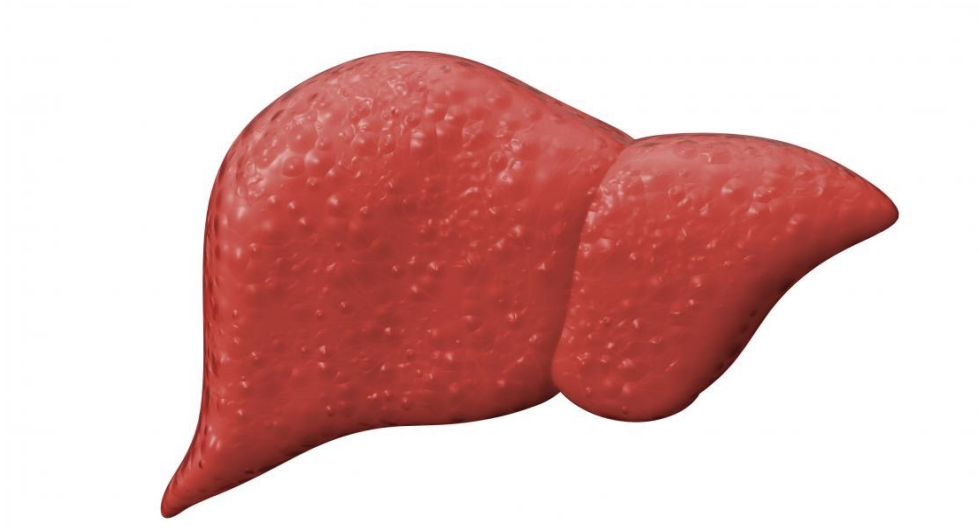
My Patient Has Cirrhosis: Seven Things to Know

Kathy Crow, M.S., PA-C

Texas Liver Tumor Center

University Health /UT Health



Disclosure Statement

- The speaker has nothing to disclose.

Learning Objectives

- Review the stages and etiology of cirrhosis
- Define and describe portal hypertension
- Describe seven complications of cirrhosis
- Review screening and management strategies in the patient with cirrhosis

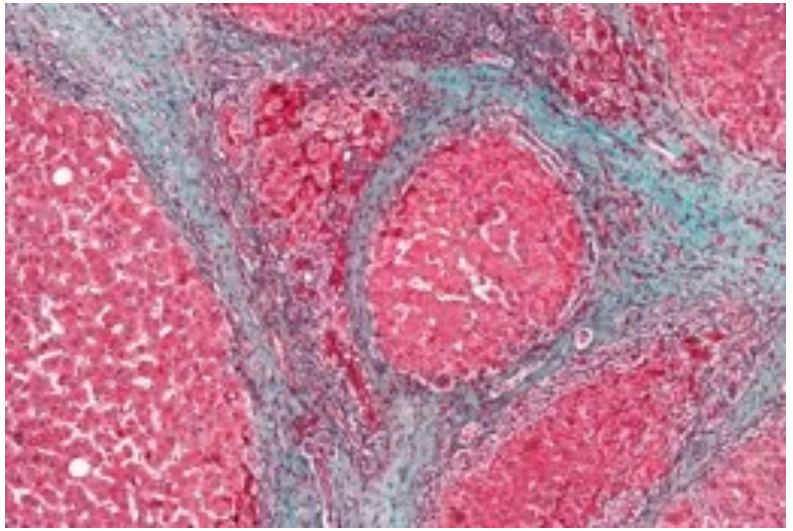
Cirrhosis

Defined:

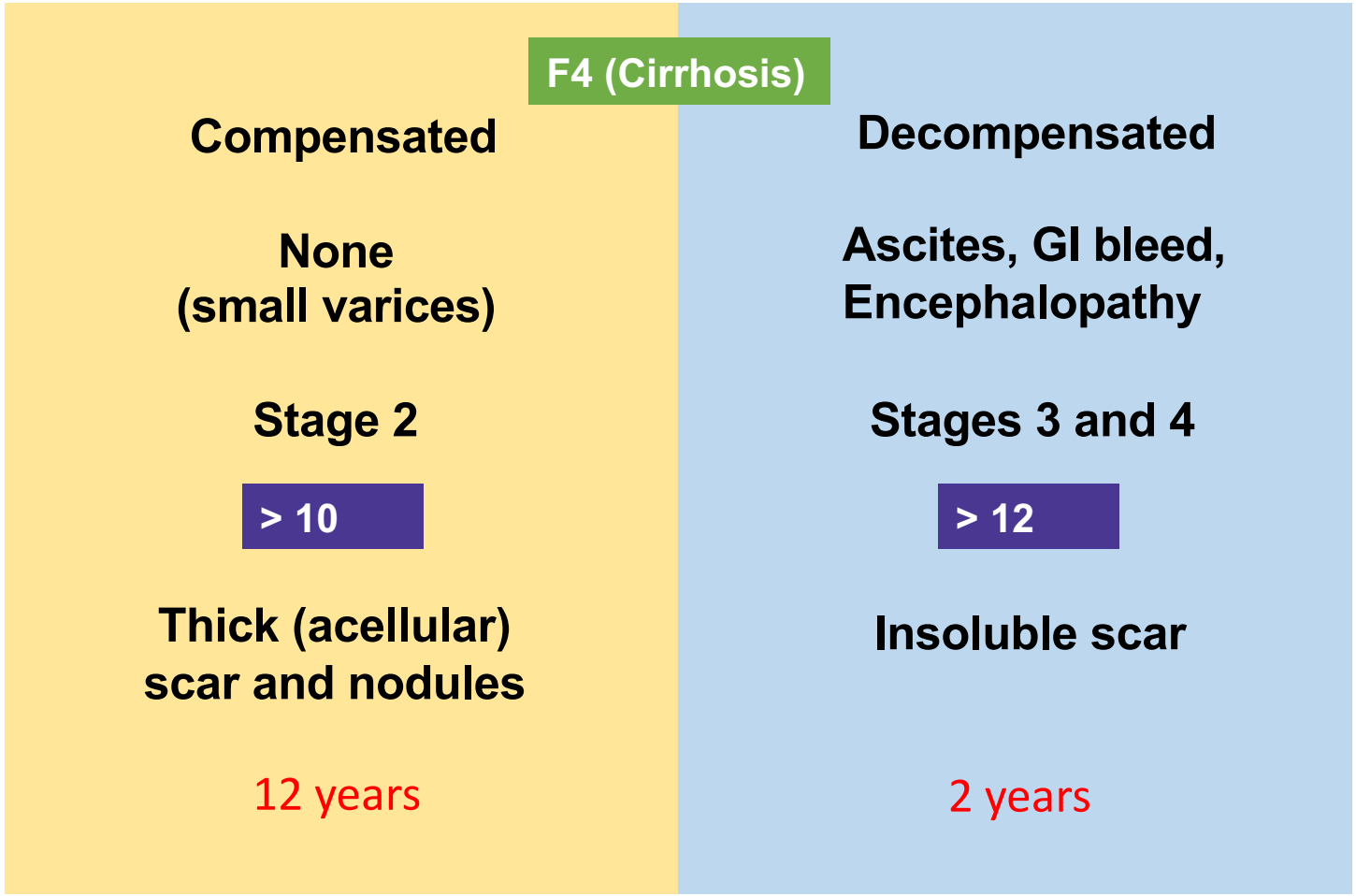
Progressive disease due to scarring from chronic liver injury.

Goal:

Manage early cirrhosis to prolong the compensated stage and
prevent complications



Cirrhosis Classification



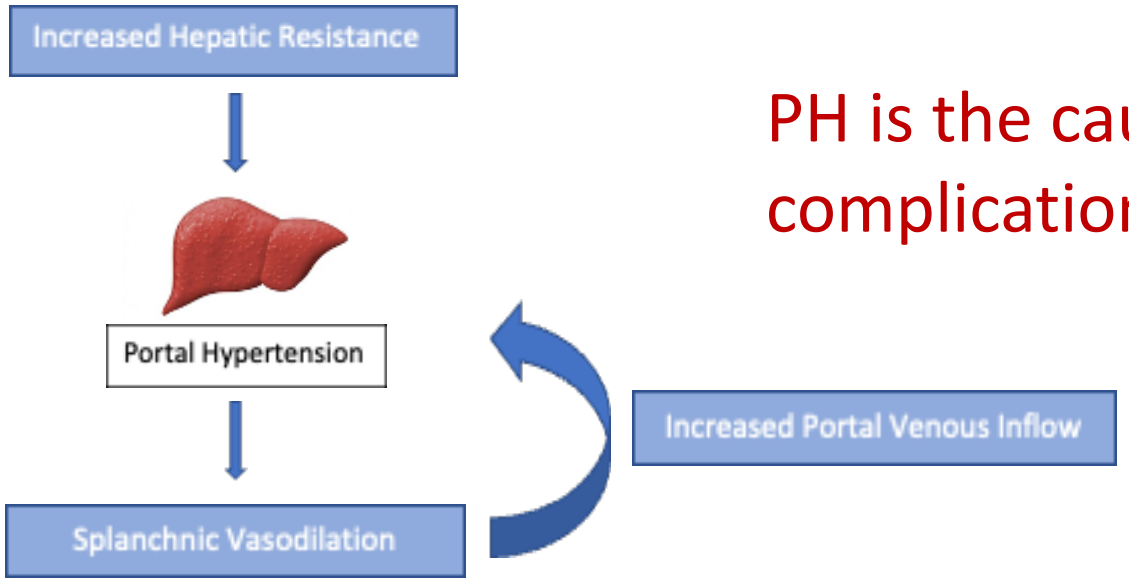
Garcia-Tsao G, et al. *Hepatology.* 2010; 51:1445-9; Viral Hepatitis and Liver Disease: https://www.hepatitis.va.gov/cirrhosis/background/stages.asp

Compensated Cirrhosis

- Clinical Signs
  - Platelets <150,000
  - AST > ALT without alcohol consumption
    - Liver enzymes may be normal
  - Albumin < 3.5 mg/dL
  - Total bilirubin > 1.0-1.2
  - Muscle wasting

What is Portal Hypertension?

- Intrahepatic vascular resistance to portal blood flow due to distortion of the architecture of the liver from fibrosis/scarring.
- Splanchnic vasodilation occurs as a response, increasing the portal blood flow and worsening the portal pressure elevation.



PH is the cause of most cirrhosis complications

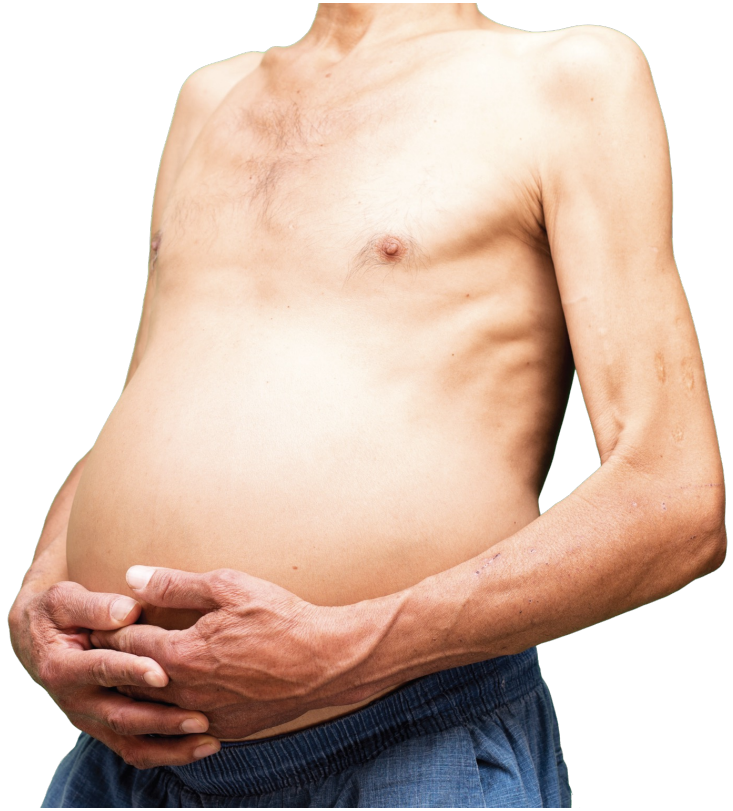
Gracia-Sancho, J. and Laleman, W. (2016), Mechanisms of portal hypertension: Bench to bedside. Clinical Liver Disease, 8: 160-166. https://doi.org/10.1002/cld.604

Ascites

Ascites

- Most common complication of cirrhosis
  - 58% will develop within 10 years
  - May have peripheral edema

- Goals of therapy
  - Minimize ascitic fluid volume
  - Decrease peripheral edema
  - Avoid intravascular volume depletion
  - Protect the kidneys



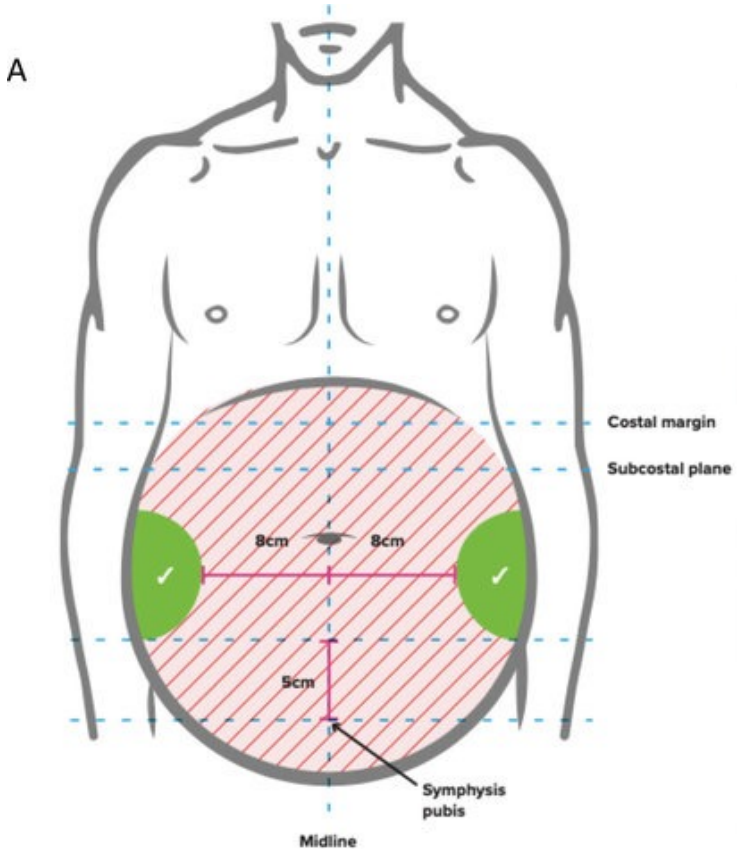
Ascites Treatment

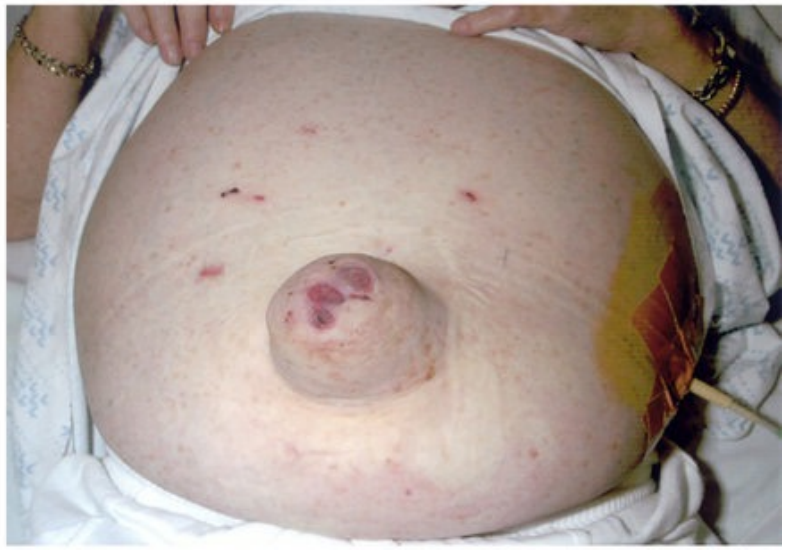
- Diuretics
  - Moderate ascites: Monotherapy with spironolactone 100 mg daily.
  - Recurrent/severe ascites: Combination therapy with furosemide 40 mg BID and spironolactone 100 mg daily
- Must monitor for adverse events
  - Hyperkalemia or hypokalemia
  - Renal stress indicated by rising creatinine
  - Hyponatremia < 130 mmol/L
  - Muscle cramps

Diagnosis, Evaluation, and Management of Ascites, Spontaneous Bacterial Peritonitis and Hepatorenal Syndrome: 2021 Practice Guidance by the American Association for the Study of Liver DiseasesScott W. Biggins, Paulo Angeli, Guadalupe Garcia-Tsao, Pere Ginès, Simon C. Ling, Mitra K. Nadim, Florence Wong, W. Ray Kim

Paracentesis

Paracentesis > 5L requires albumin infusion (20-25% albumin) at 8g albumin/L of ascites removed.





Guidelines on the management of ascites in cirrhosis Guruprasad P Aithal ,1,2 Naaventhan Palaniyappan,1,2 Louise China,3 Suvi Härmälä,4 Lucia Macken ,5,6 Jennifer M Ryan,3,7 Emilie A Wilkes,2,8 Kevin Moore,3 Joanna A Leithead,9 Peter C Hayes,10 Alastair J O'Brien ,3 Sumita Verma

Aithal GP, et al. Gut 2021;70:9–29. doi:10.1136/gutjnl-2020-321790

Salt and Fluid

- Recommended
  - No ADDED salt (5-6.5 g/day)
    - Avoid processed or pre-cooked foods
- Not Recommended
  - No salt or salt < 5 g/day
    - Does not improve ascites control
    - Worsens complications
    - Poor Compliance
  - Fluid restriction
    - Unless clinically hypervoluemic or severe hyponatremic

Diagnosis, Evaluation, and Management of Ascites, Spontaneous Bacterial Peritonitis and Hepatorenal Syndrome: 2021 Practice Guidance by the American Association for the Study of Liver DiseasesScott W. Biggins, Paulo Angeli, Guadalupe Garcia-Tsao, Pere Ginès, Simon C. Ling, Mitra K. Nadim, Florence Wong, W. Ray Kim

Guidelines on the management of ascites in cirrhosis Guruprasad P Aithal ,1,2 Naaventhan Palaniyappan,1,2 Louise China,3 Suvi Härmälä,4 Lucia Macken ,5,6 Jennifer M Ryan,3,7 Emilie A Wilkes,2,8 Kevin Moore,3 Joanna A Leithead,9 Peter C Hayes,10 Alastair J O'Brien ,3 Sumita Verma

Ascites Key Points

- Most common complication
- Medical management should include lasix and spironolactone
- Paracentesis for recurrent large ascites/symptomatic. Albumin if >5L removed
- No added salt diet is recommended.
- Avoid fluid restriction and "no salt" diet

Varices

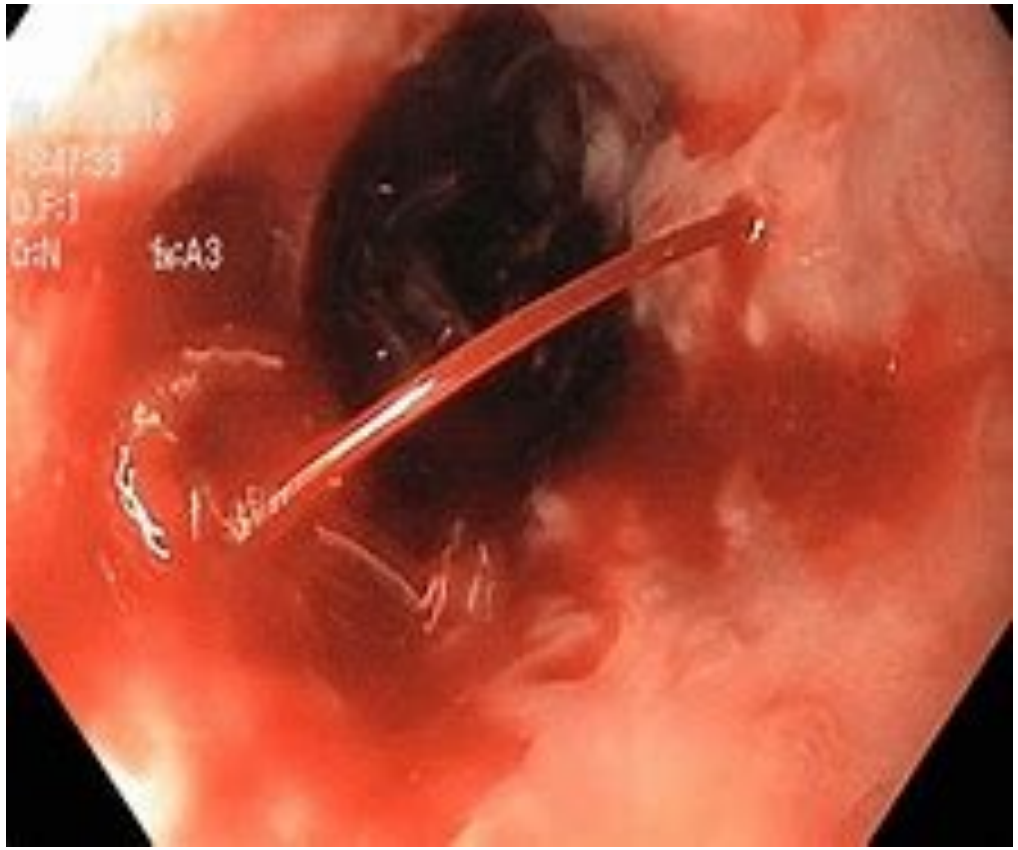
Esophageal Varices and hemorrhage

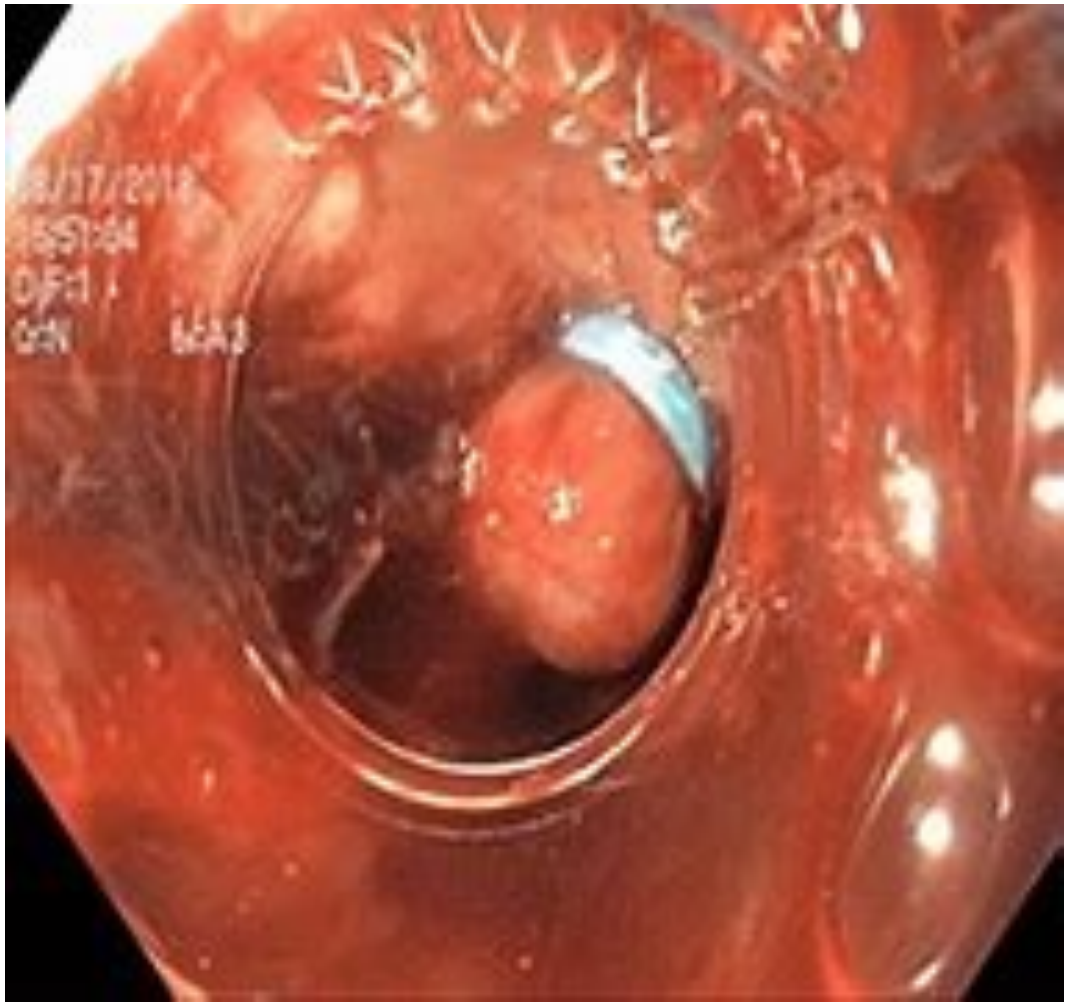
- One half of patients with cirrhosis have esophageal varices (EV)
  - 30% of compensated cirrhotics
  - 60% of decompensated cirrhotics
- One third of all patients with varices will hemorrhage
- Major cause of morbidity and mortality
  - Annual rate of mortality at first hemorrhage: 12%
  - Annual rate of mortality for recurrent hemorrhage: 15-20%
- Risk is related to size and appearance of the varices and degree of hepatic dysfunction

Screening is Critical: EGD

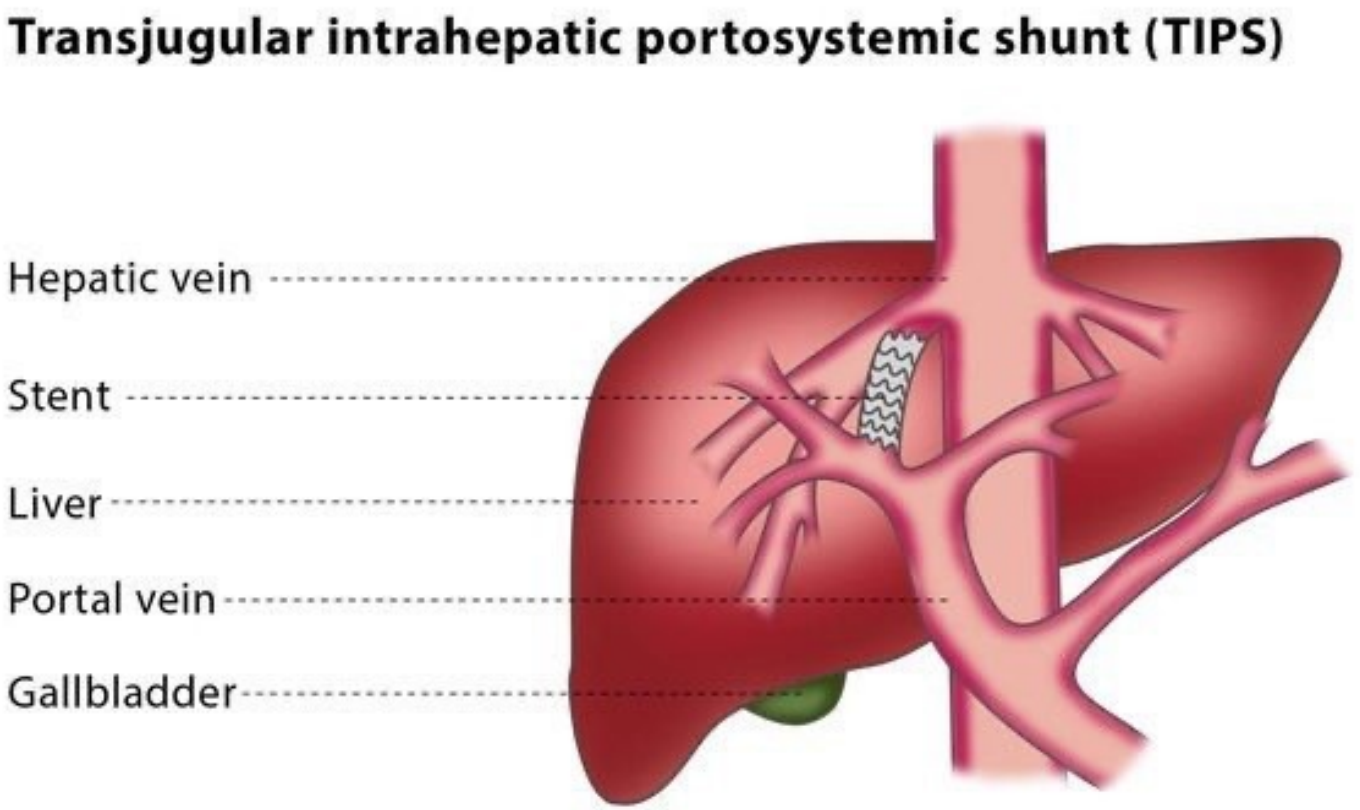
- All cirrhotic patients should have an initial screening EGD
  - Compensated without varices: repeat every 2-3 years
  - Small varices: repeat every 1-2 years
  - Decompensated and with varices: every year but may be shorter interval
- Primary prophylaxis: Beta blocker
  - propanolol 10-60mg po BID/TID. Start 10mg and titrate up.
- Seconday prophylaxis:
  - banding
  - transjugular intrahepatic portosystemic shunt (TIPS)

Banding





TIPS



Also reduces refractory ascites, improves portal gastropathy, may improve hepatorenal syndrome

Major complication: hepatic encephalopathy

Esophageal Varices Key Points

- Hemorrhage is life threatening
- Initial screening EGD for all newly diagnosed cirrhotics
- Follow up EGDs based on findings
- Prevention starts with beta blocker therapy
- After hemorrhage:
  - Continue beta blocker
  - Follow up banding
- Recurrent hemorrhage:
  - Consider TIPS: high risk for hepatic encephalopathy

Hepatic Encephalopathy (HE)

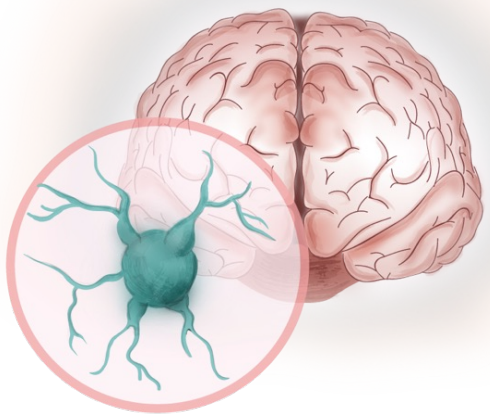
Hepatic Encephalopathy

- Frequent complication
- Debilitating manifestation
- Spectrum of neurological cognitive disturbance and altered level of consciousness
- Sleep patterns, personality traits, intellect
- Blood ammonia level not required

Hepatic Encephalopathy (West Haven Criteria)		
Covert	Grade 1	Inattention, euphoria/anxiety, altered sleep pattern, ↓attention span
Overt	Grade 2	Lethargy, behavior Δ's, time disorientation, asterixis, personality Δ's, hypoactive DTRs
	Grade 3	Somnolence to semistupor, responsive to stimuli, time & place, disorientation, asterixis, hyperactive DTRs
	Grade 4	Coma

Vilstrup H, et al. *Hepatol*, 2014

HE Classification



Episodic
Recurrent
Persistent

Precipitating Factors

- Infections
- GI bleed
- Diuretic overdose
- Electrolyte imbalance
- Constipation
- Drugs (e.g., opioids, benzodiazepines)
- Portosystemic shunts: spontaneous vs iatrogenic

Vilstrup H, et al. *Hepatol*, 2014

Diagnosis of Exclusion

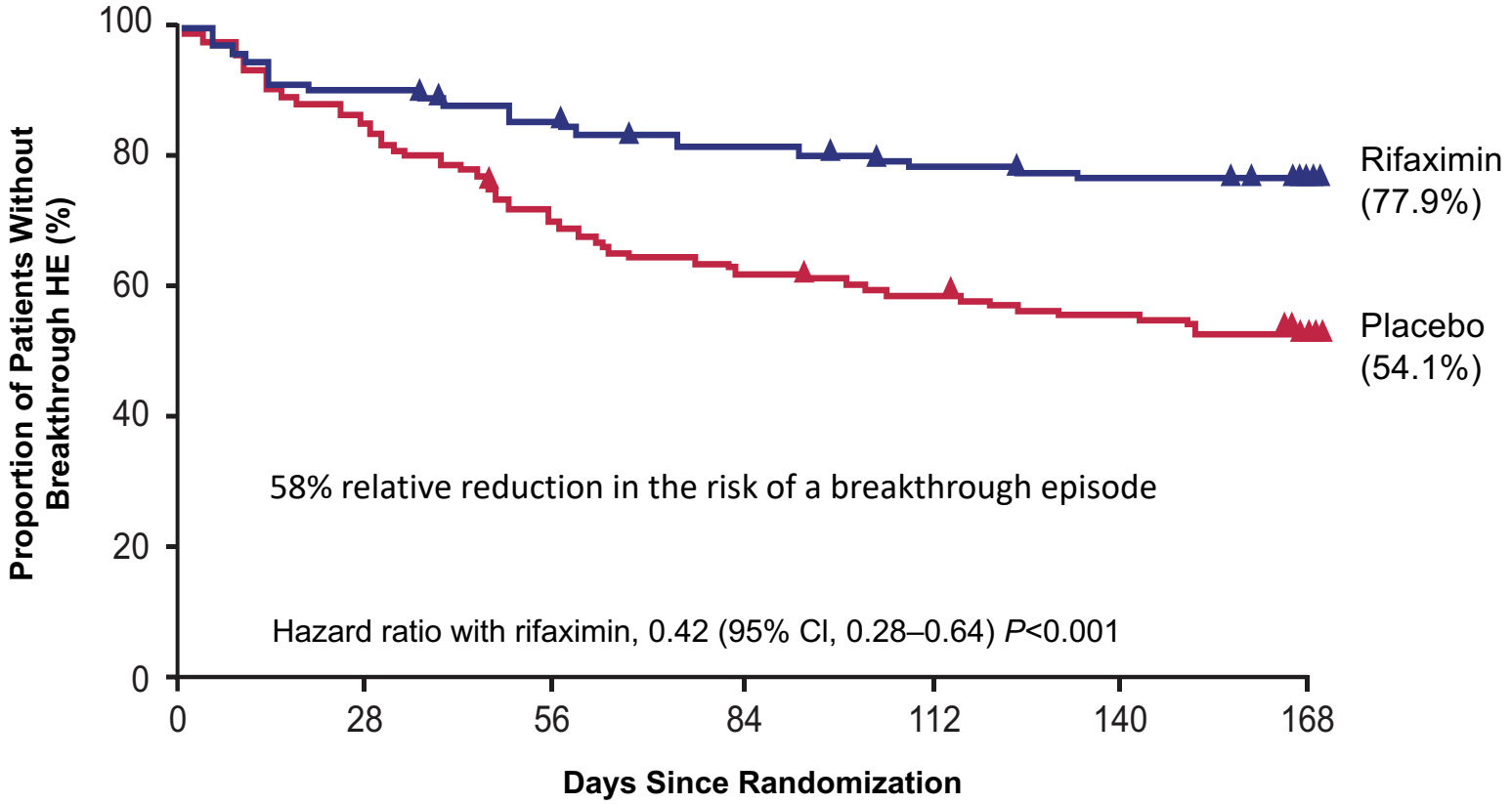
- Rule out other causes
- First symptom is typically sleep disruption
- In hospitalized patients:
  - Determine precipitating factors
  - Treat: Rapid response to treatment confirms HE. Lack of response in 72 hours, look for different etiology
- EEG, CT or MRI do not diagnosis HE.
  - Use to rule out other brain pathology

https://my.clevelandclinic.org/departments/digestive/medical-professionals/hepatology/hepatic-encephalopathy#laboratory-abnormalities-tab

Treatment for HE

Treatment	Mode of action	Recommended time to use
Lactulose	Reduces ammonia production by acidification of colon Acts as laxative Aids gut microbiome repair	1st line treatment for OHE
Rifaximin	Nonabsorbable antibiotic with high efficacy Reduces ammonia production	Secondary prophylaxis or in patients who are intolerant to lactulose

Rifaximin + Lactulose* vs Placebo + Lactulose*: Time to First Breakthrough HE Episode Primary Endpoint



*Rifaximin 550 mg or placebo twice daily. 91% of patients in both arms received concomitant lactulose.

Bass NM, et al. *N Engl J Med*. 2010; 362:1071-1081.

HE Key Points

- Can be difficult to diagnosis in early cirrhosis
- HE increases mortality
- Advanced cirrhotics are high risk
- Diagnosis of exclusion: rule out other causes
- Serial ammonia levels are not useful in clinical practice
- Treatment should include lactulose and rifaximin

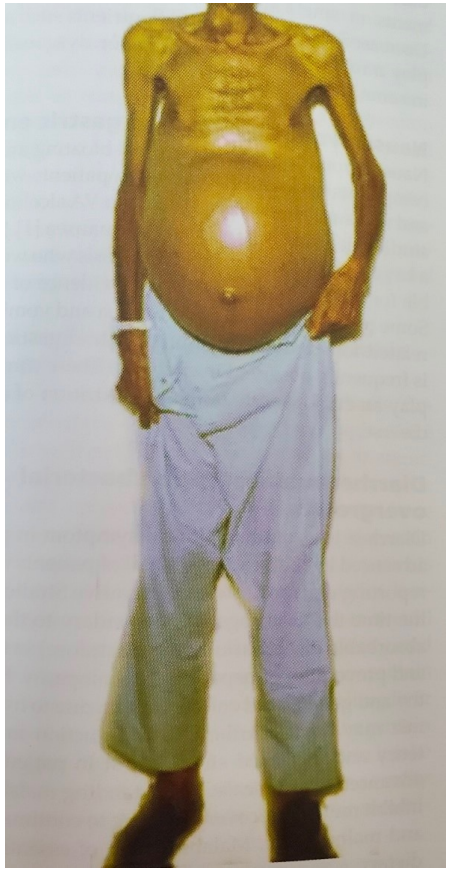
Nutrition

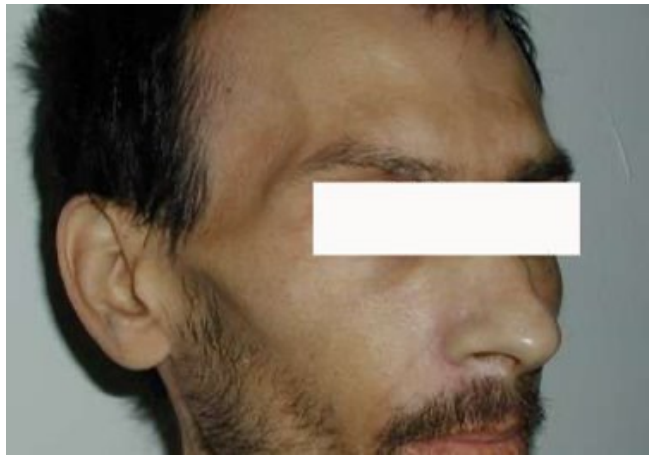
Malnutrition and Vitamin Deficiencies

- Definition of Malnutrition
  - Clinical syndrome that results from a deficiency or excess of nutrients causing measurable adverse effects on tissue/body form or function and clinical outcome.
  - Spectrum of nutritional disorders from underweight to obese
- Manifests as frailty and sarcopenia
  - Frailty: decreased physiologic reserve and increased vulnerability to health stressors
  - Sarcopenia: decreased muscle mass, strength, and performance

Lai, J.C., Tandon, P., Bernal, W., Tapper, E.B., Ekong, U., Dasarathy, S. and Carey, E.J. (2021), Malnutrition, Frailty, and Sarcopenia in Patients With Cirrhosis: 2021 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology, 74: 1611-1644. https://doi.org/10.1002/hep.32049

Malnutrition





Muscle Wasting
Temporal Wasting

Struggle with malabsorption, maldigestion, pancreatic enzyme deficiency, bacterial overgrowth, impaired bile salt regulation

Hypermetabolism: catabolic state
Reduced hepatic glycogen synthesis and storage.
Whole body protein breakdown

Lai, J.C., Tandon, P., Bernal, W., Tapper, E.B., Ekong, U., Dasarathy, S. and Carey, E.J. (2021), Malnutrition, Frailty, and Sarcopenia in Patients With Cirrhosis: 2021 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology, 74: 1611-1644. https://doi.org/10.1002/hep.32049

Vitamin Deficiencies

- Micronutrients
  - Folate, thiamine
  - Zinc
  - Selenium
  - Magnesium
  - Fat soluable vitamins
- Nutritional consultation/education is critical
  - Increased protein intake: 0.45 x weight in pounds = daily grams protein
    - Dairy and plant protein better tolerated
  - No salt added diet

https://txliver.com/health-and-wellness/

McClain CJ. Nutrition in Patients With Cirrhosis. *Gastroenterol Hepatol (N Y)*. 2016;12(8):507-510.

Foods to decrease or avoid

- Fructose and corn syrup: may increase fat deposition in liver
- Omega-6 fatty acids: may lead to toxic lipid metabolites. Promote inflammation.
  - Corn, sunflower, safflower, soy, sesame oils
- Fried food, added salt, raw or undercooked shellfish
- Processed foods

https://www.mountsinai.org/health-library/supplement/omega-6-fatty-acids

McClain CJ. Nutrition in Patients With Cirrhosis. *Gastroenterol Hepatol (N Y)*. 2016;12(8):507-510.

Recommendations

- Increase omega-3 fatty acids
  - Salmon
  - Flax seeds, chia seeds
  - Walnuts
- Small frequent meals
- Small nighttime snack of carbohydrate and protein
  - Milk and crackers
  - Apple and peanut butter
- Mediterranean style diet

https://txliver.com/health-and-wellness/

McClain CJ. Nutrition in Patients With Cirrhosis. *Gastroenterol Hepatol (N Y)*. 2016;12(8):507-510.

Malnutrition/Vitamins Key Points

- Dietician consultation highly recommended
- Avoid malnutrition leading to frailty and sarcopenia
  - Smaller, more frequent meals
  - Increase high quality plant and dairy proteins
  - Increase omega-3 fatty acids and limit omega-6 fatty acids
- Small carb/protein snack before bed
- Multivitamin okay in early/compensated cirrhosis
- Mediterranean diet well studied and beneficial

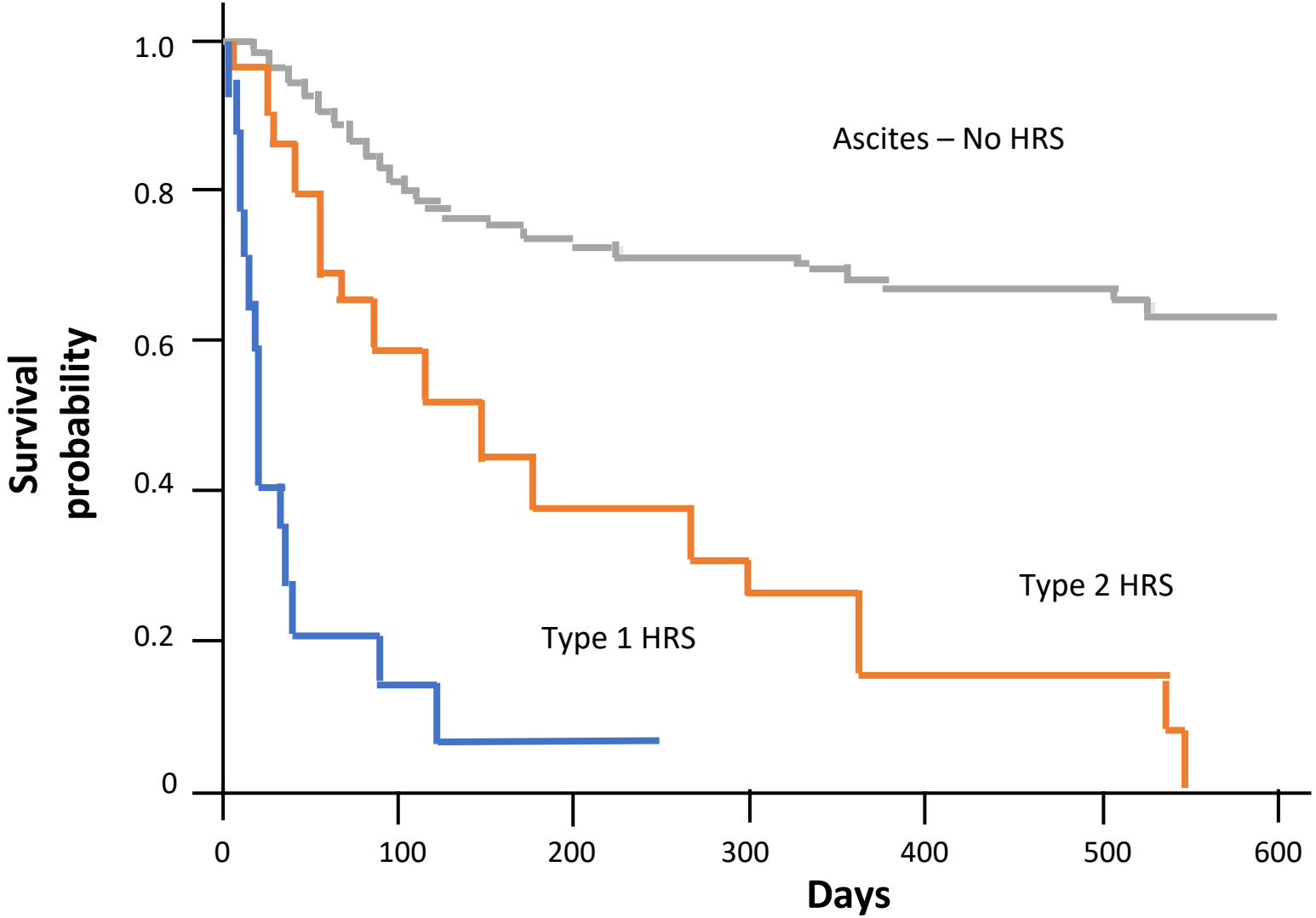
Hepatorenal Syndrome (HRS)

Hepatorenal Syndrome

- Defined:
  - Functional, progressive, kidney failure in advanced liver disease
  - Potentially reversible but can be rapidly fatal
- Pathogenesis
  - RAAS and sympathetic nervous system activation due to reduced portal blood flow leading to vasodilator release and blood pooling in the splanchnic circulation
  - Includes both hemodynamic and inflammatory changes
- Hallmark feature: intense renal vasoconstriction with peripheral arterial vasodilation

Flamm SL, Brown K, Wadei HM, et al. The Current Management of Hepatorenal Syndrome-Acute Kidney Injury in the United States and the Potential of Terlipressin [published correction appears in Liver Transpl. 2022 Jan;28(1):144]. *Liver Transpl*. 2021;27(8):1191-1202. doi:10.1002/lt.26072

Survival in Patients With Ascites and HRS



Arroyo et al. *J Hepatol*. 2007.

Credit to Robert S. Brown Jr., MD, MPH

Using Serum Cr to Measure Renal Function

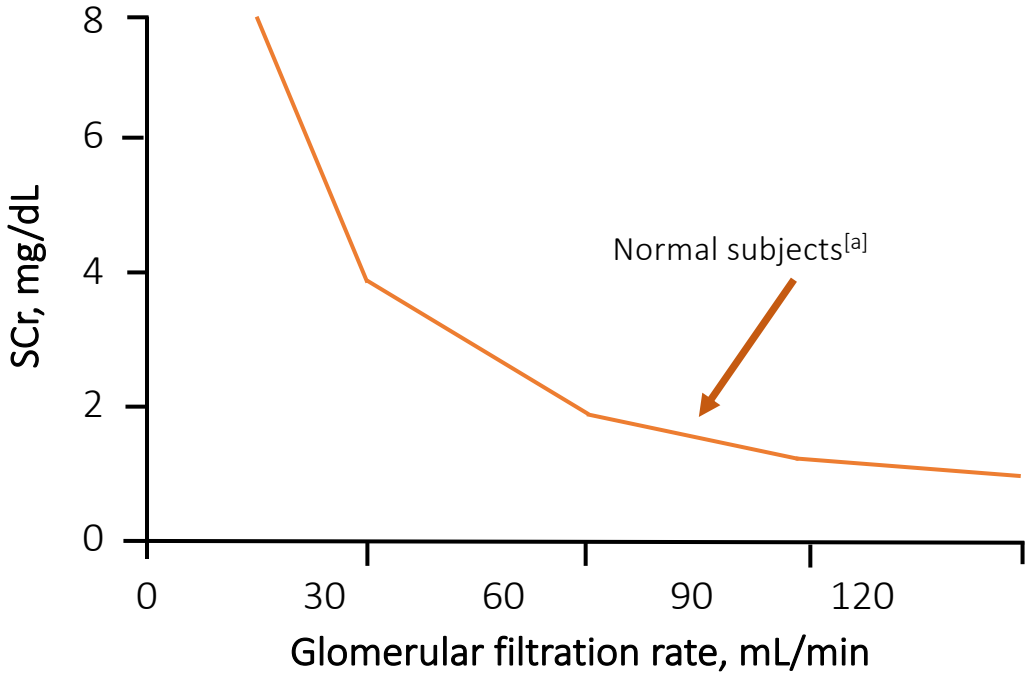
- Pros
  - Easily obtainable[a]
  - Inexpensive[a]
  - Repeated measurements seem to be reliable
  - Included in MELD score[a]
- Cons
  - Overestimates GFR[a-c]
    - Decreased creatine
    - Low muscle mass
    - Poor protein diet
    - High urine secretion
  - Low sensitivity
  - Interlaboratory variability

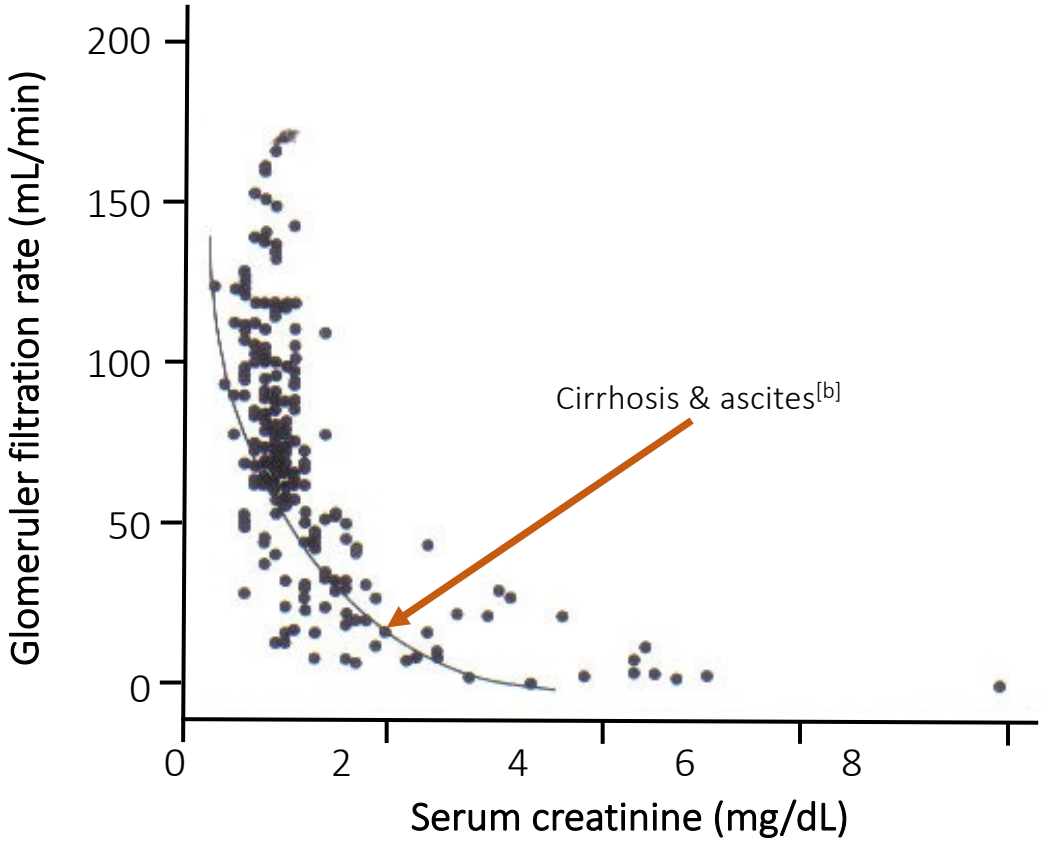
a. Piano S et al. *Liver Int*. 2017; 37(Suppl. 1):116-122; b. Cárdenas A, Gines P. *Curr Opin Crit. Care*. 2011;17:184-189; c. Francoz C et al. *J Hepatol*. 2016;65:809-824.

Credit to Robert S. Brown Jr., MD, MPH

Relationship Between Serum Creatinine and GFR in Patients With Cirrhosis

Serum creatinine of 1.5 g/dL corresponds to GFR of ~30 mL/min





a. Inker LA, Perrone R. *UpToDate*; b. Arroyo V et al. *Zakim and Boyer's Hepatology*. A Textbook of Liver Disease. 2006.

Credit to Robert S. Brown Jr., MD, MPH

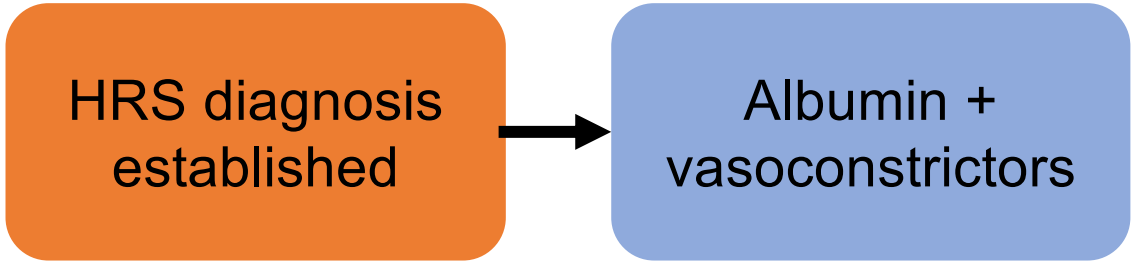
Criteria to Diagnose HRS-AKI

Cirrhosis with ascites
Diagnosis of AKI according to International Club of Ascites-Acute Kidney Injury† criteria
No response after 2 consecutive days of diuretic withdrawal and plasma volume expansion with albumin infusion (1 g/kg body weight per day)
Absence of shock
No current or recent use of nephrotoxic drugs (NSAIDs, aminoglycosides, or iodinated contrast media)
No signs of structural kidney injury, as indicated by proteinuria (>500 mg per day), microhematuria (>50 red blood cells per high-power field), and/or abnormal renal ultrasonography

†Increase in serum creatinine ≥0.3 mg/dL from baseline within 48 hours or a percent increase in serum creatinine of ≥50% which is known or presumed to have occurred within the preceding 7 days.

Credit to Robert S. Brown Jr., MD, MPH

HRS Treatment: General Concepts



Rationale for vasoconstriction:

- Counteract splanchnic arterial vasodilation, improving renal perfusion

EASL 2018 guidelines

HRS Treatments	Targets	Mechanisms of Action
Norepinephrine, Noradrenaline	α1 and α2 adrenergic receptor agonist β1 adrenergic receptor agonist	Systemic vasoconstriction Increased heart rate, cardiac output
Midodrine	α1-adrenergic receptor agonist	Systemic vasoconstriction
Octreotide	Somatostatin analogue	Splanchnic vasoconstriction
Terlipressin*	Vasopressin analogue	Splanchnic vasoconstriction

*Terlipressin currently under review by FDA. Approval expected in 2022.

EASL. *J Hepatol*. 2018;69:406-460.

Non-pharmacologic HRS Management

Transplantation	All patients with cirrhosis and AKI should be considered for urgent liver transplant (LT) evaluation given the high short-term mortality even in responders to vasoconstrictors Simultaneous liver-kidney transplantation may be necessary for patients who are not expected to recover kidney function post-transplantation
Renal Replacement Therapy (RRT)	Use RRT in candidates for LT with worsening renal function, electrolyte disturbances or increasing volume overload unresponsive to vasoconstrictor therapy Initiation of RRT in patients who are not candidates for LT must be made after defining goals of care with the patient and their families
Multidisciplinary Teams	Given the complexity of patients with suspected HRS-AKI, decisions about management should be made by multidisciplinary teams Team should include specialists in hepatology, nephrology, critical care, and transplant surgery

Credit to Robert S. Brown Jr., MD, MPH

HRS Key Points

- The goals of HRS-AKI treatment are to reverse renal failure and prolong survival
- There are no approved drugs in the US for treatment and mortality remains high
- Liver transplantation is the cure, but is only an option in a minority of patients
  - There are many contraindications to transplantation and organ availability is limited
- Renal replacement therapy is a temporary option but is known to confer an extremely poor short-term prognosis
  - A bridge to liver transplantation

Flamm SL et al. *Liver Transpl*. 2021;27:1191-1202. Credit to Robert S. Brown Jr., MD, MPH

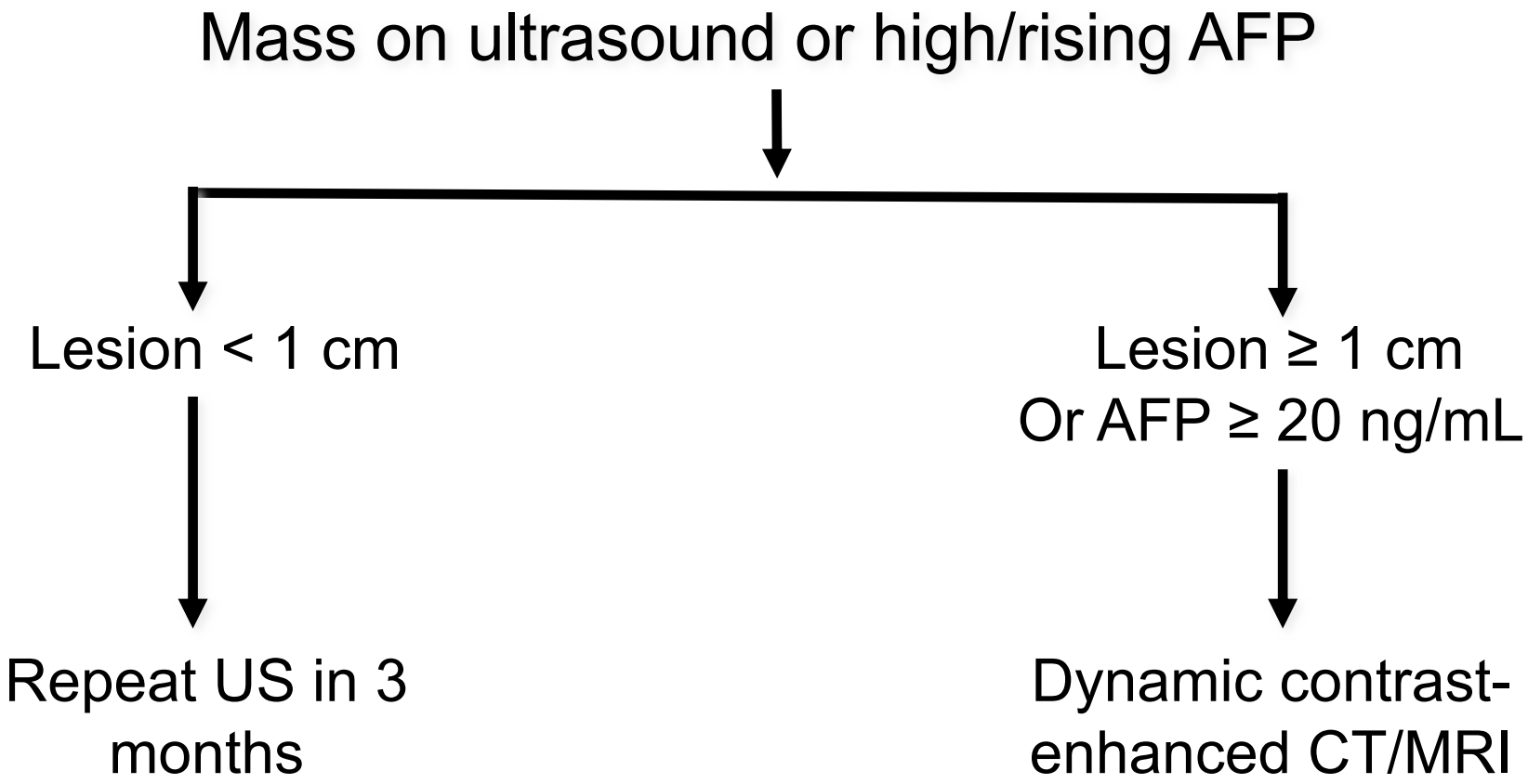
Hepatocellular Carcinoma

(HCC) Screening

All cirrhotic patients:
AASLD recommends HCC screening every
6 months with ultrasound +/- AFP

No current guidelines for screening in NAFLD or
NASH without cirrhosis

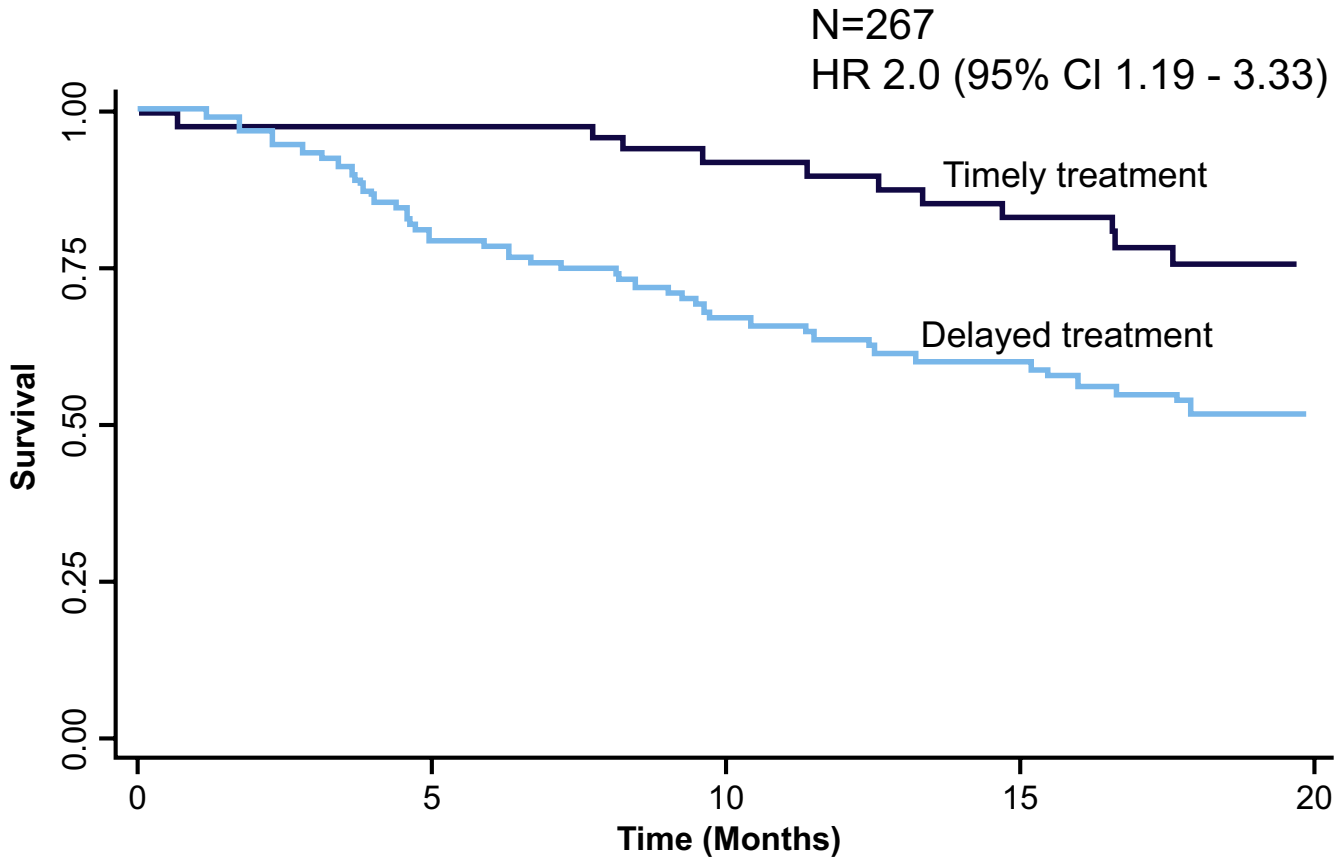
HCC Diagnosis in Patients With Chronic Liver Disease (Cirrhosis)



HCC Treatment

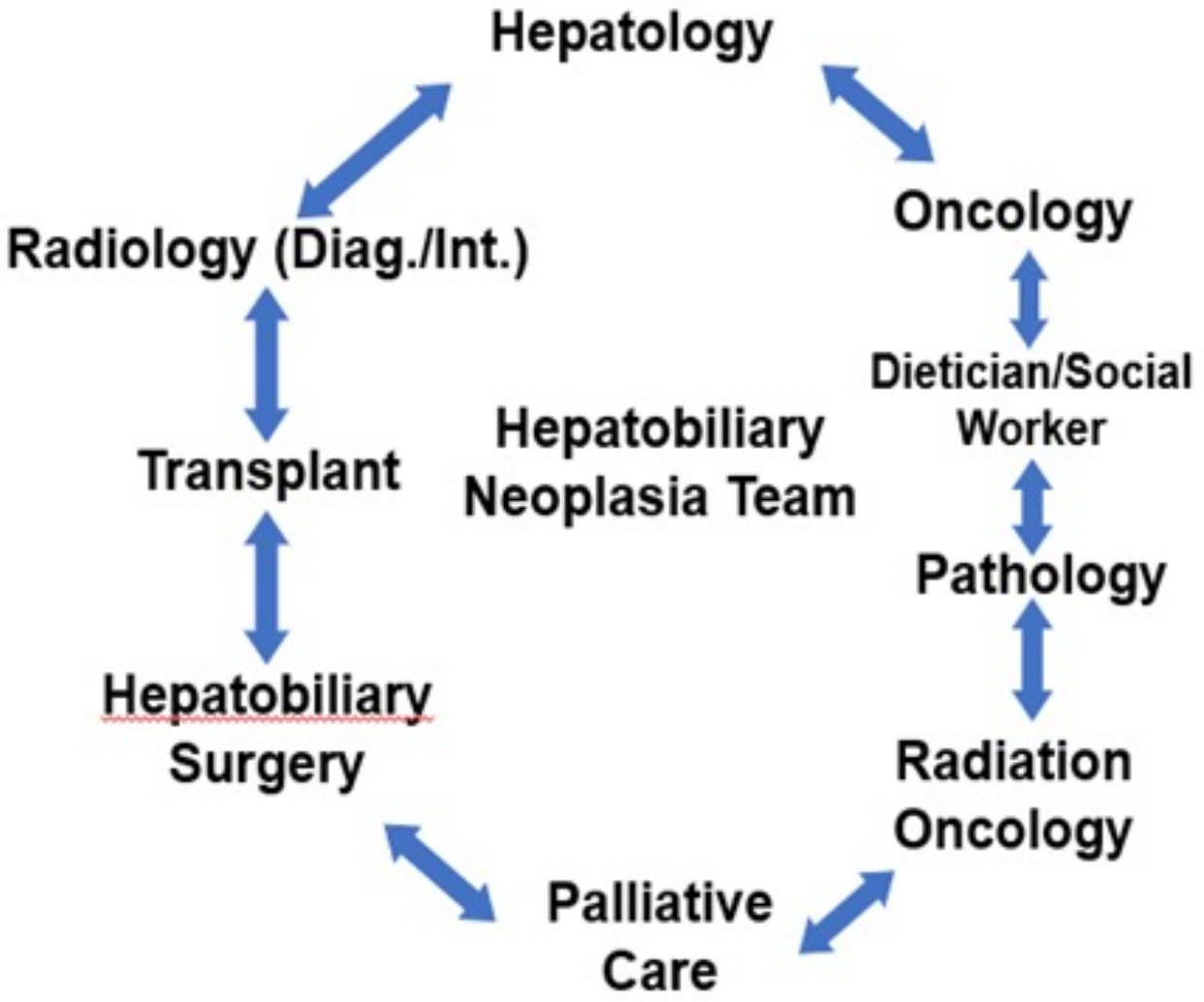
- Depends on size, number, and tumor location
- Locoregional treatment by interventional radiology
  - Microwave ablation
  - Transarterial chemoembolization (TACE)
  - Y90 radioembolization (Y90 or TARE)
- Systemic treatment through medical oncologist: immunotherapy
- Surgical Resection
- Liver transplantation
  - Cadaveric
  - Living donor liver

Therapeutic Delays Associated with Worse Survival



Median time to treat 1.7 months, with 31% having delays > 3 mo

Singal, et al. *J Natl Comp Cancer Network*. 2013.



Multidisciplinary Care

HCC Key Points

- All cirrhotics should be screened every 6 months with ultrasound and AFP
- Nodules < 1 cm with normal AFP should be surveilled every three months
- Nodules > 1 cm or AFP > 20 need multiphasic CT or MRI
- Multidisciplinary care is essential for timely diagnosis and treatment of HCC
- Transplant is the cure

Post-Transplant Management

Post-Transplant Risks

- Two main risks: Infection and Rejection
  - Acute rejection may occur in up to 10% of recipients
- All patients must take anti-rejection meds (immunosuppressants)

TABLE 5. Unwanted Side Effects of Immunosuppressives

Side Effect	Corticosteroids	CNIs	mTOR Inhibitors	Mycophenolate Mofetil
Kidney injury	−	+++	+ (proteinuria)	−
Bone disease	+++	−	−	−
Gastrointestinal	+/−	−	−	+
Bone marrow suppression	−	−	−	+
Pulmonary fibrosis	−	−	+	−
Hypercholesterolemia	+	+	+++	−
Diabetes	++	+ (tacrolimus)	−	−
Hypertension	+	++	+	−

Other Risks Post-Transplant

TABLE 2. Prevalence of Cardiovascular Risk Factors and CKD in LT Recipients Beyond the First Posttransplant Year

	Prevalence Rate
Cardiovascular risk factor	
Metabolic syndrome*	50%-60%
Systemic hypertension	40%-85%
DM	10%-64%
Obesity	24%-64%
Dyslipidemia	40%-66%
Cigarette smoking	10%-40%
CKD (stage 3-4)†	30%-80%
End-stage kidney disease	5%-8%

*Any 3 of the following: hypertension, obesity, dyslipidemia, and DM.
†Estimated glomerular filtration rate = 15 to <60 mL/minute/1.73 m^2.

TABLE 10. Relative Risks of De Novo Malignancies in LT Recipients Versus a Sex- and Age-Matched Population

Malignancy	Relative Risk
Skin cancers	
Squamous and basal cell carcinoma	20%-70%
Melanoma	2%-5% (estimate)
Lymphoma	10%-30%
Oropharyngeal cancer, including esophageal cancer	3%-14% (as high as 25% if the prior diagnosis was alcoholic cirrhosis)
Lung cancer	1.7%-2.5%
Colorectal cancer	25%-30% if ulcerative colitis is present
Kidney cancer	5%-30%

Most Common Infections

TABLE 12. Prophylactic Strategies for Common Organisms That Affect LT Recipients

Organism	Agent/Dosage	Duration	Comments
CMV			
Donor-positive/ recipient-negative	Valganciclovir (900 mg/day) or intravenous ganciclovir (5 mg/kg/day)	3-6 months	Valganciclovir is not FDA-approved for LT. Prolonged-duration regimens are effective in kidney transplantation.
Recipient-positive	Valganciclovir (900 mg/day), intravenous ganciclovir, or weekly CMV viral load monitoring and antiviral initiation when viremia is identified	3 months	Valganciclovir is not FDA-approved for LT.
Fungi	Fluconazole (100-400 mg daily), itraconazole (200 mg twice daily), caspofungin (50 mg daily), or liposomal amphotericin (1 mg/kg/day)	4-6 weeks? (optimal duration unknown)	Reserve for high-risk individuals (pretransplant fungal colonization, renal replacement therapy, massive transfusion, choledochojejunostomy, reoperation, retransplantation, or hepatic iron overload).
P. jirovecii (*P. carinii*)	Trimethoprim sulfamethoxazole (single strength daily or double strength 3 times per week), dapsone (100 mg daily), or atovaquone (1500 mg daily)	6-12 months (optimal duration unknown)	A longer duration of therapy should be considered for patients on augmented immunosuppression. Lifelong therapy should be considered for HIV-infected recipients.
TB (latent infection)	Isoniazid (300 mg daily)	9 months	Monitor for hepatotoxicity.

- CMV one of the most common and serious post-transplant infections (16-56% in SOT recipients).
- Can lead to loss of transplanted organ and failure to graft.
- LIVTENCITY (maribavir) was recently FDA approved for the treatment of CMV infection/disease that is refractory to treatment with ganciclovir, valganciclovir, cidofovir or foscarnet.

Signs of Liver Rejection

- Sometimes asymptomatic
- Some of the more common signs & symptoms
  - Fever
  - Headache
  - Fatigue
  - Nausea
  - Loss of appetite
  - Pruritus
  - Dark-colored urine
  - Jaundice
  - Abdominal tenderness

Summary

- Ascites: Prevent and control with lasix, spironolactone
- Esophageal Varices:
  - EGD in all new cirrhosis patients to screen for EV
  - Compensated without varices: repeat every 2-3 years
  - Small varices: repeat every 1-2 years
  - Decompensated and with varices: every year but may be shorter interval
  - Primary prophylaxis: Beta blocker- propanolol
- HE:
  - Blood ammonia levels not clinically useful
  - Prevent and control with lactulose & rifaximin
- Malnutrition and vitamin deficiencies:
  - Dietary counseling and nutrition support
  - Increased protein
  - No salt added

Summary, con't

- HRS:
  - Prompt identification and treatment is essential
  - Multidisciplinary specialist care needed
- HCC:
  - Screen cirrhotic patients every 6 months with US +/- AFP
  - Nodules > 1cm or AFP >20 need multiphasic CT or MRI
  - Refer to multidisciplinary center for care and consider transplant
- Post transplant management
  - Risk of rejection and risk of infection must be carefully managed