Managing Complications of Cirrhosis: Hepatic Encephalopathy (HE), Hepatorenal Syndrome (HRS) and Ascites

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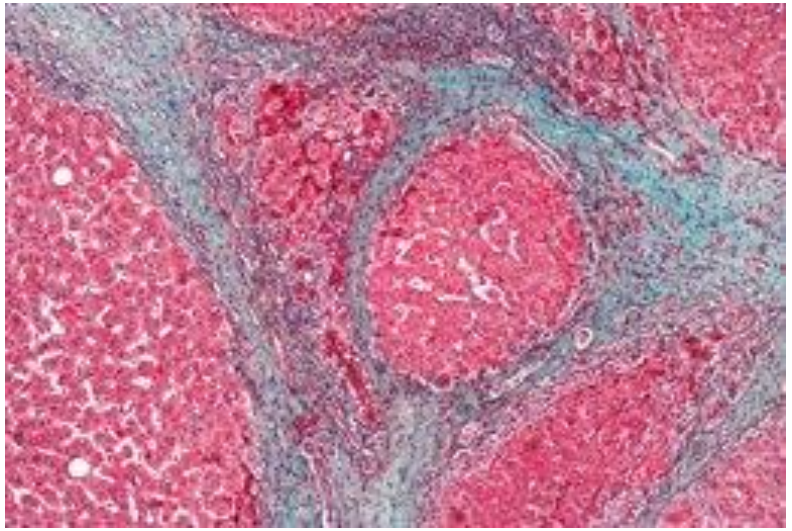
Cirrhosis

Defined:

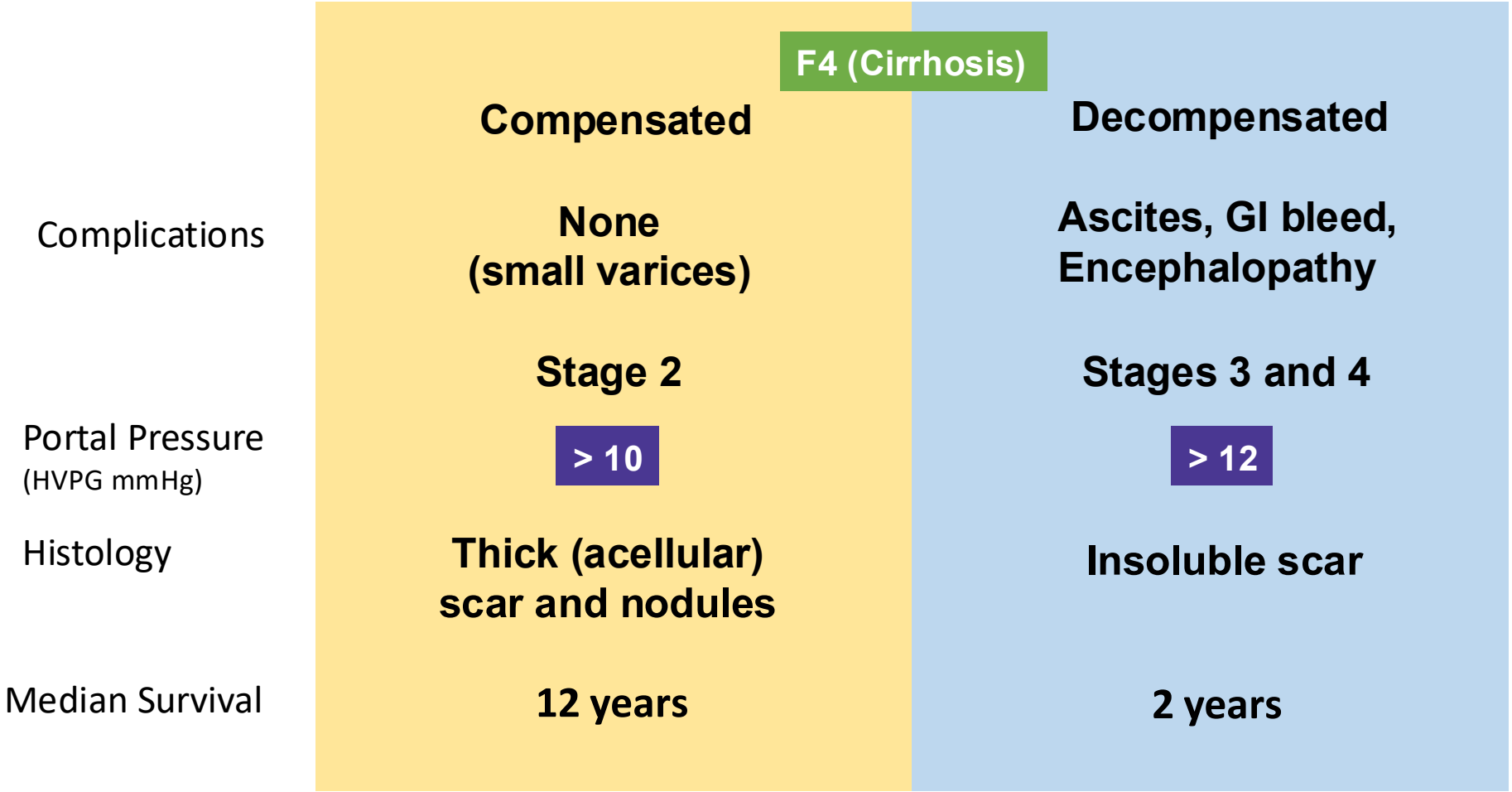
Progressive disease due to scarring from chronic liver injury.

Goal:

Manage early cirrhosis to prolong the compensated stage and
prevent complications



Cirrhosis Classification



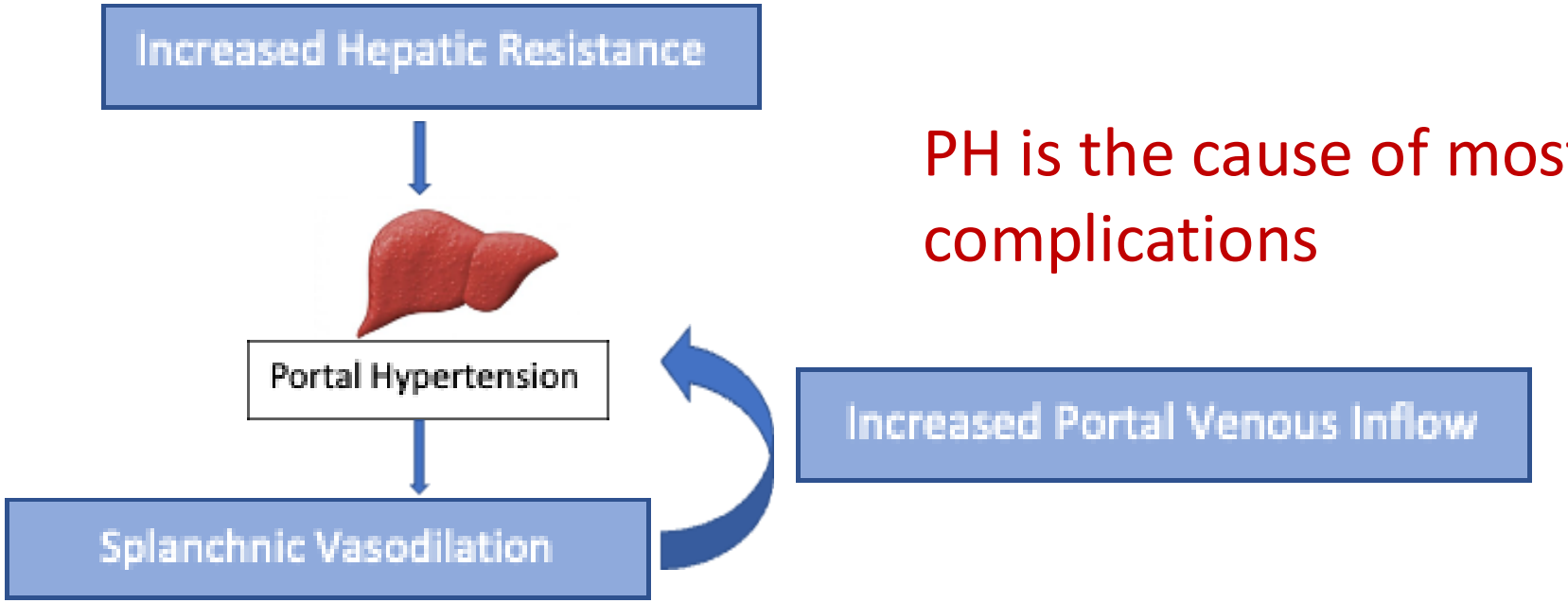
Garcia-Tsao G, et al. *Hepatology.* 2010; 51:1445-9; Viral Hepatitis and Liver Disease: https://www.hepatitis.va.gov/cirrhosis/background/stages.asp

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

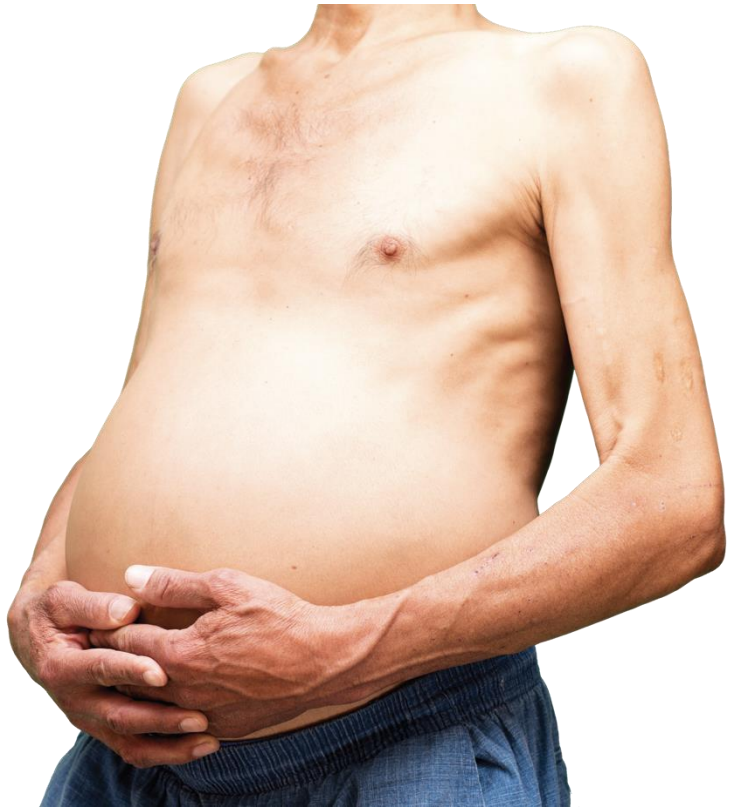
Gracia-Sancho, J. and Laleman, W. (2016), Mechanisms of portal hypertension: Bench to bedside. Clinical Liver Disease, 8: 160-166. https://doi.org/10.1002/cld.604

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



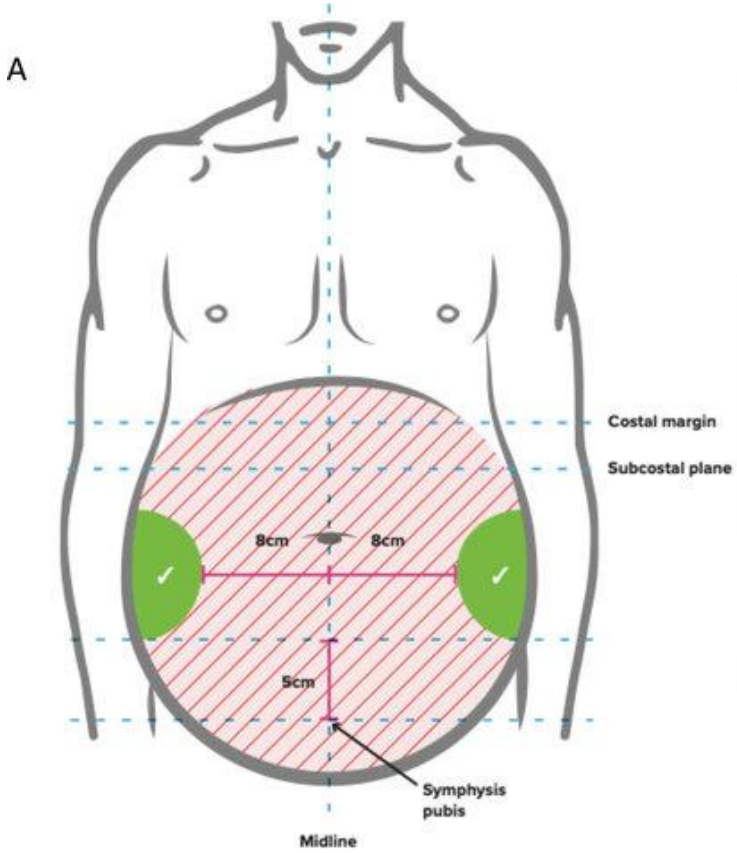
Ascites Treatment

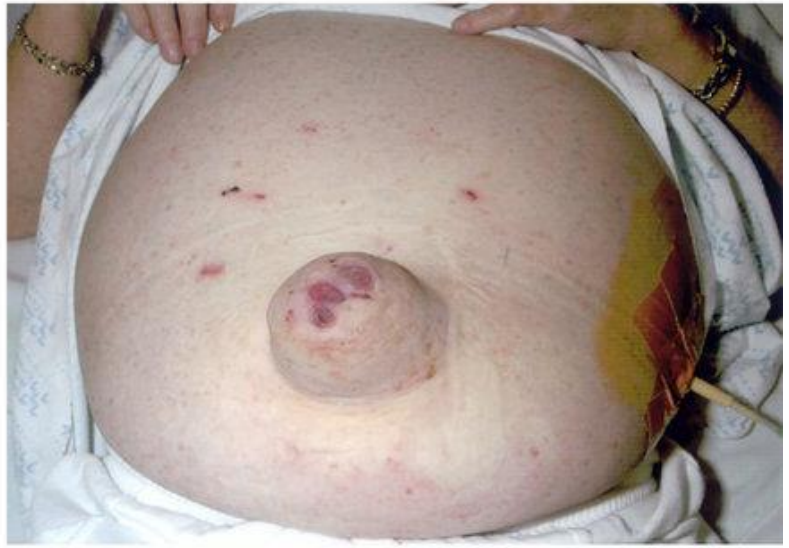
- Diuretics
  - Moderate ascites: Monotherapy with spironolactone 100 mg daily.
  - Recurrent/severe ascites: Combination therapy with furosemide 40 mg BID and spironolactone 100 mg daily
- Must monitor for adverse events
  - Hyperkalemia or hypokalemia
  - Renal stress indicated by rising creatinine
  - 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 8 g 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; equivalent of <2 g sodium per 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 hypervolemic or severe hyponatremic

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Ascites Key Points

- Most common complication
- Medical management should include furosemide 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

Hepatic Encephalopathy (HE)

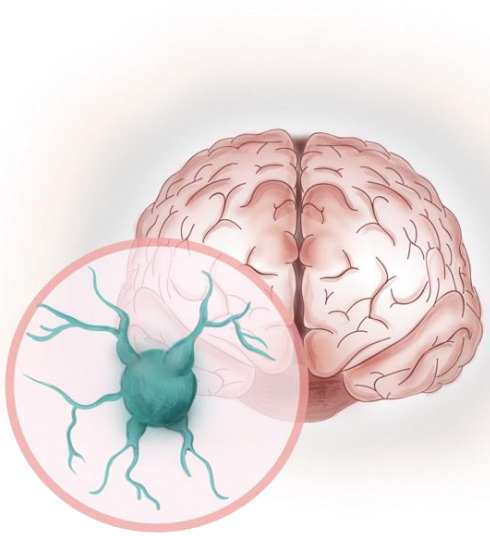
Hepatic Encephalopathy (HE)

- 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

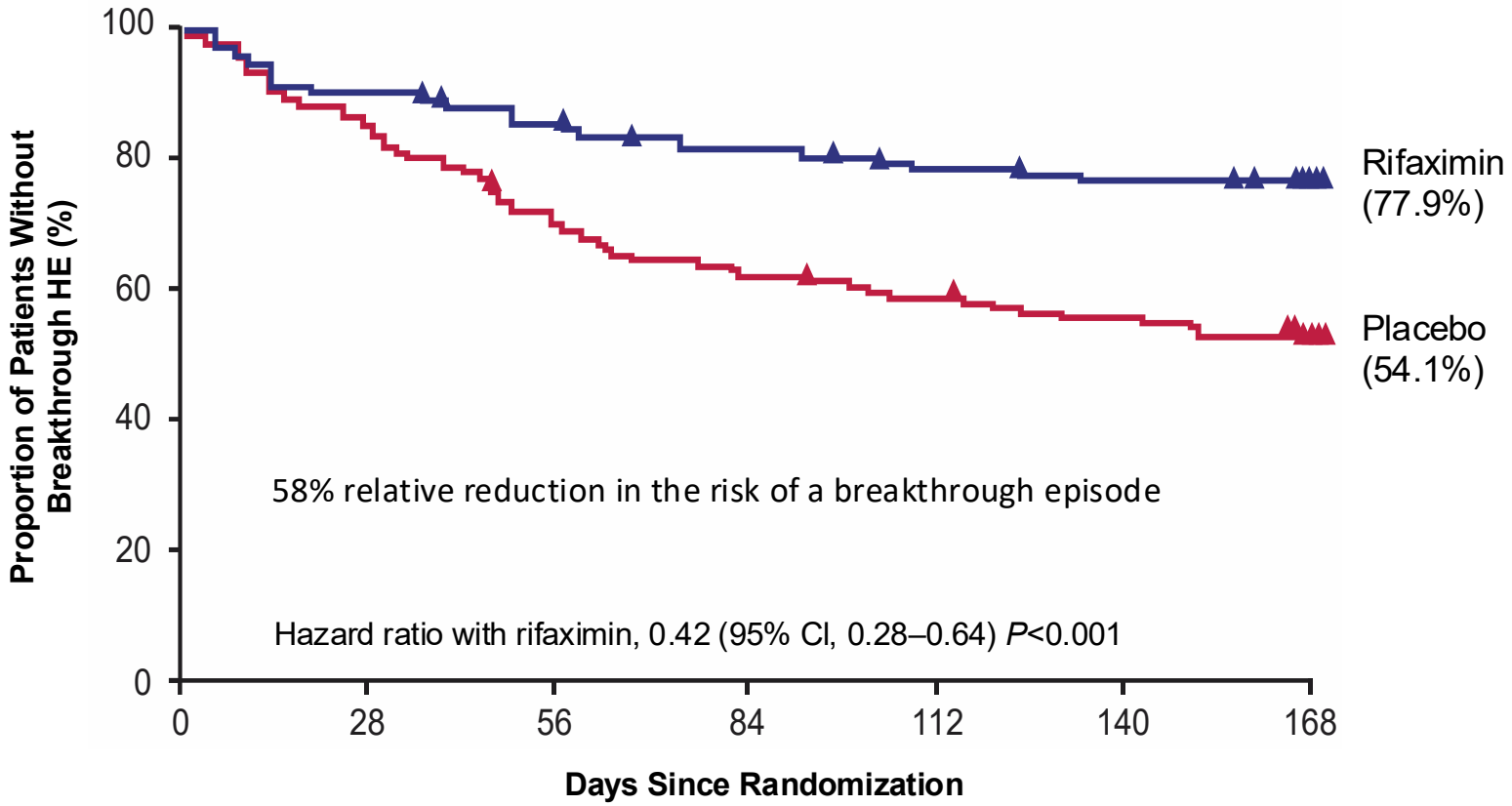
- Rule out other causes
- First symptom is typically sleep disruption
- In hospitalized patients:
  - Determine precipitating factors
  - Treat: Rapid response to treatment confirms HE. Lack of response in 72 hours, look for different etiology
- EEG, CT or MRI do not diagnosis HE.
  - Use to rule out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

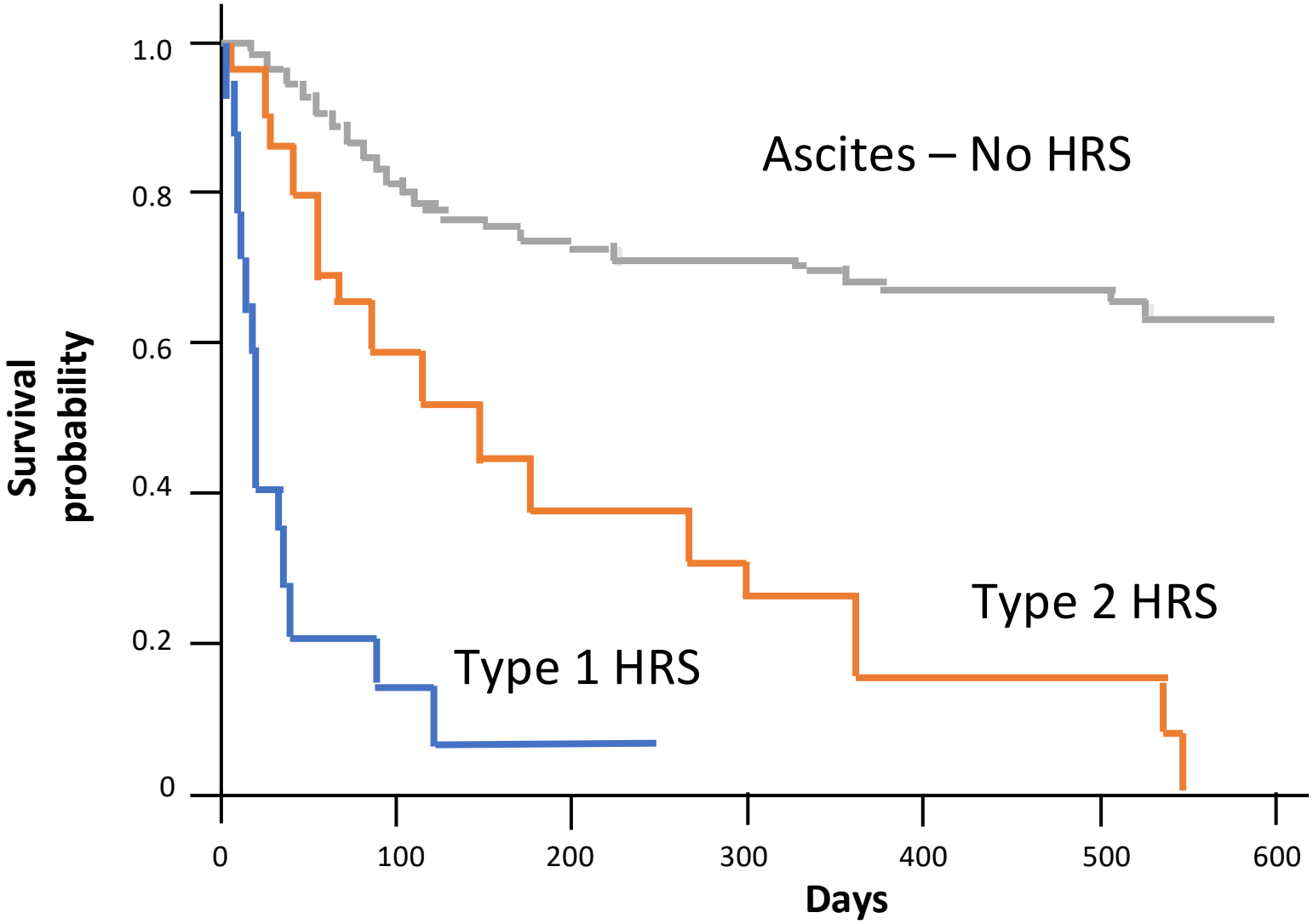
- Can be difficult to diagnosis in early cirrhosis
- HE increases mortality
- Advanced cirrhotics are high risk
- Diagnosis of exclusion: Rule out other causes
- Serial ammonia levels are not useful in clinical practice
- Treatment should include lactulose and rifaximin

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

Survival in Patients With Ascites and HRS



Arroyo et al. *J Hepatol*. 2007.

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

Diagnosis of HRS-AKI

- Cirrhosis with ascites
- No response to withdrawal of diuretics or volume expansion with albumin (max of 1 g/kg body weight per day)
- Absence of shock
- No recent use of nephrotoxic drugs (e.g., NSAIDs)
- No signs of structural kidney injury

Developing Therapies for HRS is a Balance

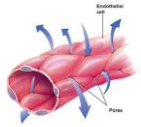
Full **V1a** agonist

Vasoconstriction

Excess amount → ischemia

Modest amount → efficacy

Full **V2** agonist

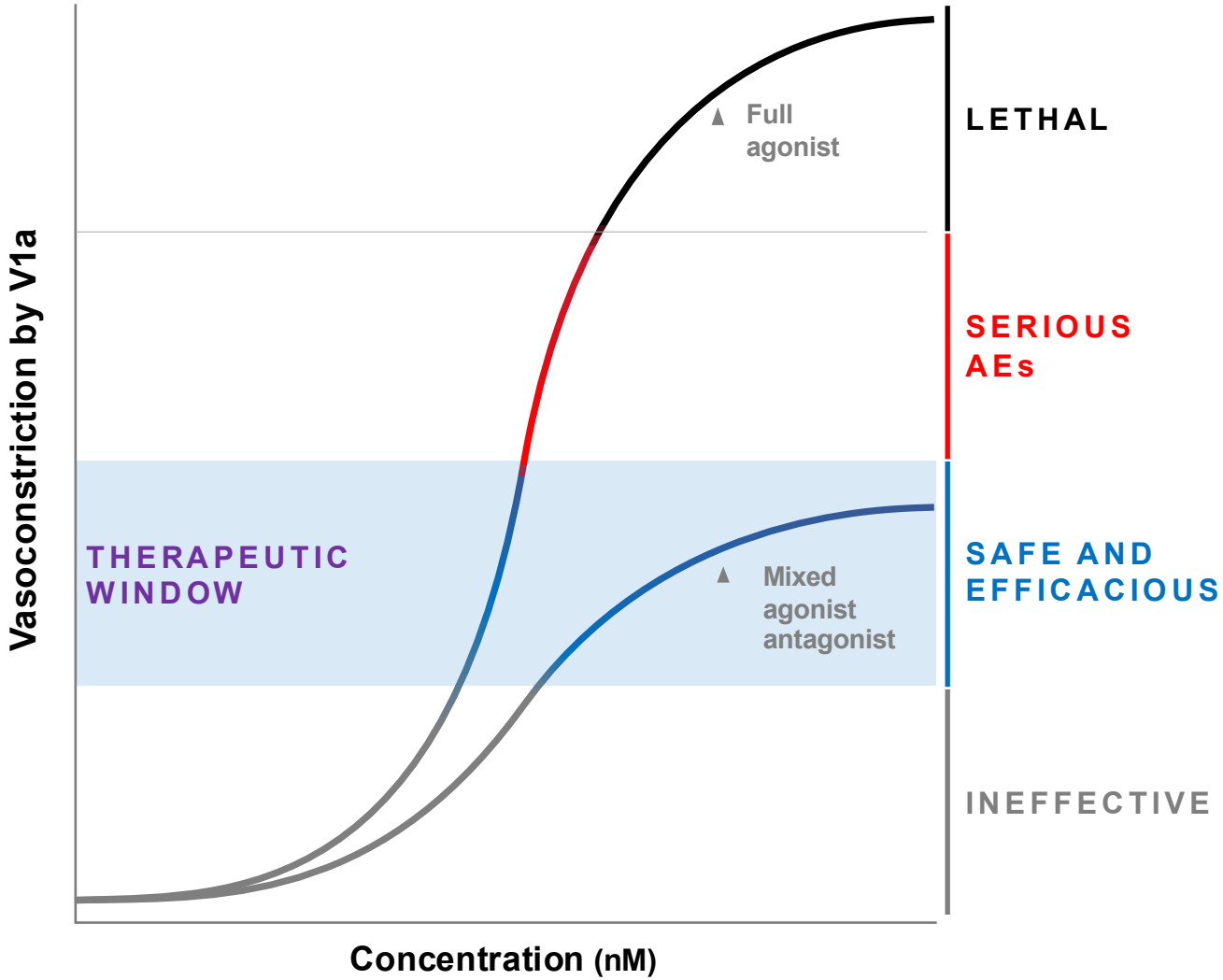


Endothelial vWF factor release

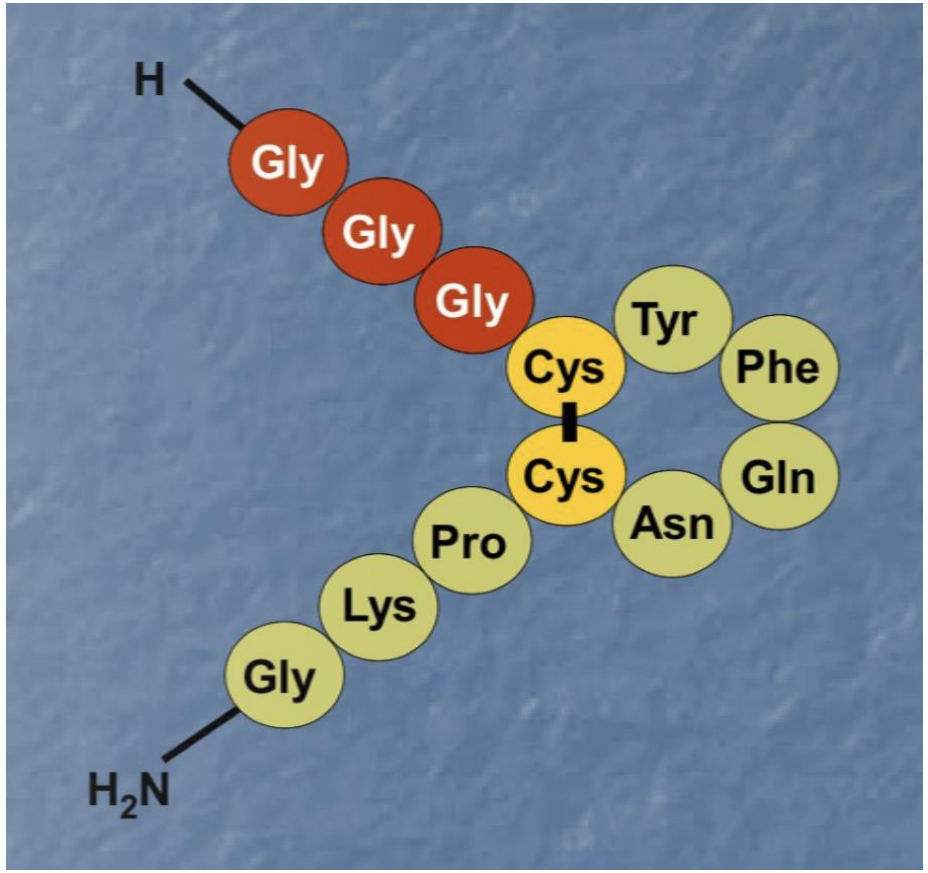
Renal retention of H_20

Volume overload, edema, fluid retention, respiratory SAEs

Increased vascular permeability



Terlipressin



Synthetic 12 amino acid peptide, pro-drug of L-vasopressin

Approved as IV bolus but can be used as IV infusion

Partial V1 agonist (6-fold higher affinity for V1 than V2)

- Constricts vasculature
- Splanchnic vasoconstriction reduces portal blood flow and portal pressure
- Systemic vasoconstriction
  - Increases effective blood volume
  - Reduces renin and angiotensin
  - Can lead to renal vasodilation
  - Can lead to improvement in serum creatinine

Full V-2 agonist

- May cause hyponatremia
- May cause fluid overload (i.e. pulmonary edema)

Jamil et al. *J Exp Pharmacol*. 2018.

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

Summary

- Recognize potential signs of cirrhosis
- Ascites: Prevent and control with furosemide and spironolactone
- HE:
  - Blood ammonia levels not clinically useful
  - Prevent and control with lactulose & rifaximin
- HRS:
  - Prompt identification and treatment is essential
  - Multidisciplinary specialist care needed