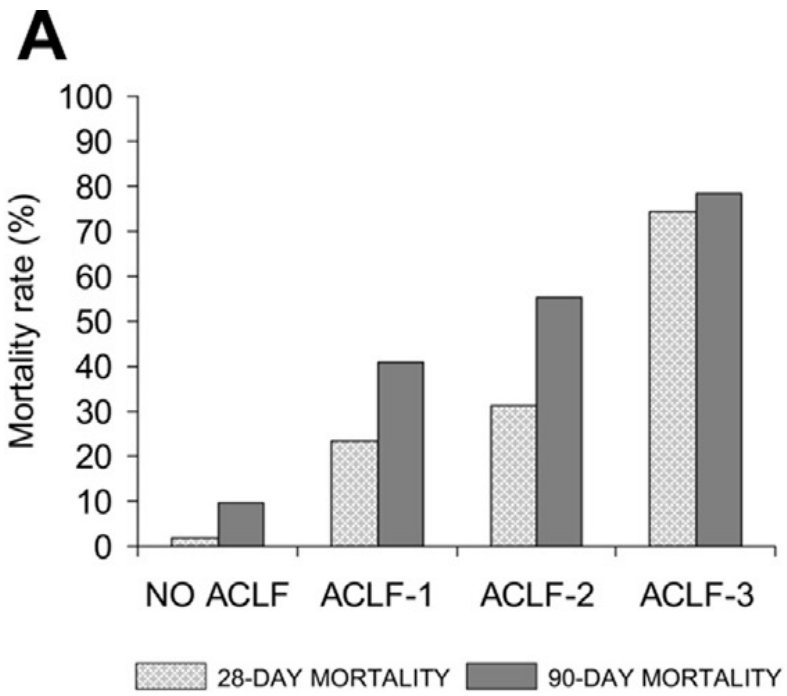
- Common precipitants
  - Viral infection
  - Alcohol use
  - Hepatotoxicity
  - Ischemia
  - Surgery
  - Sepsis

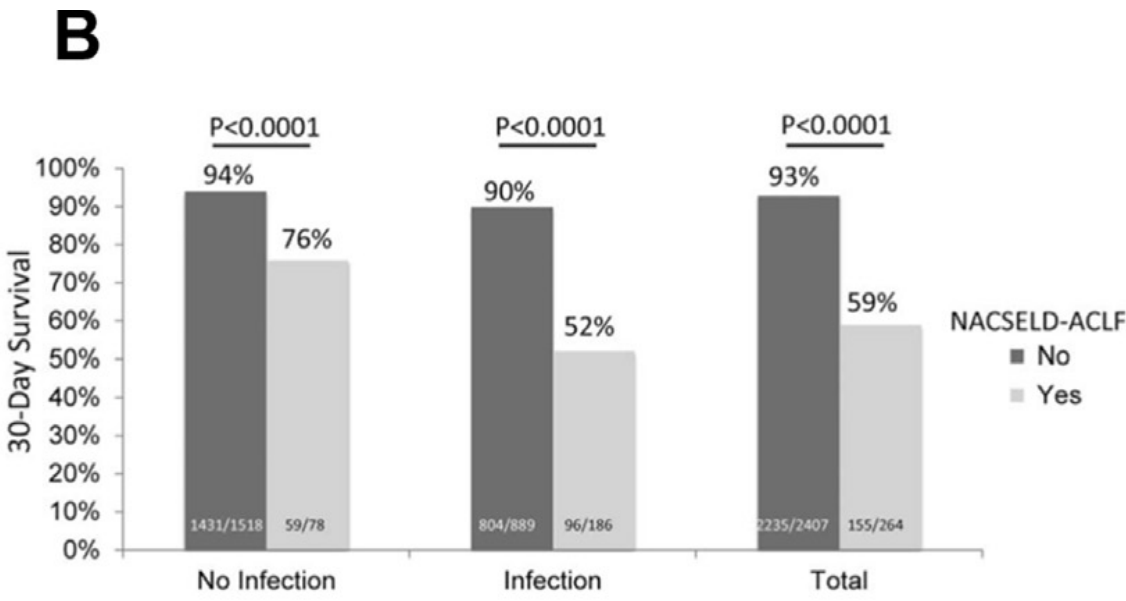
Inflammation

↓

Organ Failure

Mortality associated with ACLF





Gastroenterology 2013;144(7):1426-37

Hepatology, 2018. 67(6): 2367-2374

Prevention of ACLF

- Stop Proton Pump Inhibitors
- Use non-selective beta-blockers
- Manage Acute Kidney Injury aggressively
- Treat infections early
- Evidence-based use of albumin
- Suspect and treat adrenal failure

Prevention of ACLF

- Proton Pump Inhibitors
  - Impair neutrophil function
  - Reduce gastric acid, alter microbiota
  - Use leads to more frequent readmissions
  - Higher incidence of spontaneous bacterial peritonitis
  - Use H2 blockers as substitute

Prevention of ACLF

- Stop Proton Pump Inhibitors
- Use non-selective beta-blockers
  - May improve outcomes from ACLF (28 day)
  - Primary prophylaxis from variceal bleeding
    - CTP A and B with large varices
    - CTP C with any varices
  - For any patient with clinically significant portal hypertension and compensated cirrhosis
  - Avoid in patients with ascites and SBp < 90 or AKI

Prevention of ACLF

- Stop Proton Pump Inhibitors
- Use non-selective beta-blockers
- Manage Acute Kidney Injury aggressively
  - Increase in creatinine of $\geq$ 0.3 in 48^{o} or 1.5 x baseline
  - Diagnose accurately
    - Una < 10
    - Exclude intra or post renal causes
  - Volume expansion
  - Vasopressors (norepi > midodrine/octreotide/alb)
  - Dialysis when appropriate

Prevention of ACLF

- Stop Proton Pump Inhibitors
- Use non-selective beta-blockers
- Manage Acute Kidney Injury aggressively
- Treat infections early
  - Tap ascites (neutracytic ascites $\geq$ 250 PMNs)
  - Treat empirically (for picture of sepsis)
  - 3rd Gen Cephalosporin for SBP & Variceal Bleeding
  - IV albumin

Prevention of ACLF

- Stop Proton Pump Inhibitors
- Use non-selective beta-blockers
- Manage Acute Kidney Injury aggressively
- Treat infections early
- Evidence-based use of albumin
  - Prevent post-tap circulatory dysfunction
  - Prevent AKI/HRS in SBP (day 1 and 3)
  - Treat AKI

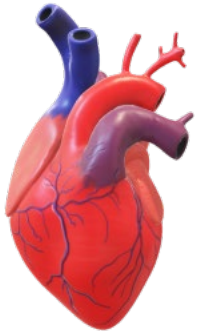
Prevention of ACLF

- Stop Proton Pump Inhibitors
- Use non-selective beta-blockers
- Manage Acute Kidney Injury aggressively
- Treat infections early
- Evidence-based use of albumin
- Suspect and treat adrenal failure
  - ~40% with AD have low morning cortisol
  - Functional adrenal failure
  - Glucocorticoid replacement

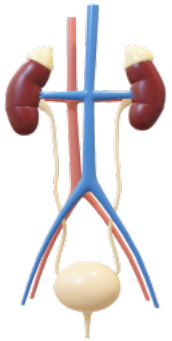
Management

Infection

Cardiovascular & Circulatory Failure

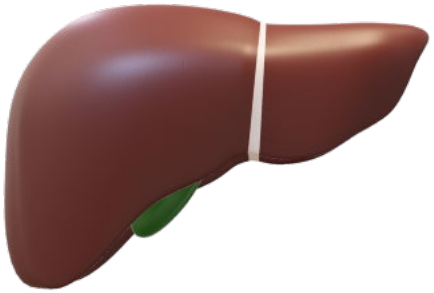


Renal Failure



Encephalopathy

Coagulation and Bleeding

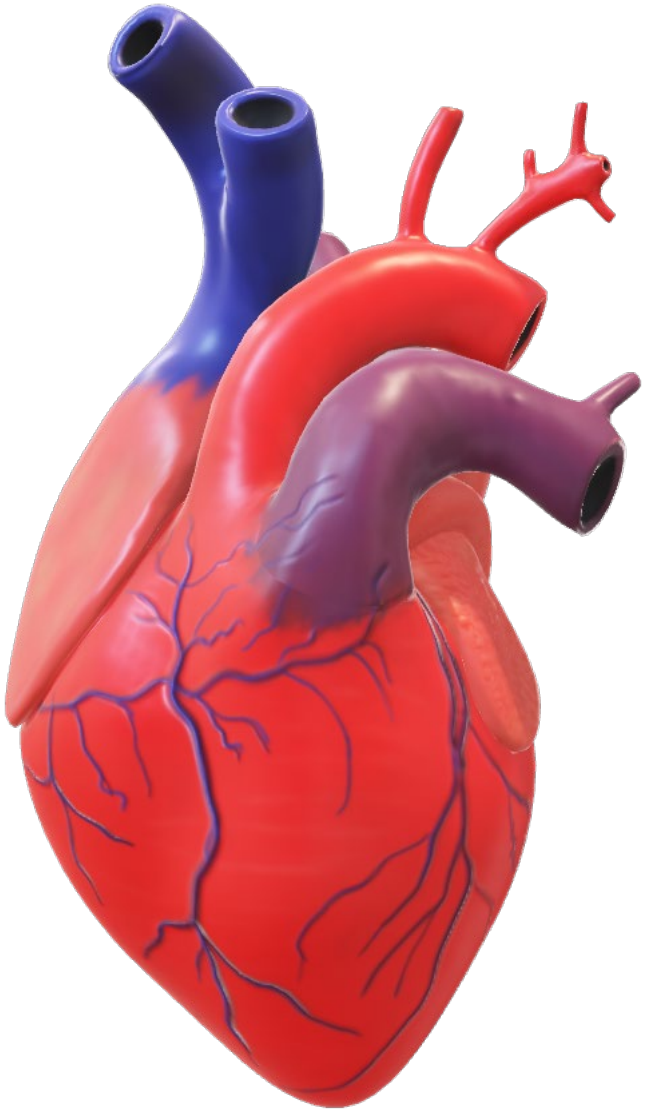


Infection

Infection

- Common in ACLF patients
- Empiric antibiotics are prudent with onset of Systemic Inflammatory Response Syndrome
  - 3rd Generation Cephalosporin
  - Piperacillin/tazobactam
- Albumin is beneficial
  - Binds inflammatory mediators
  - Increases TNF-mediated bacterial clearance
- Pressor support when needed

Cardiovascular & Circulatory Failure



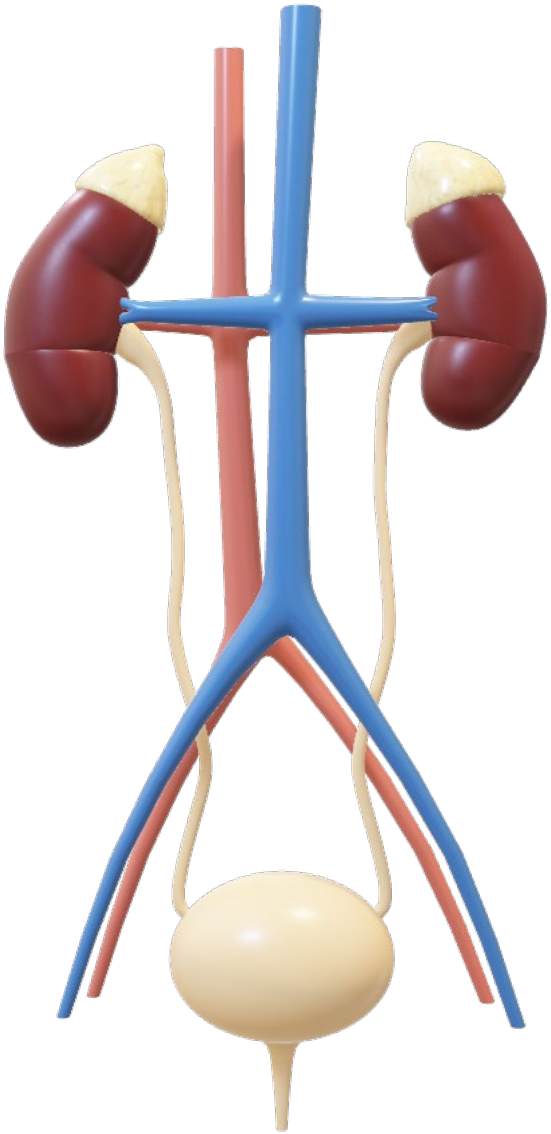
Cardiovascular & Circulatory Failure

- Predisposing states
  - Cirrhotic cardiomyopathy
    - Impaired contractility
    - Impaired diastolic relaxation
    - Prolonged QT
  - Adrenal failure
- Management
  - Volume expansion with crystalloid, albumin
  - Vasopressor to achieve MAP ~ 65 mm/Hg
    - Norepinephrine 0.01 – 0.3 μg/kg/min
    - Vasopressin 0.01 – 0.04 units/min

Cardiovascular & Circulatory Failure

- Adrenal failure
  - Low perfusion
  - Persistent shock
  - Management
    - Morning cortisol
    - Hydrocortisone 50 – 100 mg every 6-8 hours

Renal Failure



Renal Failure

- AKI more structural, less HRS
- Multifactorial
  - Hepatorenal physiology (renal vasoconstriction)
  - Acute tubular necrosis
  - Nephrotoxin
- Albumin and pressor support (norepinephrine 0.01 – 0.3 μg/kg/min)
- Renal replacement therapy
  - Continuous veno-venous hemodialysis
  - Slow low efficiency dialysis

Encephalopathy

Encephalopathy

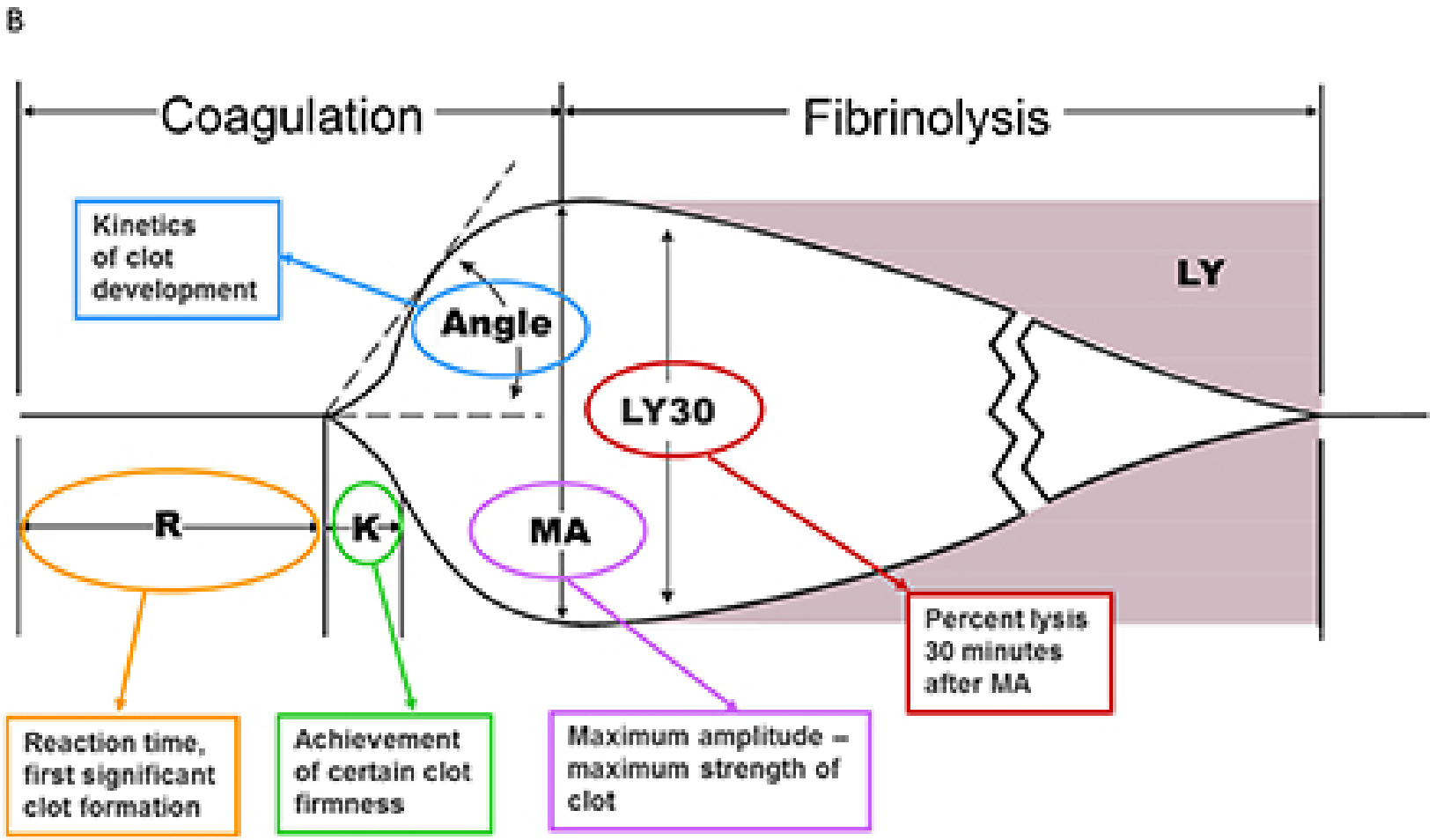
- Hepatic encephalopathy portends poor outcome
- Differential diagnostic considerations
- Arterial ammonia can be measured
- Directed therapy
  - Lactulose
  - Rifaximin
  - Combination therapy confers survival benefit

Coagulation and Bleeding

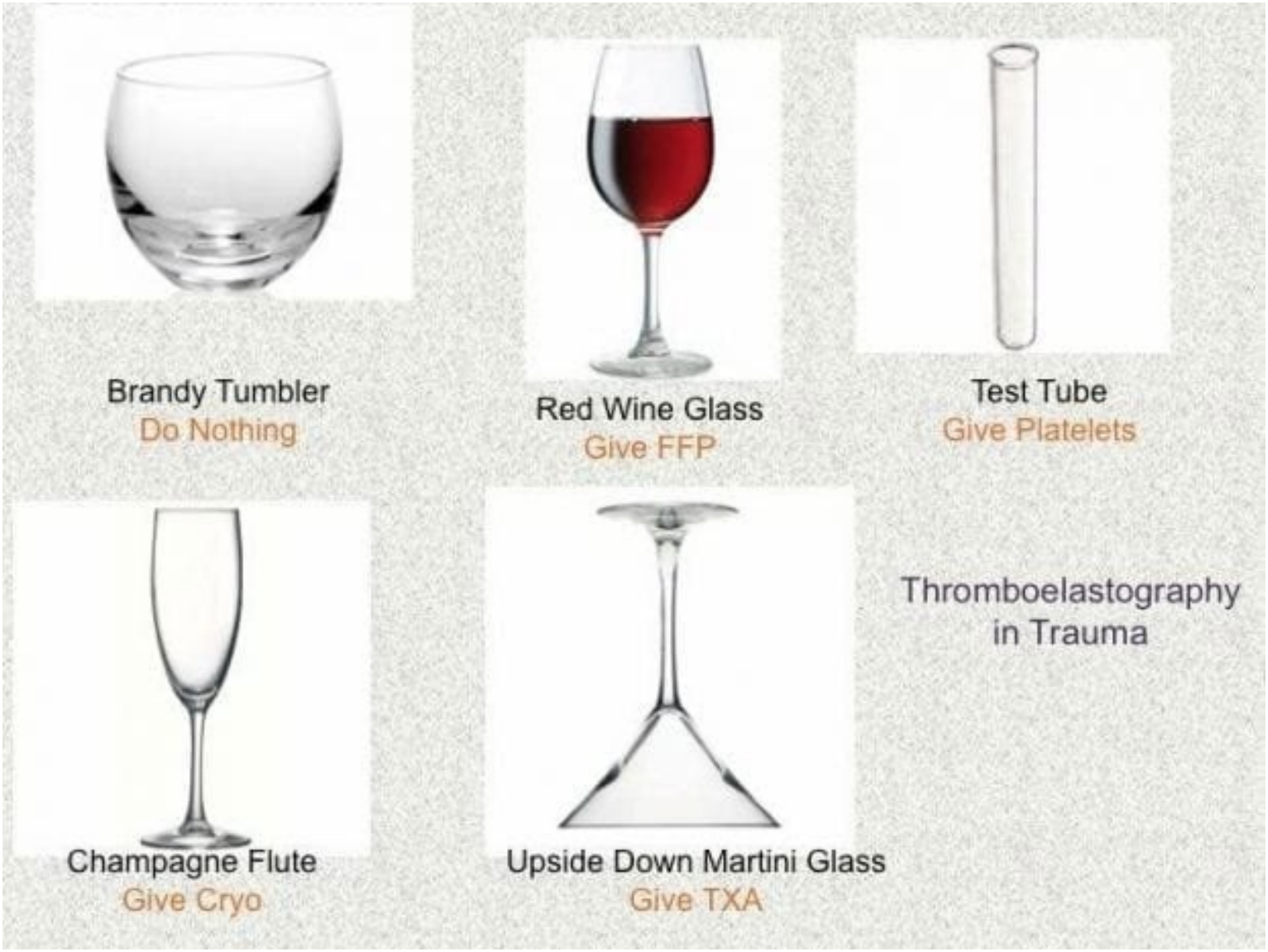
Coagulation

- High risk of thrombosis; administer prophylaxis
- Correction
  - Fresh frozen plasma
  - Cryoprecipitate
- Thromboelastography
  - Platelet function
  - Hyperfibrinolysis
  - Premature clot dissolution

Coagulation



Using the Thromboelastogram

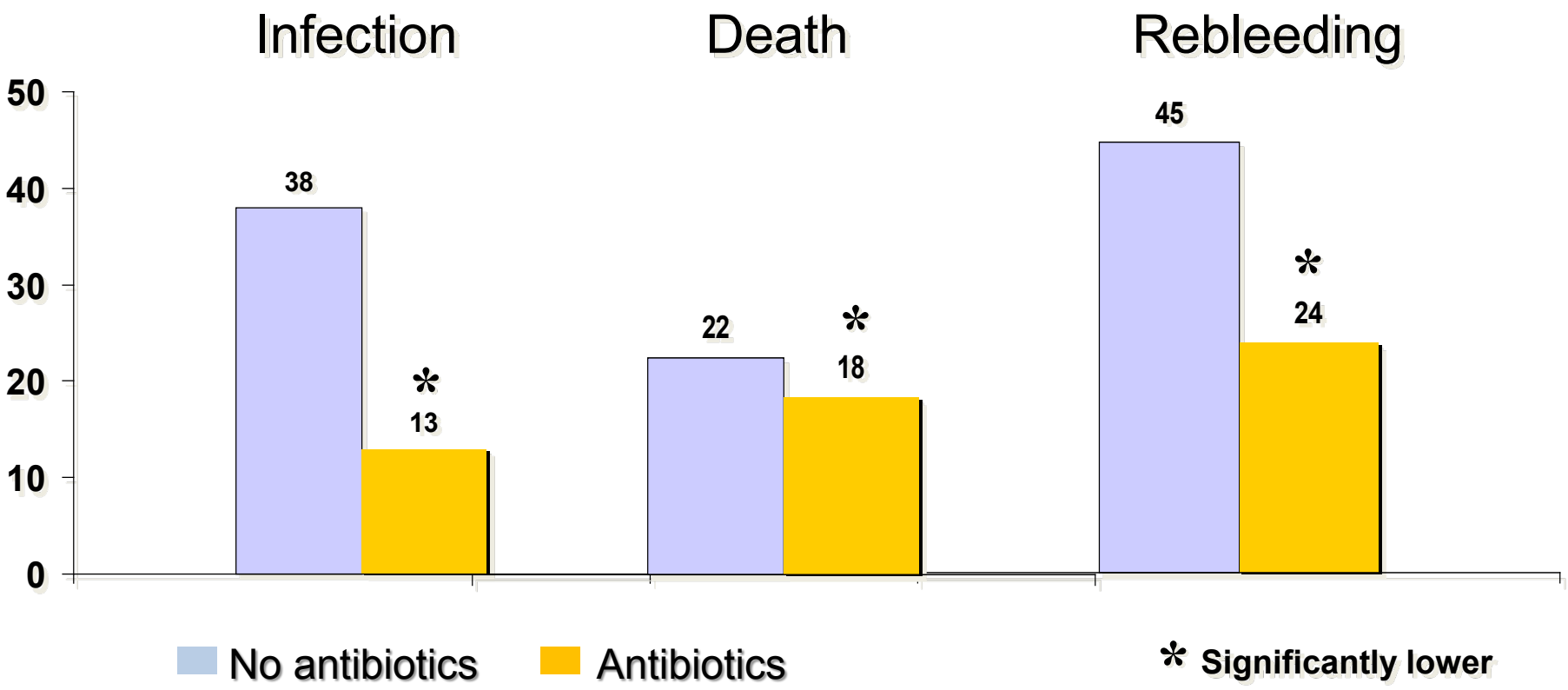


https://litfl.com/thromboelastogram-teg/

General Approach to Variceal Bleeding

- Suspect portal hypertension
- Antibiotics
- Blood product support
- Targeted pharmacotherapy
- Endoscopy
- TIPS

Prophylactic Antibiotics Improve Outcomes in Cirrhotic Patients with GI Hemorrhage



Chavez-Tapia et al. Cochrane 2010 . CD002907; Soares-Weiser et al. Cochrane 2002 CD002907

Blood Product Support

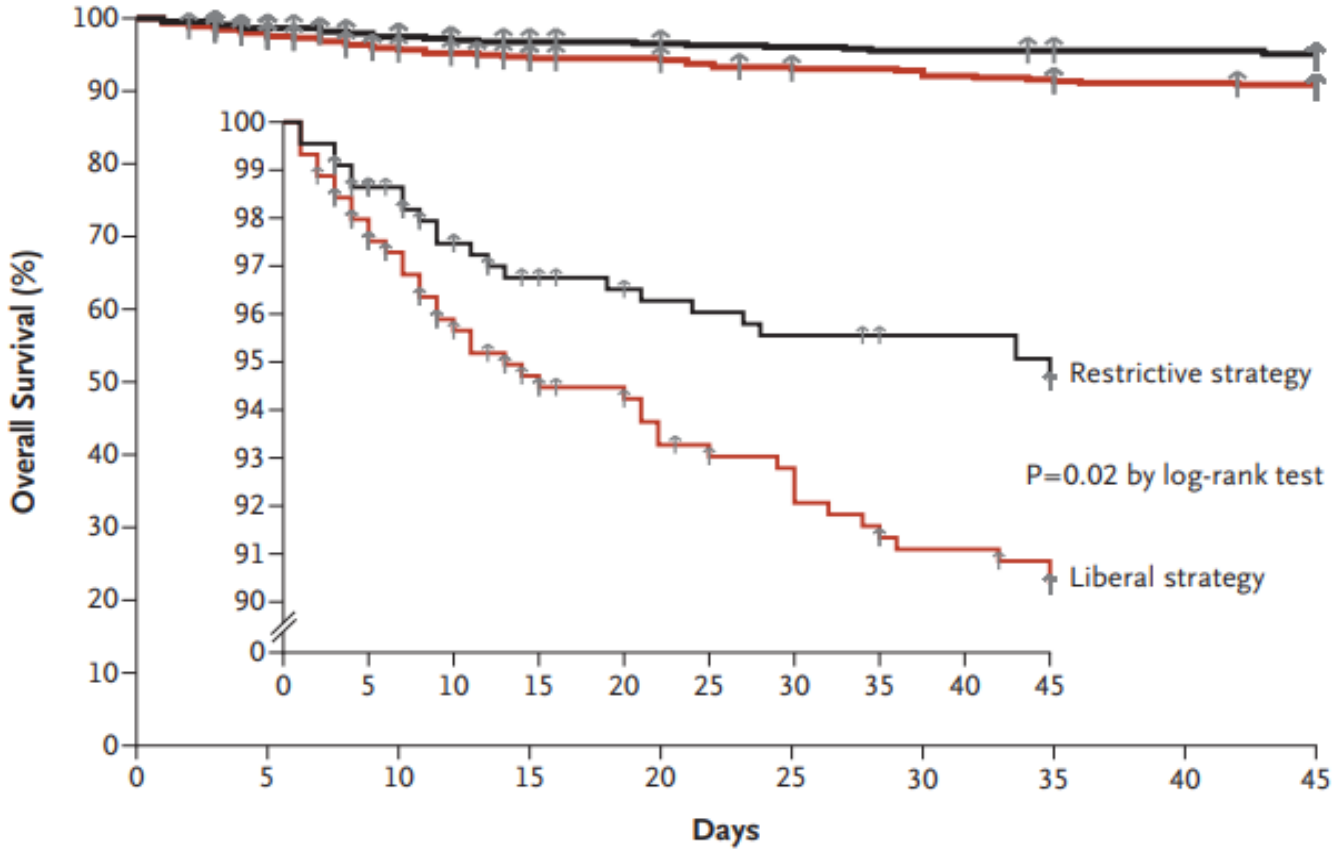
- Restitution of blood volume can lead to worse outcomes; higher rebleeding, and worse survival in Child's A and B
- Target hemoglobin in range of 7-9 g/dL
- Plasma and platelets are of little benefit in the acute setting

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 3, 2013 VOL. 368 NO. 1

Transfusion Strategies for Acute Upper Gastrointestinal Bleeding

Càndid Villanueva, M.D., Alan Colomo, M.D., Alba Bosch, M.D., Mar Concepción, M.D., Virginia Hernandez-Gea, M.D., Carles Aracil, M.D., Isabel Graupera, M.D., María Poca, M.D.,



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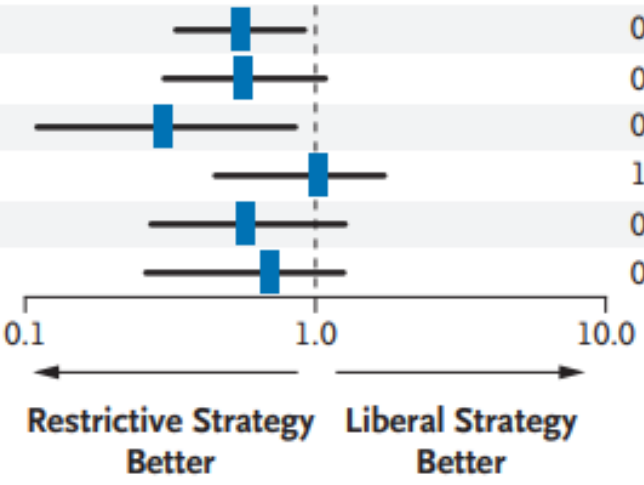
Subgroup	Restrictive Strategy	Liberal Strategy	Hazard Ratio (95% CI)	P Value
	no. of patients/total no. (%)			
Overall	23/444 (5)	41/445 (9)	0.55 (0.33–0.92)	0.02
Patients with cirrhosis	15/139 (11)	25/138 (18)	0.57 (0.30–1.08)	0.08
Child–Pugh class A or B	5/113 (4)	13/109 (12)	0.30 (0.11–0.85)	0.02
Child–Pugh class C	10/26 (38)	12/29 (41)	1.04 (0.45–2.37)	0.91
Bleeding from varices	10/93 (11)	17/97 (18)	0.58 (0.27–1.27)	0.18
Bleeding from peptic ulcer	7/228 (3)	11/209 (5)	0.70 (0.26–1.25)	0.26



AP&T Alimentary Pharmacology and Therapeutics

Meta-analysis: vasoactive medications for the management of acute variceal bleeds

M. Wells, N. Chande, P. Adams, M. Beaton, M. Levstik, E. Boyce & M. Mrkobrada

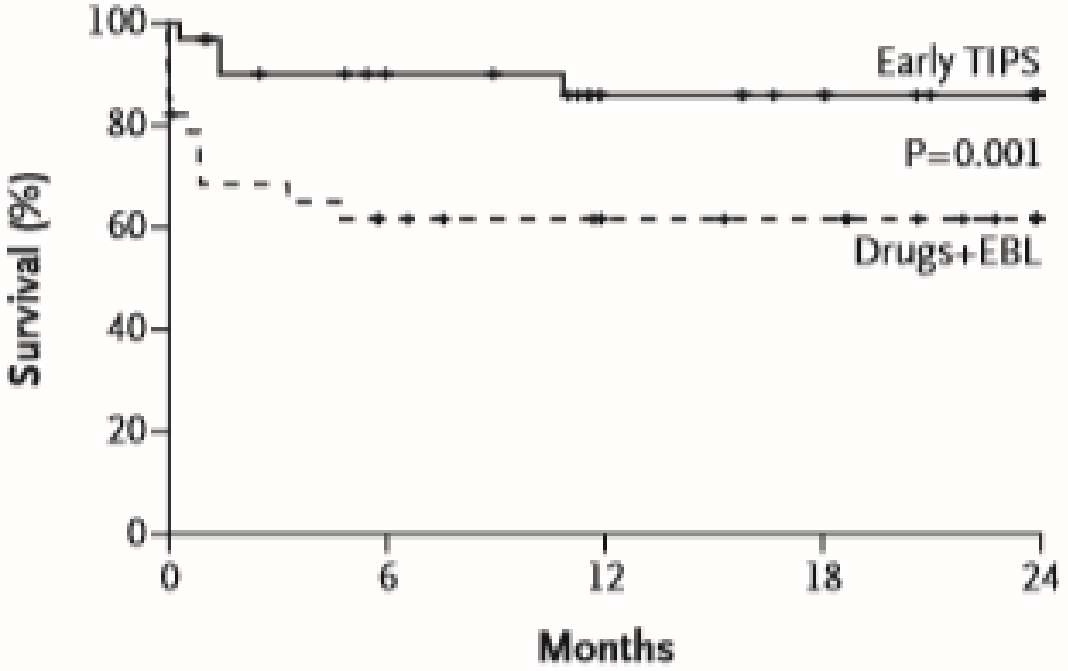
Aliment Pharmacol Ther 2012; 35: 1267–1278

- Vasoactive agents associated with
  - lower risk of all-cause mortality
  - Transfusion requirements
  - Bleeding control
  - Shorter LOS
- Which agent you use is less important
  - Octreotide IV 50 μg bolus, 50 μg/hr
  - Up to 5 days

ORIGINAL ARTICLE

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



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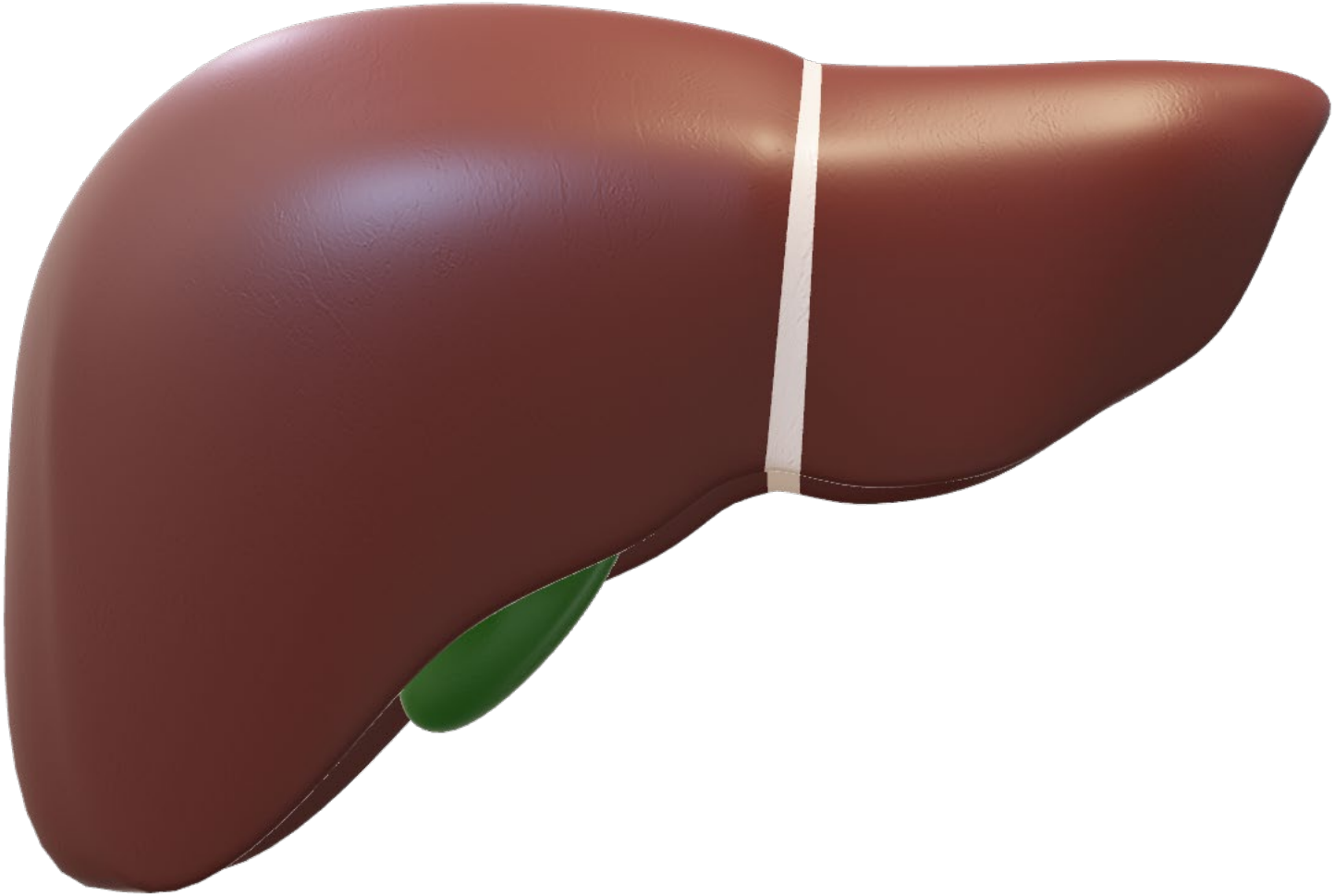
- Reasonable in carefully selected high risk patients
  - PG > 20 mmHg
  - Child class B with bleeding
  - Child Class C
- Early TIPS (within 72 hours) reduced rebleeding and mortality
- Survival benefit unconfirmed

Emerging Treatments

- Hemostatic Powder
- Statins
- Esophageal Stents
- EUS guided glue or coils



Liver Transplantation for ACLF

- ACLF patients usually have a high MELD Na score
- Post liver transplant survival at 90 days approximates those without pre-transplant ACLF
- Usual eligibility and listing criteria apply
- All patients with ACLF should be considered for transplantation.

Dual Organ Transplantation

- GFR < 60 ml/min for 90 days & GFR < 35 ml/min at time of listing
- Sustained AKI
  - RRT for > 6 weeks
  - GFR < 25 mg/min for > 6 weeks
- Metabolic disease

Evolving Therapie

- Extracorporeal Liver Supp
  - Molecular Adsorbent R iating System (MARS
  - Fractionated Plasm aration and Adsorption FPSA)
  - Bio-Artificia

No Proven Survival Benefit !!!!

Key Points

1. Mortality in Acute on Chronic Liver Failure (ACLF) rises with the number of organs involved.
2. Management of ACLF involves judicious use of PPI, non-selective beta-blocker, early recognition and treatment of AKI with volume expansion and replacement therapy, and vigilance for those factors that can contribute to circulatory failure including infection and adrenal failure.
3. Variceal bleeding requires early antibiotics, urgent endoscopy, vasoactive meds, and restrictive transfusion. Consider TIPS when bleeding is refractory.
4. Any patient with ACLF should be considered for transplantation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FOR THE STUDY OF
CHRONIC LIVER FAILURE

The North American Consortium for the Study of End Stage Liver Disease