Cirrhosis for the Hospitalist

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HARVARD MEDICAL SCHOOL
TEACHING AFFILIATE

I have no disclosures relevant to this presentation.

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Learning Objectives

- Natural history and outcome of cirrhosis
- Initial management of complications of cirrhosis
- Updates/Recent studies on management of complications of cirrhosis
- Appropriate timing of referral for liver transplantation
- Pre-operative risk assessment in cirrhotics

Patient RS

52 year old with alcoholic and HCV cirrhosis
Sober for 5 years

Recently developed ascites → now on Furosemide, Spironolactone, low salt diet

Family thinks he is unsafe to drive due to inattention → Lactulose recently started

Comes in to ER with diffuse abdominal pain and distension and confusion

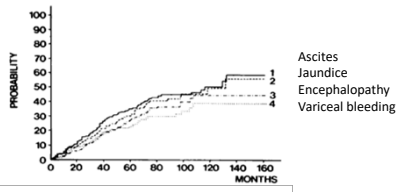
While he is being evaluated in ER, his wife asks you how long he can live like this?

Natural History of Chronic Liver Disease

Chronic Liver Disease → Compensated Cirrhosis → Decompensated Cirrhosis → Death

Ascites
Jaundice
Encephalopathy
Variceal Hemorrhage

Probability of Hepatic Decompensation: 58% over 10 years



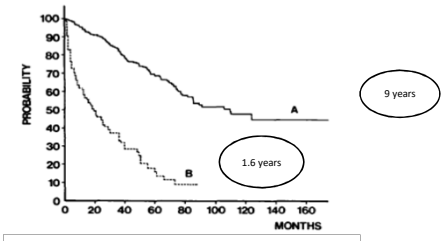
Ascites
Jaundice
Encephalopathy
Variceal bleeding

Hepatology 1987; 7: 122-128

Risk Factors for Hepatic Decompensation

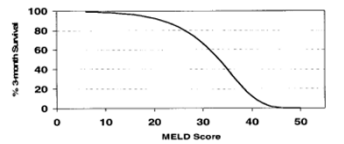
- GI Bleeding
- Infection
- Alcohol intake
- Medications
- Dehydration
- Constipation
- Obesity (Hepatology 2011; 54: 555)
- Surgery
- Ongoing viral infection

Hepatic Decompensation Reduces Survival



Hepatology 1987; 7: 122-128

Prediction of 3-Month Survival in Cirrhotics



MELD score = 3.8 ln (bilirubin) + 11.2 ln (INR) + 9.6 ln (creatinine) + 6

Prediction of 1 Year Survival in Cirrhotics: 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

Management Considerations in Cirrhosis

- Preventing and treating complications
- Determining appropriateness and timing for liver transplantation referral
- Pre-operative risk assessment in cirrhotics

Natural History of Cirrhotic Ascites

Portal Hypertension
No Ascites

Uncomplicated Ascites

Ascites + Hyponatremia

Refractory Ascites

Management of Ascites

- 50% of compensated cirrhotics will develop ascites 10 years from diagnosis
- 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) not data supported
- SAAG of ≥ 1.1 is 97% accurate for portal hypertension

AASLD Guidelines: Hepatology 2013; 57: 1651–1653.

Treatment Options for Cirrhotics with Ascites

- Cessation of Alcohol use
- Sodium restricted diet (2000mg/day) and education
- Dual diuretics:Spironolactone and Furosemide, orally with single daily dosing
- Most patients do not need fluid restriction
- Ratio Spironolactone 100mg: Furosemide 40mg, increase every 3-5 days
- Maximum doses are Spironolactone 400mg: Furosemide 160mg
- Amiloride 10-40mg substituted for Spironolactone for tender gynecomastia
- Consider stopping NSAIDS, ACE Inhibitors, Angiotensin Receptor blockers, Propranolol
- Liver transplant evaluation
- Weekly albumin infusion in decompensated cirrhotics improves overall survival (ANSWER study)

Lancet 2018; 391: 2417-2429.

Over the last few months R.S. has been unable to receive diuretics due to hyponatremia.
What are other management steps that might be considered for his ascites:

1) TIPS
2) Large volume paracentesis with albumin repletion
3) Liberalize his 2g/day sodium diet to 4g/day
4) Urgent liver transplant listing: refractory ascites gives extra listing points
5) Increasing non-selective beta-blocker

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Management of Refractory Ascites

- 10% of cirrhotics 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

Hepatology 2010; 52: 1017-1022.
Hepatology 2016; 63: 1968-1976.

Large Scale Randomized Controlled Trials of TIPS vs. LVP for Refractory Ascites

N	Control of Ascites	Survival	Encephalopathy
60	61% vs. 18% (p=.006)	69% vs. 52% (p=.11)	58% vs. 48%*
70	51% vs. 17% (p=.003)	41% vs. 35% (p=.29)	77% vs. 66%
109	58% vs. 16% (p<.001)	40% vs. 37%*	60% vs. 34% (p=.058)
66	79% vs. 42% (p=.001)	77% vs. 52% (p=.021)	Severe (p=0.39)

* P value not significant.

AASLD Guidelines: Hepatology 2013; 57: 1651–1653

RS has admission sodium of 121, creatinine of 2.1, and evidence of SBP on tap (>250 PMNs). In addition to starting Ceftriaxone, your next steps in management should include:

1) Stop Nadolol
2) Albumin infusion 1.5mg/kg IV
3) Check urinalysis
4) Start Pentoxyfylline 300mg TID
5) A,B and C

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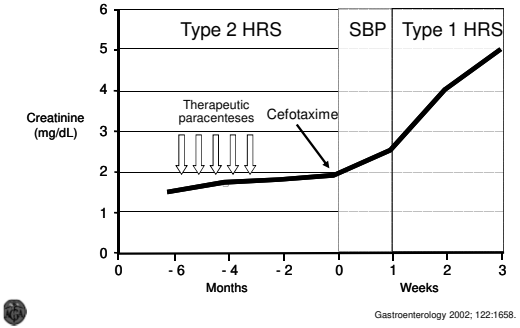
Hepatorenal Syndrome

Hepatorenal Syndrome – clinical features

- Cirrhosis with ascites
- Serum creatinine > 1.5mg/dL
- No creatinine improvement after 2 days diuretic withdrawal
- No creatinine improvement after volume expansion with albumin (1g/kg up to 100g)
- Absence of shock, nephrotoxins
- Bland urine sediment/no parenchymal kidney disease

AASLD Guidelines: Hepatology 2013; 57: 1651–1653.

Natural History of Hepatorenal Syndrome

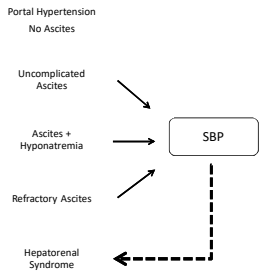


Gastroenterology 2002; 122:1658.

Hepatorenal Syndrome – management

- Treatment of underlying liver disease (alcoholic hepatitis, HBV)
- Prevention with albumin infusion in SBP
- Cessation of nonselective beta blockers in SBP
- Albumin/Octreotide/Midodrine
- In ICU, Norepinephrine (or Vasopressin) + Albumin
- Terlipressin – not approved in U.S.
- Hemodialysis as bridge to liver recovery or transplant
- TIPS
- Liver transplantation

Natural History of Cirrhotic Ascites



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

Best Pract Res Clin Gastroenterol 2007; 21: 77-93.
Gastroenterology 2014; 146: 1680-1690.

Spontaneous Bacterial Peritonitis: Primary & Secondary Prophylaxis

- Childs B or C cirrhotics hospitalized with GI bleeding (IV Ceftriaxone)
- Cirrhotics with ascites total protein <1g/dL hospitalized for something other than GI bleeding
- Ascites total protein <1.5g/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

Hepatology 2013; 57: 1651-1653

R.S. is being treated for SBP, but his encephalopathy persists. Lactulose was held on admission due to concern for intravascular volume depletion. Other potential treatment options for encephalopathy include:

1) Hemodialysis
2) Rifaximin 550mg BID
3) 4 Liters Polyethylene Glycol (PEG)
4) Neomycin 6g BID
5) Protein restriction

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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

A Few Words on Ammonia….

- Ammonia is produced by enterocytes from glutamine and colonic bacteria catabolism of nitrogenous sources → portal vein
- A healthy liver clears almost all portal vein ammonia → converts to urea or glutamine
- Ammonia is neurotoxin involved in hepatic encephalopathy (HE), but mechanism is not understood
- Elevated serum ammonia is not required to make diagnosis of HE
- Elevated serum ammonia is not specific for HE
- Can be measured in arterial or venous blood
- Ammonia levels influenced by how blood sample is obtained and handled
- Serum ammonia levels should NOT be used to screen for HE in asymptomatic cirrhotic patients
- Serial ammonia levels not necessary in monitoring response to HE treatment

On day #2, R.S. has massive hematemesis. Urgent endoscopy shows grade III esophageal varices with red wale signs. He has 3 bands placed. Next steps should include all of the following except:

1) Octreotide IV for 72 hours
2) Consider TIPS before he rebleeds
3) Transfuse to keep hemoglobin > 10g/dL
4) Continue Ceftriaxone treatment for SBP

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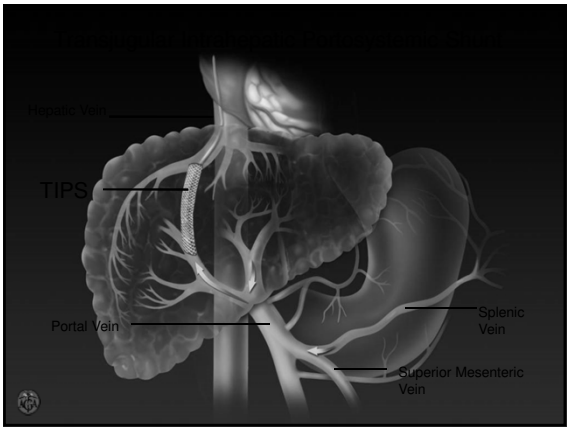
Management of Acute Variceal Hemorrhage

- 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 cirrhotics or Childs B with active bleeding

AASLD Guidelines Hepatology 2017; 65: 310-335.
Hepatology 2019; 69: 282-293.

Management of Acute Bleeding in Cirrhotics

- Management of acute bleeding in cirrhotics 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 ≥ 100-120mg/dL
    (Cryoprecipitate less volume than FFP)
  - Consider antifibrinolytic (Tranexamic or Aminocaproic acid)
- Thrombopoietin (TPO) receptor agonists not effective in acute bleeding



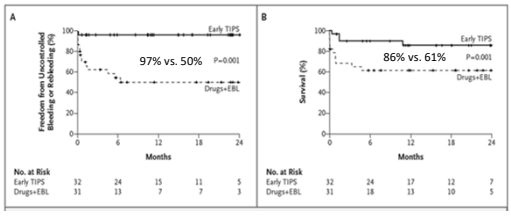
Early TIPS An Option for Variceal Hemorrhage

- 63 Child B/C cirrhotics with acute variceal bleeding
- All had vasoactive drugs and endoscopic therapy, then randomized:
- 32 underwent TIPS within 72 hours of admission
- 31 continued vasoactive drugs for 3-5 days → Nadolol/Propranolol and continued banding
- 7/31 needed rescue TIPS
- Median follow-up 16 months
- At 1 year, episodes of encephalopathy 18% TIPS vs. 10% pharmacologic (p=.80)
- No significant differences in adverse events

NEJM 2010; 362: 2370-2379.

Early TIPS An Option for Variceal Hemorrhage

Rebleeding | Survival



NEJM 2010; 362: 2370-2379.

If the EGD on R.S. showed isolated bleeding gastric varices, what would your treatment options include:

1) Consult vascular radiology for TIPS
2) Consult vascular radiology for BRTO
3) Cyanoacrylate glue injection
4) Continue IV Octreotide and proceed with urgent transplant evaluation
5) A, B or C

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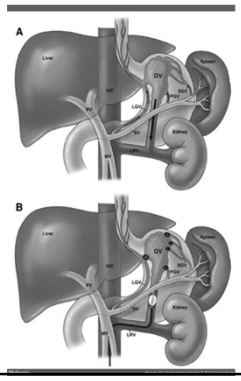
5) **A, B or C**

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

Balloon Retrograde Transcatheter Obliteration



Patient RS

R.S. is slowly recovering from SBP and variceal bleed
Continues IV Ceftriaxone for 5 days → Ciprofloxacin
Creatinine slowly normalizes
Transitions from IV Octreotide → debate about restarting Nadolol
Encephalopathy improves with initiation of Rifaximin and improvement in SBP, hyponatremia
MELD is 19

His wife asks you what else can be done?

Optimal Timing of Referral for LT

Clinical Decompensation + Biochemical Decompensation (MELD >15)

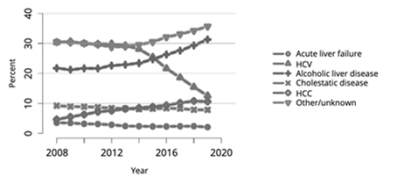
- Encephalopathy
- Ascites
- Variceal Hemorrhage or chronic GI bleed from portal hypertensive gastropathy
- Hepatocellular Carcinoma
- Hepatorenal syndrome
- Hepatopulmonary syndrome or Portopulmonary Hypertension

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
- 4 objective lab tests (Sodium, Total bilirubin, Creatinine, INR)
- Highly predictive of 3-month mortality in cirrhotics
- MELD of 15 is threshold patient survival with transplantation > survival without transplantation

Liver Disease Etiology of Adult Transplant Recipients



SRTR.transplant.hrsa.gov 2020

Exclusions for Liver Transplantation

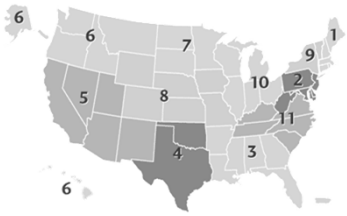
MELD Score <15
Severe cardiac or pulmonary disease
AIDS
Ongoing alcohol or illicit substance abuse
HCC with metastatic spread
Uncontrolled sepsis
Anatomic abnormality that precludes liver transplant
Intrahepatic cholangiocarcinoma
Extrahepatic malignancy
Persistent non-compliance
Lack of adequate social support system

Hepatology 2014; 59: 1144-1165.

Patient RS

- RS is listed for liver transplantation with MELD of 19
- His family wants to know how long until he gets a deceased donor liver transplant?
- What can he do to increase his chances of receiving a transplant?

Liver Transplants in 2020 in 11 UNOS Regions



REGION	2020
1	340
2	974
3	1340
4	963
5	1457
6	256
7	786
8	525
9	595
10	843
11	827

Living Donor Liver Transplantation

- ~5% of liver transplants in U.S. in 2020
- 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 living donor transplant

Patient RS

- RS has multiple ER visits for protruberant and painful umbilical hernia, ?hernia incarceration
- MELD remains ~19-20
- General surgery recommends hernia repair
- General surgery requests pre-operative "hepatology clearance"

R.S. has risk of peri-operative mortality at 30 days following elective hernia repair closest to:

1) 1%
2) 10%
3) 30%
4) 80%

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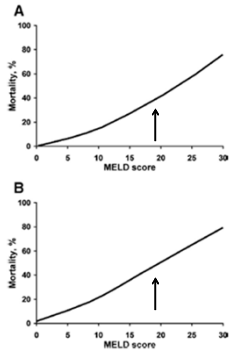
1) 1%
2) 10%
3) **30%**
4) 80%

Surgical Risk in Cirrhotics

- 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 cirrhotics 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.vocalpennscore.com) looks at urgency, type of surgery, age, albumin, platelet count, bilirubin, BMI, ASA class, +/- fatty liver

Gastroenterology 2007; 132: 1261-1269.
Hepatology 2021; 73: 204-218.

Pre-operative MELD and Post-operative Mortality



30 Day Mortality

90 Day Mortality

Gastroenterology 2007; 132: 1261-1269.

Summary

- Hepatic decompensation reduces survival
- MELD and CTP scores predict 3-month and 1-year mortality in hospitalized cirrhotics
- 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 ≥ 15 + clinical decompensation
- CTP, MELD and VOCAL-Penn score useful in estimating surgical risk in cirrhotics

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Management of Gastroesophageal Varices

- GEV present in 50% cirrhotics: 30-40% compensated, 85% decompensated
- In compensated cirrhotics, varices develop at rate of 7-8%/year
- LS < 20kPA and platelet count > 150,000 very unlikely to have GE varices
- EGD to screen for gastroesophageal varices recommended with new diagnosis of cirrhosis
- If no varices on original EGD, repeat every 2 years with ongoing liver injury (obesity, alcohol) or 3 years (abstinence, viral elimination)
- Small varices (grade 1) on original EGD → repeat 1-2 years
- EGD at time of other clinical decompensation (ascites, encephalopathy)
- If cirrhosis but no varices → prevent clinical decompensation
- Grade 1 varices → Non-selective beta blocker
- Grade 2-3 varices → Non-selective beta blocker or variceal ligation

Hepatology 2017; 65: 310-332.