

CHRONIC LIVER DISEASE AND ITS COMPLICATIONS

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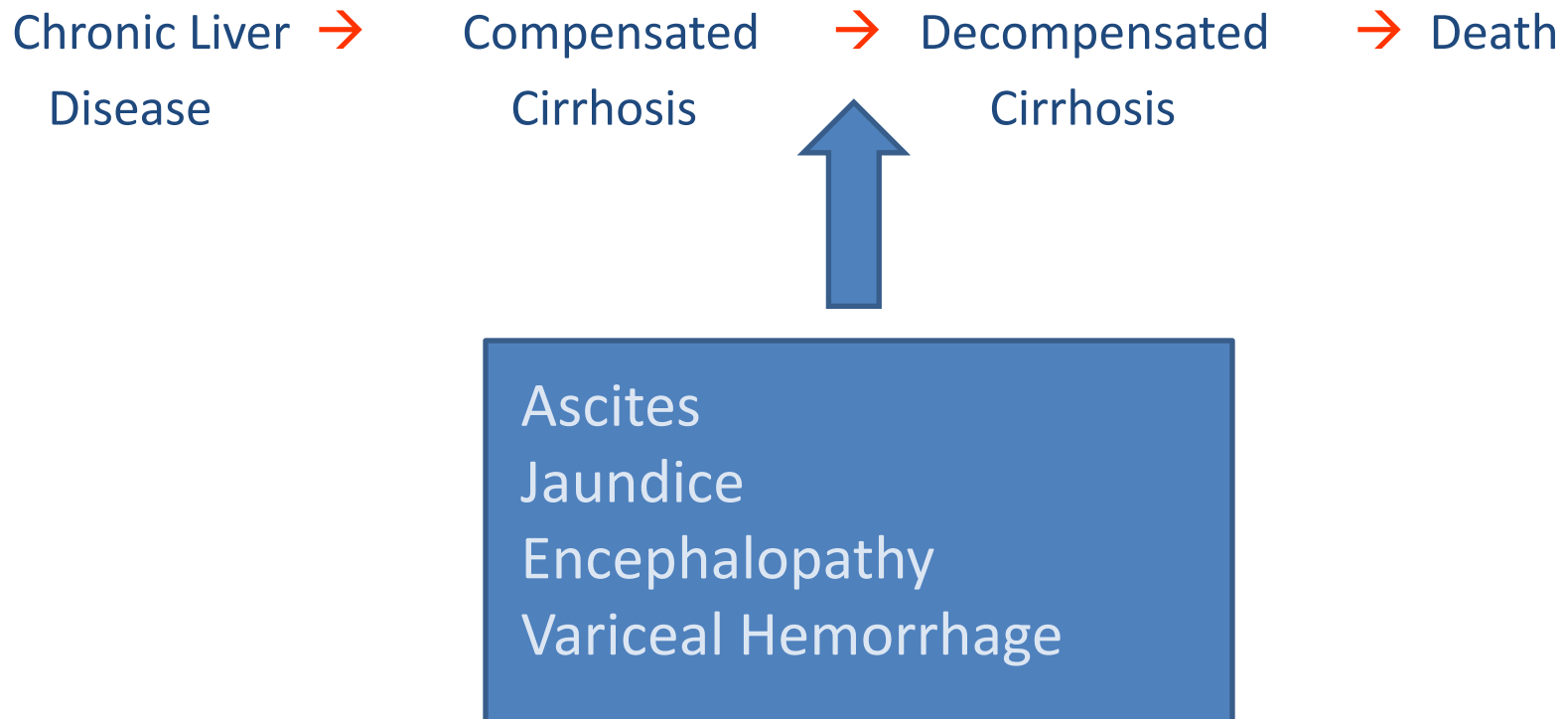
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I have no disclosures relevant to this presentation.

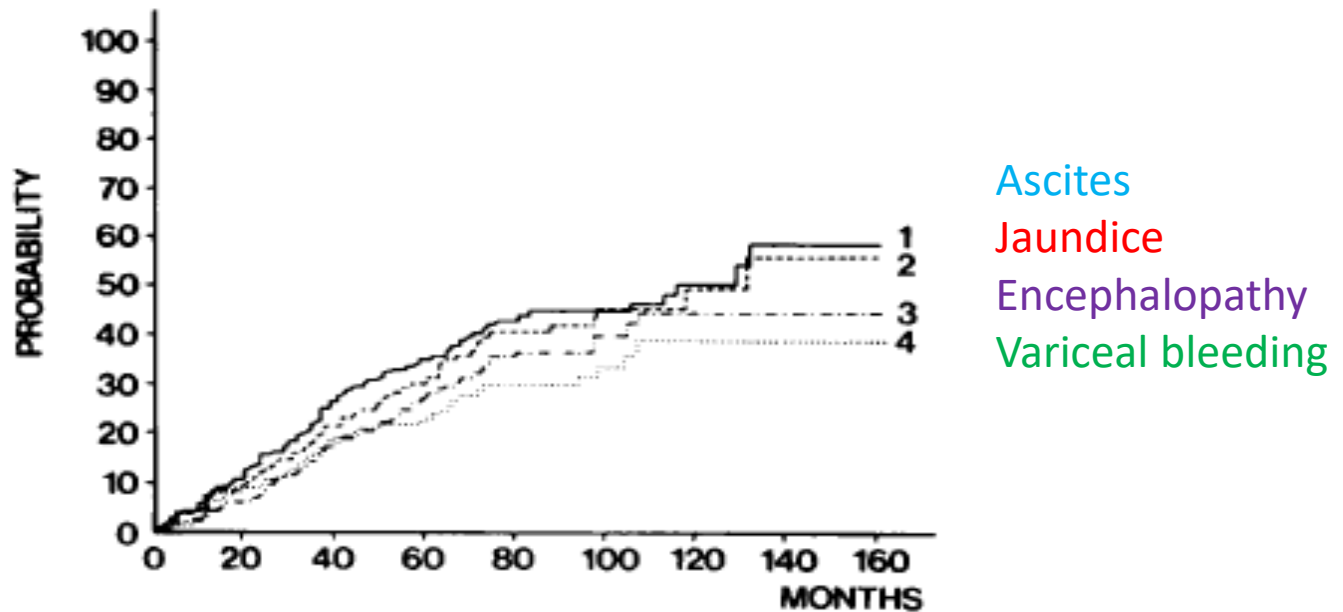
Learning Objectives

- Natural history and outcome of cirrhosis
- Initial management of complications of cirrhosis
- Recent studies on management of complications of cirrhosis
- Appropriate timing of referral for liver transplantation
- Pre-operative risk assessment in patients with cirrhosis
- A few words on Acute on Chronic Liver Failure (ACLF)

Natural History of Chronic Liver Disease



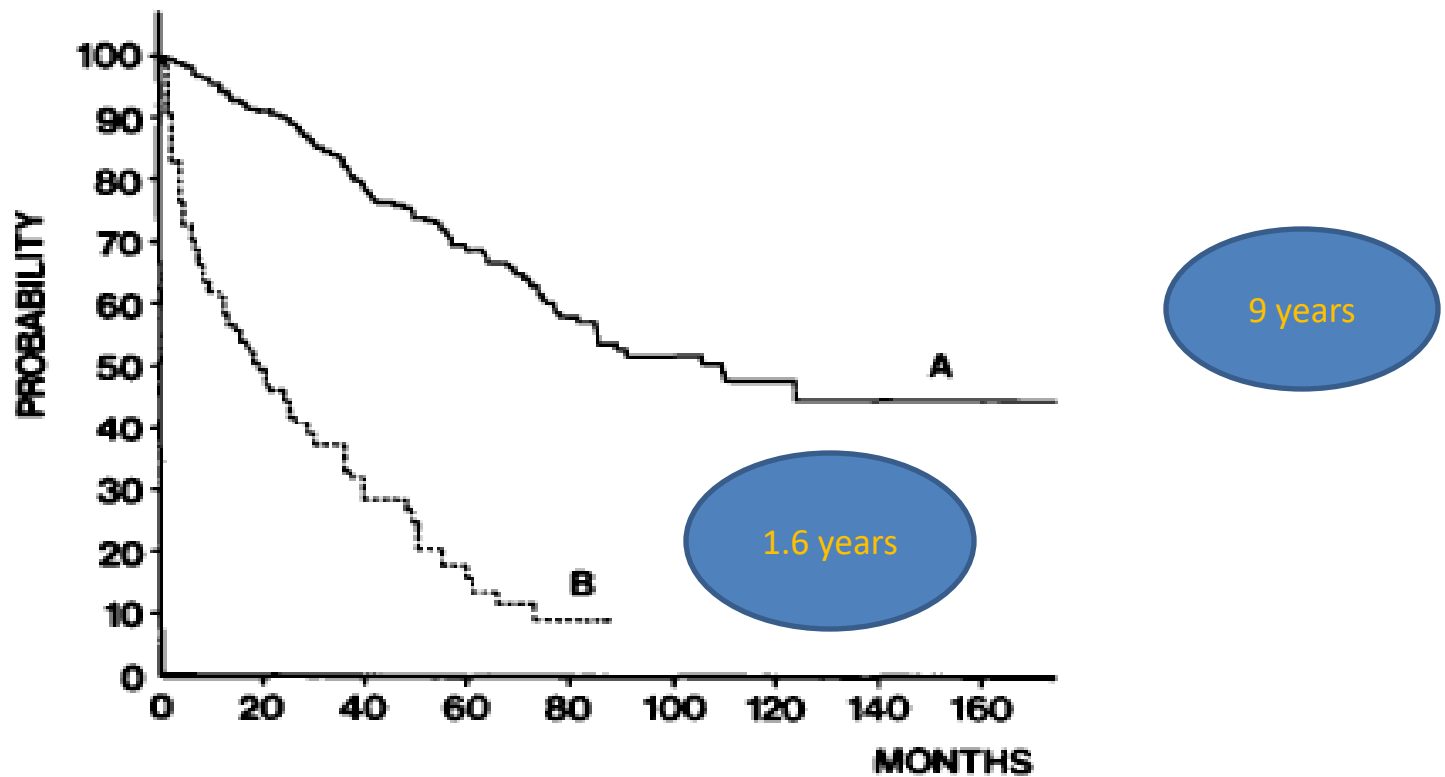
Probability of Hepatic Decompensation: 58% over 10 years



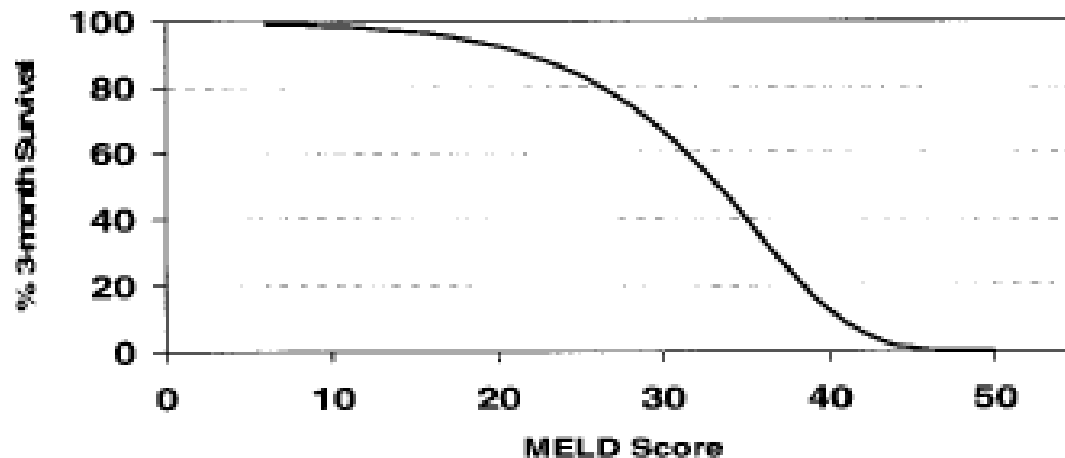
Risk Factors for Hepatic Decompensation

- GI Bleeding
- Infection
- Alcohol intake
- Medications
- Dehydration
- Constipation
- Obesity (Hepatology 2011; 54: 555)
- Surgery
- Ongoing viral infection

Hepatic Decompensation Reduces Survival



Prediction of 3-Month Survival in Patients with Cirrhosis



$$\text{MELD score} = 3.8 \ln(\text{bilirubin}) + 11.2 \ln(\text{INR}) + 9.6 \ln(\text{creatinine}) + 6$$

Prediction of 1 Year Survival in Patients with Cirrhosis: Child Turcotte Pugh Score

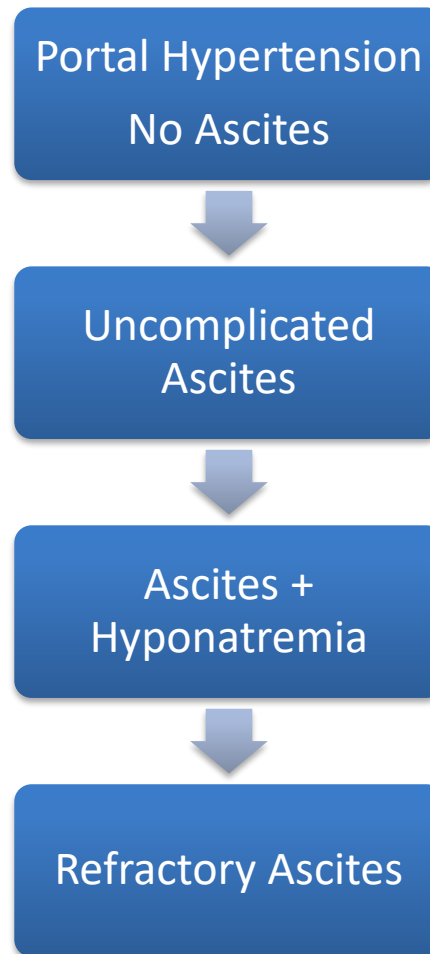
Points	1	2	3
Encephalopathy	None	1 and 2	3 and 4
Ascites	Absent	Slight	Moderate
Bilirubin (mg/dL)	1-2	2-3	>3
Albumin (g/dL)	3.5	2.8-3.5	<2.8
INR	<1.7	1.7-2.3	>2.3

5-6 A 100% 1 year survival

7-9 B 80% 1 year survival

10-15 C 45% 1 year survival

Natural History of Ascites from Cirrhosis



Management of Ascites

- 50% of compensated patients with cirrhosis will develop ascites 10 years from diagnosis
- Development of ascites associated with reduction in 5-year survival from 80% to 30%
- Ascites most common complication of cirrhosis that leads to hospital admission
- New-onset ascites requires diagnostic paracentesis
- Bleeding complications in less 1/1,000 who require paracentesis
- Use of blood products (FFP/platelets) for paracentesis not data supported
- SAAG of ≥ 1.1 is 97% accurate for portal hypertension
- High ascites total protein ($>2.5\text{g/dL}$) suggests cardiac ascites

Treatment Options for Patients with Cirrhosis with Ascites

- Cessation of Alcohol use
- Sodium restricted diet (2000mg/day) and education
- Spironolactone 100mg alone may be effective in new ascites
- Dual diuretics: Spironolactone and Furosemide, orally with single daily dosing
- Ratio Spironolactone 100mg: Furosemide 40mg, increase every 3-5 days
- Fluid restriction not necessary unless serum sodium ≤ 125 mmol/L
- Maximum doses are Spironolactone 400mg: Furosemide 160mg
- Amiloride or Eplerenone substituted for Spironolactone or tender gynecomastia
- Consider stopping NSAIDS, ACE Inhibitors, Angiotensin Receptor blockers, Propranolol
- Liver transplant evaluation
- Albumin infusion in patients with cirrhosis and ascites remains controversial (ANSWER vs. MACTH study)

Lancet 2018; 391: 2417-2429.

J Hepatology 2018; 69: 1250-1259.

Management of Refractory Ascites

- 10% of patients with cirrhosis with ascites
- Unresponsive to 2g sodium diet and high dose diuretics
OR
- Clinically significant complications of diuretics (encephalopathy, creatinine > 2g/dL, sodium < 120 mmol/L, potassium > 6 mmol/L)
- Options include serial LVPs vs. TIPS → liver transplant
- In LVP ≥ 5L, albumin infusion of 6-8g/L removed improves survival and prevents post-paracentesis circulatory dysfunction
- Use of nonselective beta blockers in refractory ascites has conflicting data, but should be reduced or discontinued in SBP < 90mmHg, acute kidney injury

TIPS for Refractory Ascites

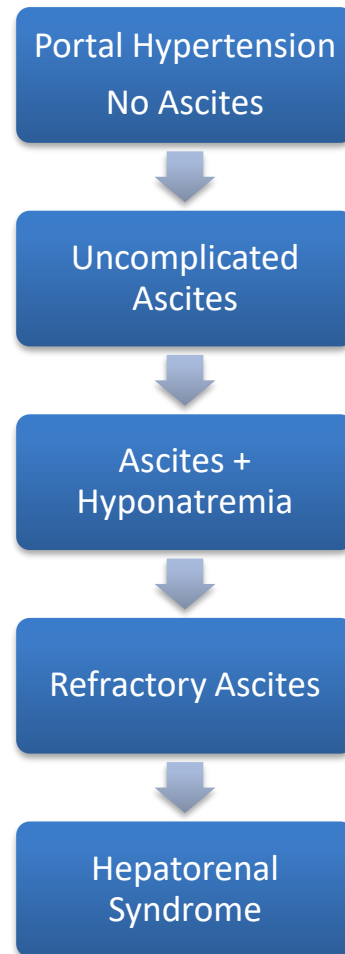
- Survival advantage with TIPS in patients with refractory ascites in several recent meta-analyses
- TIPS causes gradual suppression of neurohormonal vasoconstrictors over 4-6 months
- By 6 months about 80% of patients will clear their ascites
- Careful patient selection: MELD score < 18
- Patients with MELD > 18, hepatic encephalopathy (HE), advanced age (70), cardiopulmonary insufficiency and sarcopenia at greater risk of complications post TIPS
- TIPS stents with smaller diameter (8-10mm) have been equally effective in ascites management, reduce risk of HE

J Gastroenterology Hepatology 2015; 30: 389-395.

Semin Liver Disease 2018; 38: 87-96.

Clin Gastroenterology Hepatology 2019; 17: 2793-2799.

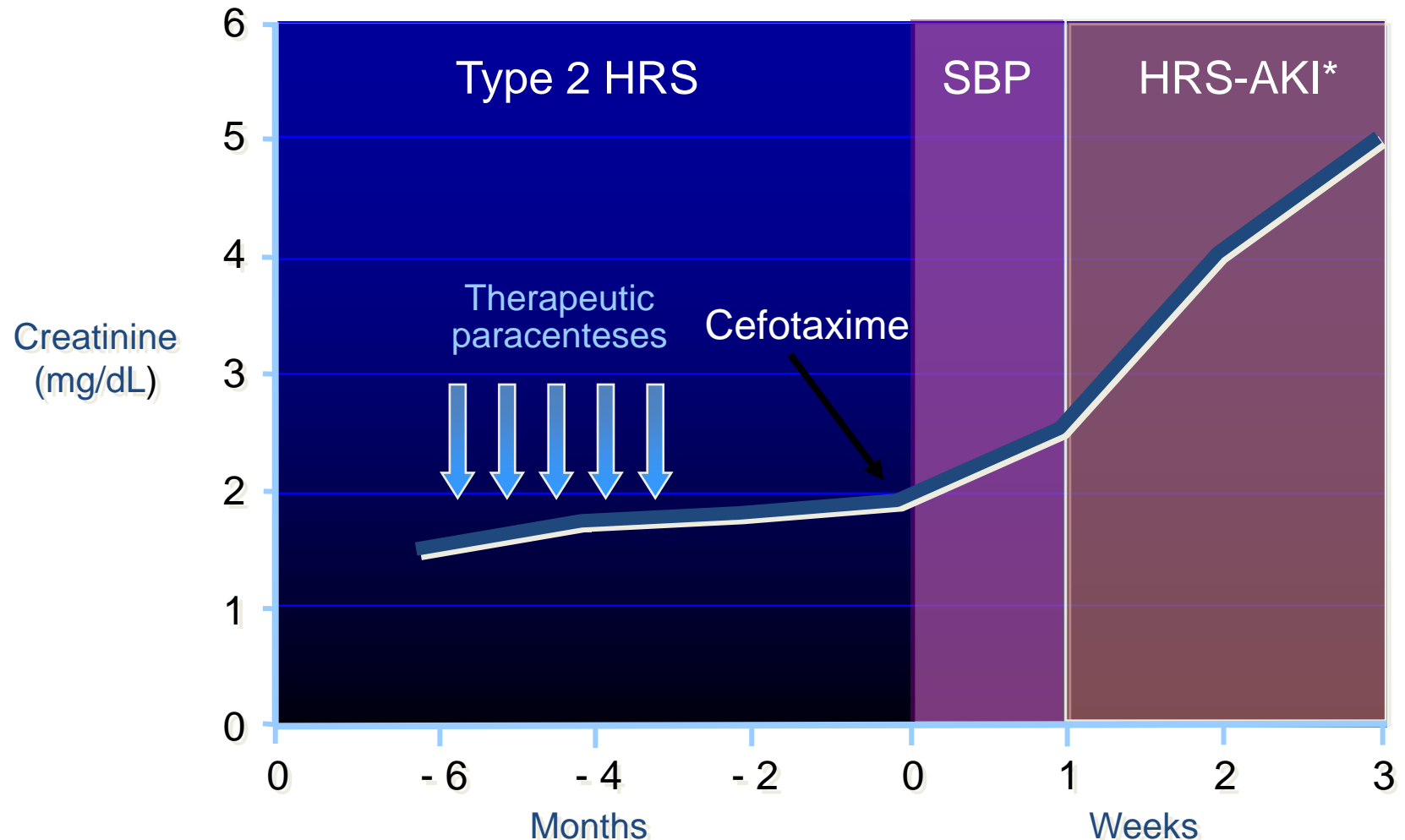
Natural History of Ascites from Cirrhosis



Hepatorenal Syndrome – clinical features

- Cirrhosis with ascites
- Diagnosis of AKI by International Club of Ascites-Acute Kidney Injury Criteria
- No creatinine improvement after 2 days diuretic withdrawal
- No creatinine improvement after 2 days volume expansion with albumin (1g/kg body weight daily)
- Absence of shock, nephrotoxins
- Bland urine sediment/no signs structural kidney injury

Natural History of Hepatorenal Syndrome



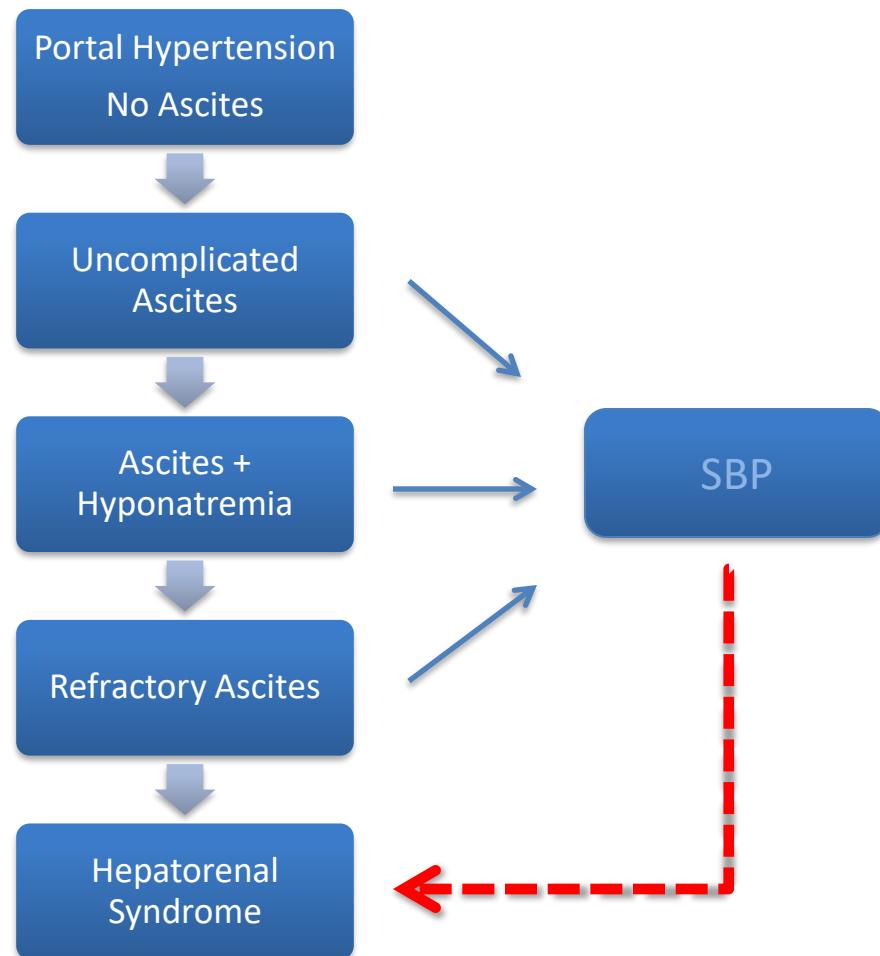
*Type I HRS now called HRS-AKI

Gastroenterology 2002; 122:1658.
Hepatology 2021; 74: 1014-1041.

Hepatorenal Syndrome – management

- Treatment of underlying liver disease (alcoholic hepatitis, HBV)
- Prevention with albumin infusion in SBP
- Cessation of nonselective beta blockers in SBP
- Treatment with vasoconstrictor drug in combination with albumin
- Terlipressin + Albumin – Terlipressin approved in U.S. in 9/2022
- Norepinephrine + Albumin equally effective to Terlipressin, less data
- Albumin/Octreotide/Midodrine
- Renal replacement therapy as bridge to liver recovery or transplant
- Liver transplantation

Natural History of Ascites from Cirrhosis



Spontaneous Bacterial Peritonitis: Treatment

Systemic antibiotics for Community Acquired SBP

- Ceftriaxone or Cefotaxime
- Avoid aminoglycosides
- Most patients will respond to 5 day course of treatment

Cessation of nonselective beta blockers

Albumin IV on Day 1 and Day 3 with any of following:

- BUN > 30mg/dL
- Creatinine > 1.0 mg/dL
- Serum bilirubin > 4mg/dL

Spontaneous Bacterial Peritonitis: Primary & Secondary Prophylaxis

- Childs B or C patients with cirrhosis hospitalized with GI bleeding (IV Ceftriaxone)
- Ascites total protein $<1.5\text{g/dL}$ AND
Renal failure (Creatinine ≥ 1.2 , BUN ≥ 25 or serum Na ≤ 130) OR
Liver failure (Child score ≥ 9 or Bilirubin ≥ 3)
- Prior history of SBP
- Trimethoprim/Sulfa 1DS tablet daily, Ciprofloxacin 500mg daily
- Intermittent/weekly dosing of antibiotics may be inferior to daily dosing

Treatment of Hepatic Encephalopathy

- Determine precipitant of hepatic encephalopathy and treat
- (Infection, Electrolytes, GI Bleeding, Constipation, Dehydration, Sedatives)
- Lower ammonia level
- Lactulose aiming for 2-4 bowel movements daily → Rifaximin
- Do not restrict protein: Maintain dietary protein intake of 1.2g to 1.5g/kg/day
- Use physical/neurologic exam rather than serial blood ammonia levels once treatment initiated

Clinically Significant Portal Hypertension: CSPH

- Clinically significant portal hypertension (CSPH) is HVP ≥ 10 mmHG
- Presence of clinical decompensation, GEV on endoscopy, portosystemic collaterals or hepatofugal flow on imaging is sufficient to diagnose CSPH
- Elastography + platelet count can be used to diagnose CSPH

Non-invasive staging of chronic liver disease	No cACLD	Possible cACLD	Highly suggestive of cACLD	cACLD	
Liver stiffness (kPa)	<10	10-15	15-20	20-25	>25
Platelet count (K/mm ³)	NR	NR	If <110 = CSPH	If <150 = CSPH	CSPH**

Risk of decompensation

CSPH: Management of Gastroesophageal Varices

- GEV present in 50% patients with cirrhosis: 30-40% compensated, 85% decompensated
- In patients with compensated cirrhosis varices develop at rate of 7-8%/year
- New diagnosis of cirrhosis: EGD to screen for varices OR ultrasound elastography + platelet count to assess for CSPH
- If varices on EGD or CSPH detected, start Carvedilol 6.25mg QD increase to 12.5mg QD if tolerated
- If no varices on original EGD, repeat EGD every 2-3 years or repeat elastography + platelet count annually
- EGD at time of clinical decompensation (ascites, encephalopathy) or assume CSPH and consider Carvedilol
- If cirrhosis, but no varices on EGD and no CSPH by elastography → prevent clinical decompensation
- Grade I varices → Non-selective beta blocker, Carvedilol preferred and if tolerated no need to repeat EGD
- Grade II-III varices → Non-selective beta blocker or band ligation

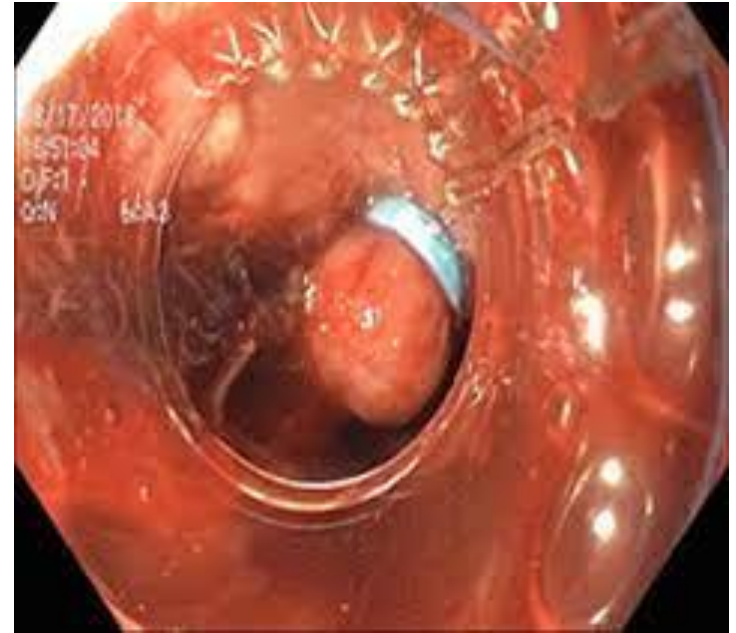
Management of Acute Bleeding in Patients with Cirrhosis

- Management of acute bleeding in patients with cirrhosis depends on location, severity and degree of hemostatic impairment
- For variceal bleeding, major cause is increased portal pressure rather than bleeding diathesis
- For non-variceal bleeding, manage INR, platelet count and fibrinogen level:
 - Vitamin K (usually IV)
 - Transfuse platelet count to $>50,000$
 - Administer source of fibrinogen to get level $\geq 100-120\text{mg/dL}$
(Cryoprecipitate less volume than FFP)
 - Consider antifibrinolytic (Tranexamic or Aminocaproic acid)
- Thrombopoietin (TPO) receptor agonists not effective in acute bleeding

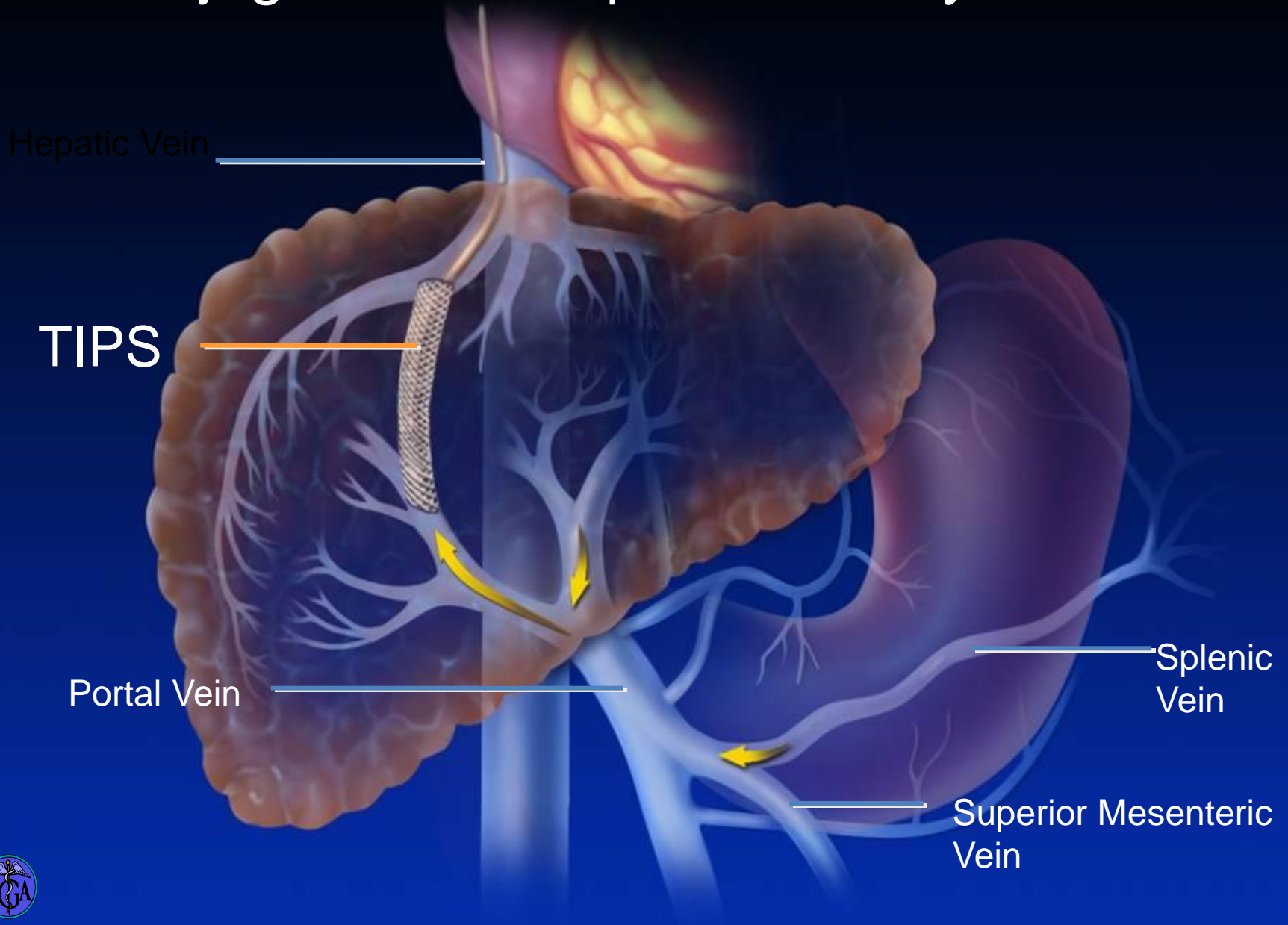
Management of Acute Variceal Hemorrhage

- Admit to ICU
- Upper endoscopy within 12 hours
- Restrictive blood volume resuscitation
Initiating PRBC transfusion at hemoglobin of 7 g/dL and maintain hemoglobin at 7-9 g/dL
- Short-term antibiotic prophylaxis (maximum 7 days)
IV Ceftriaxone 1g/24 hours is the antibiotic of choice
- Octreotide, Somatostatin, Terlipressin for 2-5 days → NSBB
- Consider TIPS in Childs C patients with cirrhosis or Childs B with active bleeding

Esophageal Varices & Band Ligation



Transjugular Intrahepatic Portosystemic Shunt



Management of Bleeding Gastric Varices

- Vasoactive drugs, restrictive transfusion, antibiotic prophylaxis
- Banding gastric varices can be technically difficult (IGV1> GOV2> GOV1)
- Cyanoacrylate glue injection
 - Polymerizes into firm clot within varix
 - Risk of distal embolization
 - Not approved by FDA for use in US, center dependent expertise
- TIPS
- Balloon-occluded retrograde obliteration (BRTO)
 - Balloon catheter in draining vessel then instill sclerosant/sponge
 - 90% long-term bleeding control
 - Can increase portal pressure: worsen esophageal varices, ascites
- EUS-guided transesophageal coiling of gastric varices

Optimal Timing of Referral for LT

Clinical Decompensation + Biochemical Decompensation (MELD >15)

- Encephalopathy
- Ascites
- Variceal Hemorrhage or chronic GI bleed from portal hypertensive gastropathy
- Hepatocellular Carcinoma
- Hepatorenal syndrome
- Hepatopulmonary syndrome or Portopulmonary Hypertension

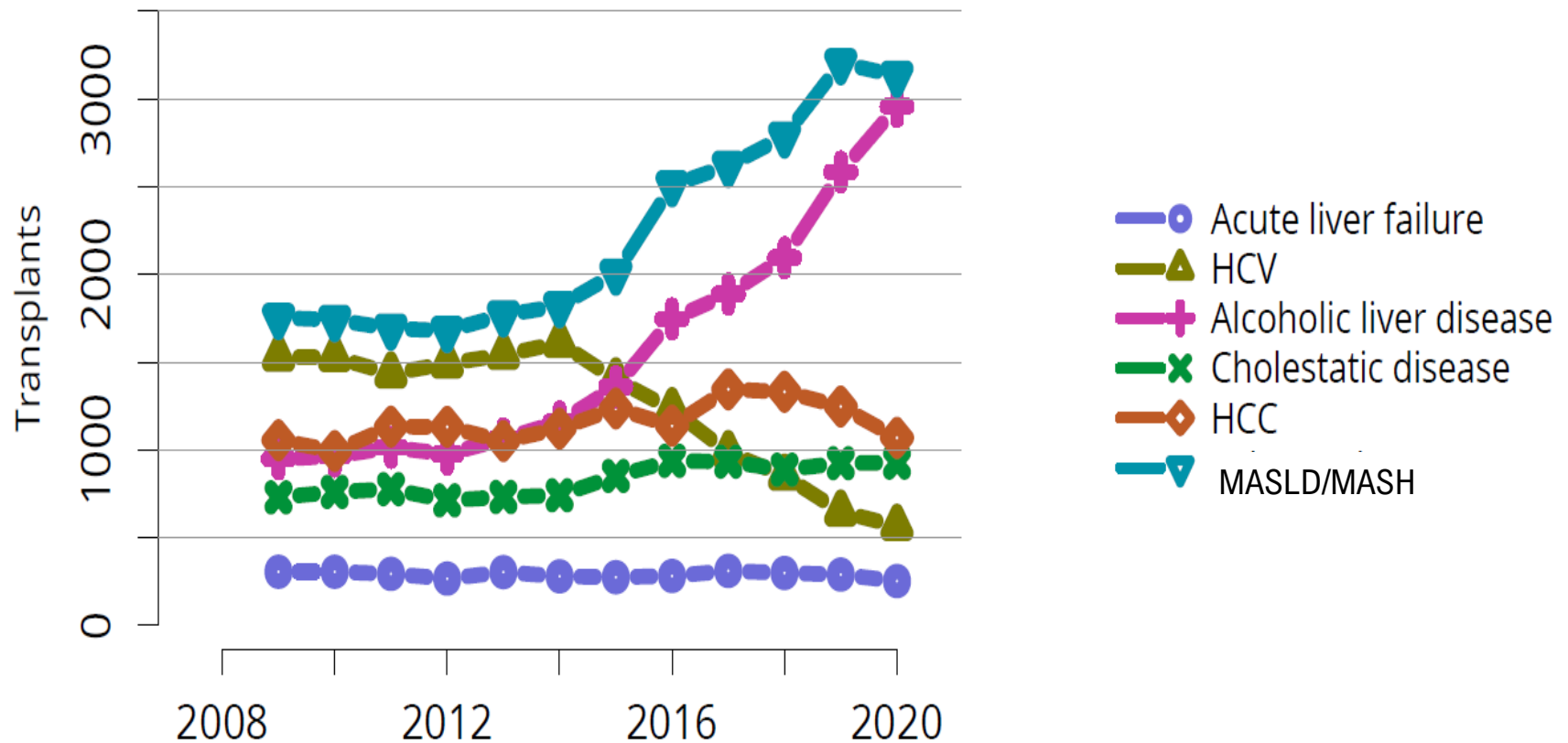
Other considerations:

- Acute Liver Failure
- Severe Alcoholic Hepatitis
- Poor quality of life or recurrent, resistant infections in PSC/PLD

Timing: What is MELD?

- Model for End-stage Liver Disease
- Originally created to predict short term mortality post TIPS
- Basis for liver allocation in U.S. since 2/2002
- MELD-Sodium used since 1/2016
- MELD 3.0 used since 7/2023 (In Epic .MELDPELD)
- 5 objective lab tests (Sodium, Total bilirubin, Creatinine, INR, Albumin + gender)
- Highly predictive of 3-month mortality in patients with cirrhosis
- MELD of 15 is threshold for patient survival with transplantation > survival without transplantation

Liver Disease Etiology of Adult Transplant Recipients



Exclusions for Liver Transplantation

MELD Score <15

Severe cardiac or pulmonary disease

AIDS

Ongoing alcohol or illicit substance abuse

HCC with metastatic spread

Uncontrolled sepsis

Anatomic abnormality that precludes liver transplant

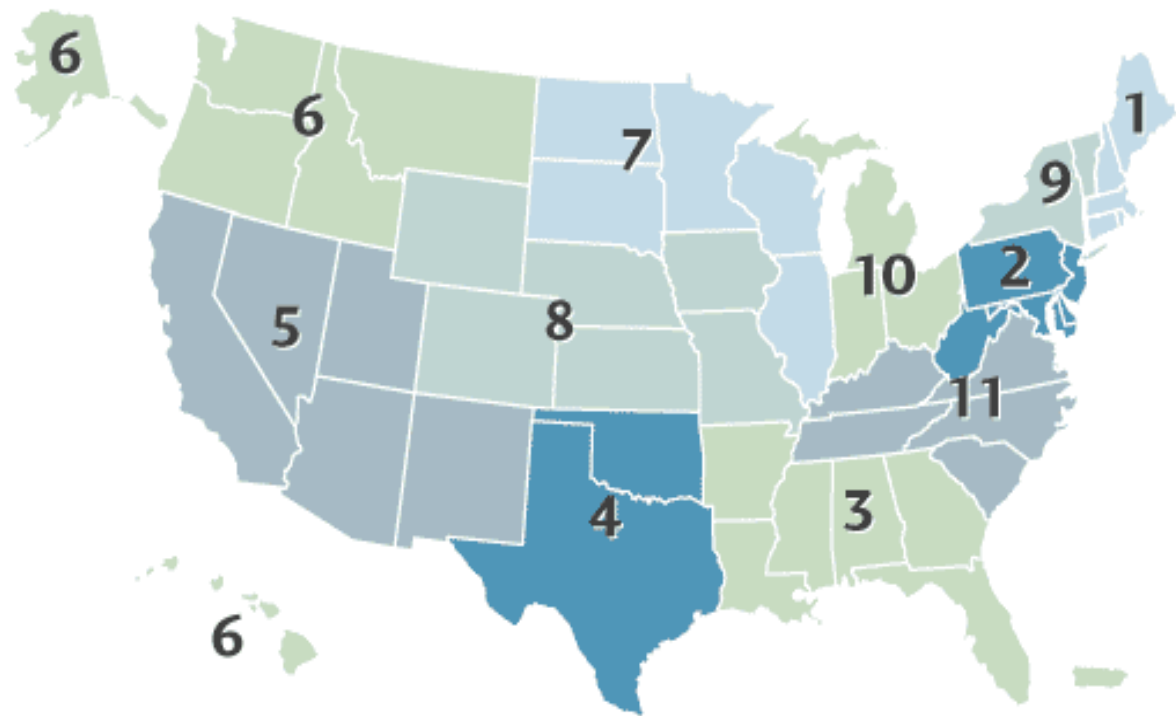
Intrahepatic cholangiocarcinoma

Extrahepatic malignancy

Persistent non-compliance

Lack of adequate social support system

Liver Transplants in 2024 in 11 UNOS Regions



REGION	2024
1	473
2	1088
3	1697
4	1260
5	1904
6	324
7	894
8	660
9	828
10	1023
11	1301

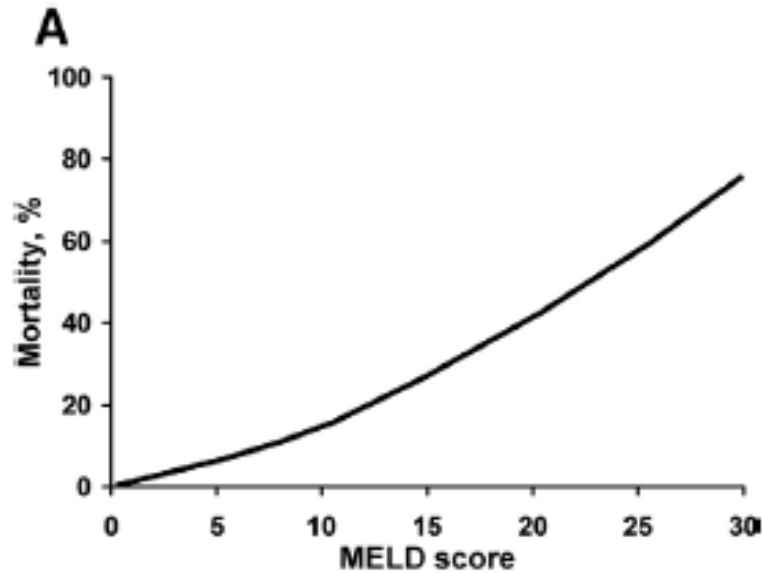
Living Donor Liver Transplantation (LDLT)

- In 2024 U.S. total LTs 11,508 (LDLT 604 or 5.25%)
- Patient must be listed for deceased donor transplant
- Anticipated prolonged time on wait list with MELD >15
- Recipients of LDLT are less sick: MELD 15-20
- Has family member or acquaintance with close relationship – no coercion
- In adult, take the right lobe (2/3 mass of liver) from donor
→ recipient
- Pediatric cases use left lobe

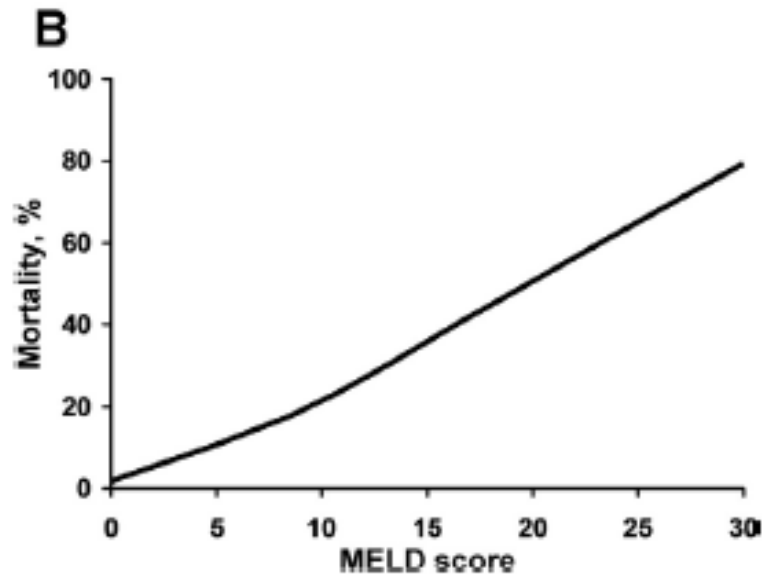
Surgical Risk in Patients with Cirrhosis

- Child-Turcotte-Pugh (CTP) and MELD score predict peri-operative morbidity and mortality
- Most CTP studies from cardiac or abdominal surgical literature
- Child's A: 10%, Child's B: 30%, Child's C: 80%
- Mayo clinic study – looked at pre-operative MELD, age and ASA class in 772 patients with cirrhosis undergoing surgery
- MELD was best predictor of 30-day and 90-day mortality
- MELD ≤ 7 : 5.7%, MELD 8-11: 10.3%, MELD 12-15: 25.4%
- VOCAL-Penn score (<http://www.vocalpenscore.com>) looks at urgency, type of surgery, age, albumin, platelet count, bilirubin, BMI, ASA class, +/- fatty liver

Pre-operative MELD and Post-operative Mortality



30 Day Mortality



90 Day Mortality



VOCAL-Penn

Cirrhosis Surgical Risk Score

Enter the following data:

SI Units ☐

Age:

Albumin:

Total Bilirubin:

Platelet Count:

BMI ≥ 30 :

MASLD:

ASA Score:

Emergency:

Surgery Type:

Predicted Postoperative Outcomes:

30-day **mortality**:

90-day **mortality**:

180-day **mortality**:

90-day **decompensation**:

VOCAL-Penn predicts post-operative mortality for patients with cirrhosis. It incorporates the type and circumstance of surgery under consideration, and utilizes other important and readily available clinical data. Predictions may be used to risk-stratify patients for surgery and help inform decisions to pursue surgical or non-surgical management.

Disclaimer: note that VOCAL-Penn predictions should not substitute for clinical judgment. They are an adjunctive tool to be used in prognostic discussions between clinicians and patients.

Questions or comments? [Email Us](#).

www.vocalpennscore.com

Acute on Chronic Liver Failure (ACLF)

Severe form of acutely decompensated cirrhosis or chronic liver disease, characterized by:

- Functional failure of one or more of the six major organ systems (liver, kidney, brain, coagulation, circulation and respiration)
- Systemic inflammation
- 28-day mortality rate of $\geq 20\%$
- Distinct entity from Acute Liver Failure (ALF) and decompensated cirrhosis

Table 1. Definitions of ACLF

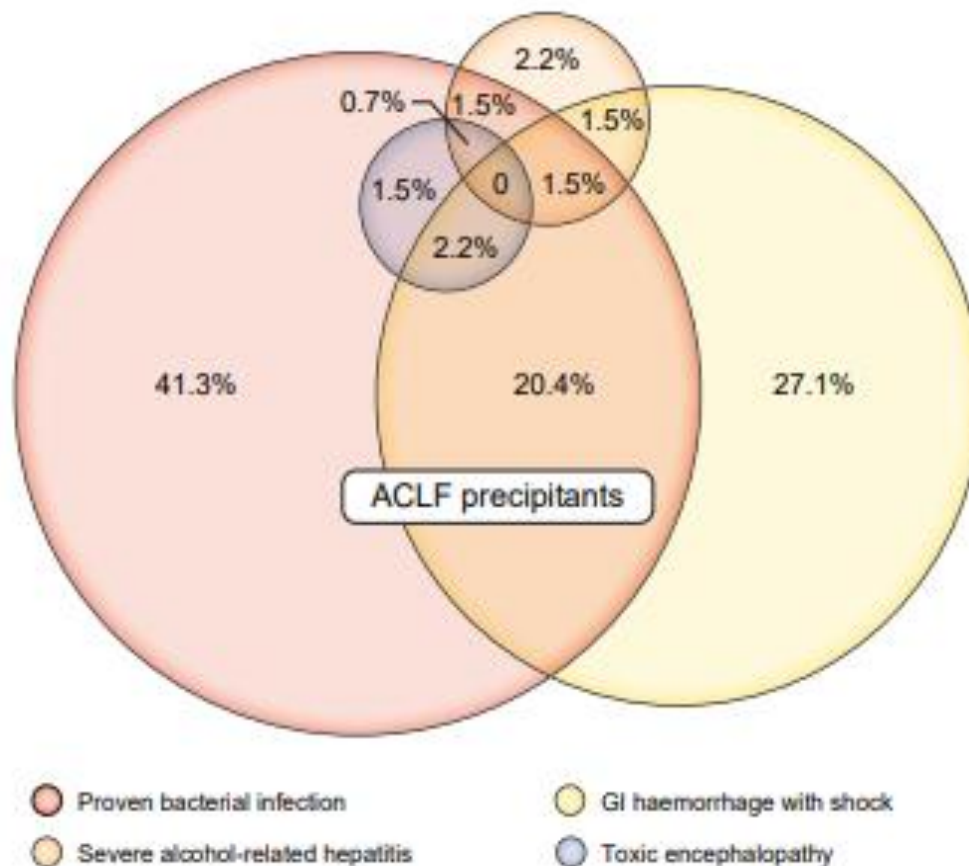
Society	EASL-CLIF	AASLD
Similarities	Acute decompensation of chronic liver disease.	
Differences	<ul style="list-style-type: none">• Chronic liver disease in the form of cirrhosis.• Acute decompensations include development of ascites, hepatic encephalopathy, gastrointestinal hemorrhage, and/or bacterial infections.	<ul style="list-style-type: none">• Chronic liver disease can be with or without cirrhosis.• Liver failure defined as elevated bilirubin and INR.• At least one extrahepatic organ failure (e.g.: neurologic, circulatory, respiratory, renal).

Acute Liver Failure vs. ACLF

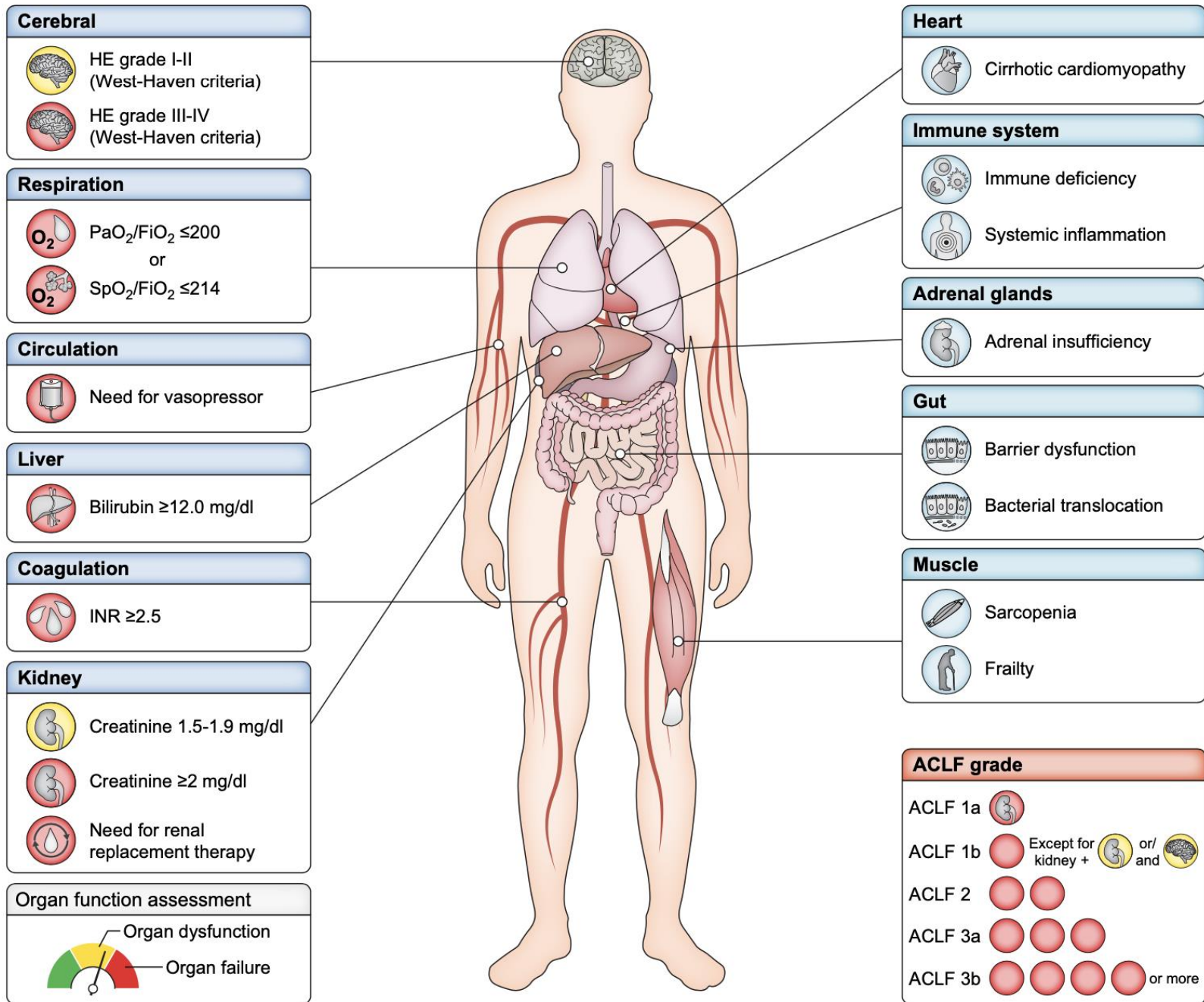
	ALF	ACLF
Age	Younger	Older
Chronic liver disease	Absent	Present Signs of portal hypertension
Precipitating factors (by frequency)	DILI, viral hepatitis, autoimmune hepatitis	Infection, alcohol, GI bleeding,
Clinical signs	Liver injury, INR>1.5, HE	Coagulopathy, elevated bilirubin, shock, multiorgan dysfunction
Liver biopsy	Necrosis and collapse	Fibrosis
CNS	Increased intracranial pressure Use CRRT early for HE	HE responds to lactulose/Rifaximin
Infection	Late (<5 d)	Early (<5 d)
Renal failure	Hypoperfusion, ATN	HRS-AKI
Respiratory	ARDS rare	ARDS common
Liver transplantation	KCC, MELD Status 1A listing	MELD No priority in MELD system

American Journal of Gastro 2023; 118: 1128-1154.

ACLF Precipitants



Worldwide also consider: HBV reactivation, Drug induced brain or kidney injury



ACLF Prognosis

A

Organ System	1 Point	2 Points	3 Points
Liver	Bilirubin <6 mg/dl	Bilirubin 6.0–11.9 mg/dl	Bilirubin ≥12 mg/dl
Kidney	Creatinine <1.5 mg/dl Creatinine 1.5–1.9 mg/dl	Creatinine 2.0–3.4 mg/dl	Creatinine ≥3.5 mg/dl or RRT
Brain (West Haven criteria)	Grade 0	Grade 1–2	Grade 3–4
Coagulation	INR <2.0	INR 2.0–2.4	INR ≥2.5
Circulation	MAP ≥70 mm Hg	MAP <70 mm Hg	Vasopressor requirement
Respiration	Pao ₂ /Fio ₂ >300 Spo ₂ /Fio ₂ >357	Pao ₂ /Fio ₂ 201–300 Spo ₂ /Fio ₂ 215–357	Pao ₂ /Fio ₂ ≤200 Spo ₂ /Fio ₂ ≤214

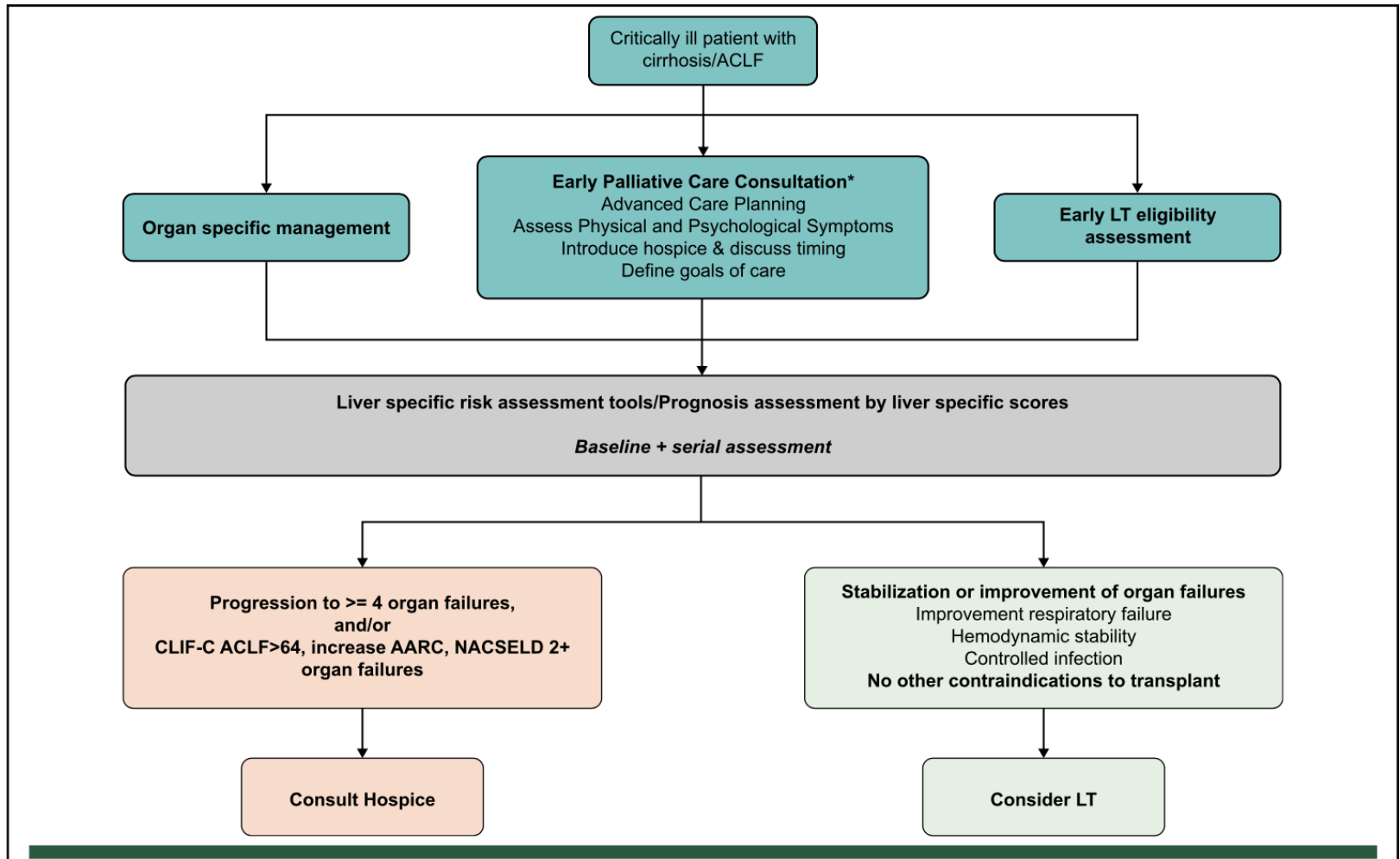
B

Patient Group	Prevalence % of patients	28-Day Mortality	Assigned Grade
Absence of OF	68.3	4.4	Absence of ACLF
Single, nonkidney OF without KD or BD	9.9	6.3	
Single KF	6.7	18.6	ACLF-1
Single, nonkidney OF with KD or BD	4.2	27.8	ACLF-1
Two OFs	7.5	32.0	ACLF-2
Three OFs	1.9	68.0	ACLF-3
Four to six OFs	1.4	88.9	ACLF-3

EASL CLIF-C score components.

Scores that account for hepatic and extrahepatic organ failures (CLIF-C, NACESLD or AARC ACLF scores) are recommended over MELD to assess critically ill patients with cirrhosis/ACLF

AASLD Practice Guidance on ACLF



Key Take Aways

- Hepatic decompensation reduces survival
- MELD and CTP scores predict 3-month and 1-year mortality in patients with cirrhosis
- TIPS > LVP in management of refractory ascites
- Prevention of HRS includes antibiotics in UGI bleeding, IV albumin in SBP/LVP
- Nonselective beta blocker cessation in SBP
- Consider early TIPS in Childs B/C variceal bleeds
- Gastric varices: cyanoacrylate glue, TIPS, BRTO, EUS coiling in select patients
- Refer for liver transplantation: MELD \geq 15 + clinical decompensation
- CTP, MELD and VOCAL-Penn score useful in estimating surgical risk in patients with cirrhosis
- ACLF is distinct entity from ALF and decompensated cirrhosis – use CLIF-C, NACSELD and AARC ACLF scores >> MELD for assessing prognosis

Select References

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A 61 year old patient with HCV cirrhosis is admitted with abdominal pain and confusion. His admission creatinine is 2.1 (baseline 1.0), and he has evidence of SBP on tap (>250 PMNs). In addition starting Ceftriaxone, your next steps in management should include:

- A) Stop Nadolol
- B) Albumin infusion 1.5g/kg IV
- C) Check urinalysis
- D) Start Pentoxifylline 300mg TID
- E) A, B and C

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- A) Stop Nadolol
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- C) Check urinalysis
- D) Start Pentoxifylline 300mg TID
- E) A, B and C

The correct answer is E. This man with cirrhosis has what appears to be acute kidney injury in the setting of spontaneous bacterial peritonitis (SBP). The urinalysis is recommended to evaluate the acute kidney injury, which could be hepatorenal syndrome (HRS) or something else. In SBP there is data to support cessation of non-selective beta blockers while the infection is being treated, as well as giving albumin infusion of 1.5 g/kg of body weight to prevent HRS on the first day of treatment. There is no data to support the use of Pentoxifylline in patients with cirrhosis with acute kidney injury or SBP.

On hospital day #2, this patient has massive hematemesis.

Urgent endoscopy shows grade III esophageal varices with red wale signs. He has 3 bands placed. Next steps should include:

- A) Octreotide IV for 72 hours
- B) Consider BRT0 before he rebleeds
- C) Transfuse to keep hemoglobin > 10g/dL
- D) Referral for urgent liver transplantation

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- C) Transfuse to keep hemoglobin > 10g/dL
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The correct answer is A. Management of an acute esophageal variceal bleeding includes upper endoscopy within 12 hours, vasoactive medications such as Octreotide for 72 hours and antibiotic prophylaxis. A hemoglobin threshold of > 7g/dL reduces the risk of rebleeding when compared to a transfusion threshold of > 9g/dL. BRTO is used in management of isolated gastric variceal bleeding. Acute variceal bleeding is not an indication for urgent liver transplantation, and it does not give additional points to the MELD score.

