Acute Decompensated Liver Failure: Diagnosis and Management

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Objectives

- Understand the underlying pathophysiology of cirrhosis and progression to acute decompensated liver failure
- Recognize the signs, symptoms, laboratory, and radiographic findings in the workup of liver failure complications
- Design a pharmacotherapeutic plan for the management of the following indications in decompensated liver failure:
  - Ascites
  - Spontaneous bacterial peritonitis
  - Esophageal variceal hemorrhage
  - Hepatic encephalopathy
  - Alcoholic hepatitis
  - Hepatorenal syndrome

Chronic Liver Disease: Epidemiology

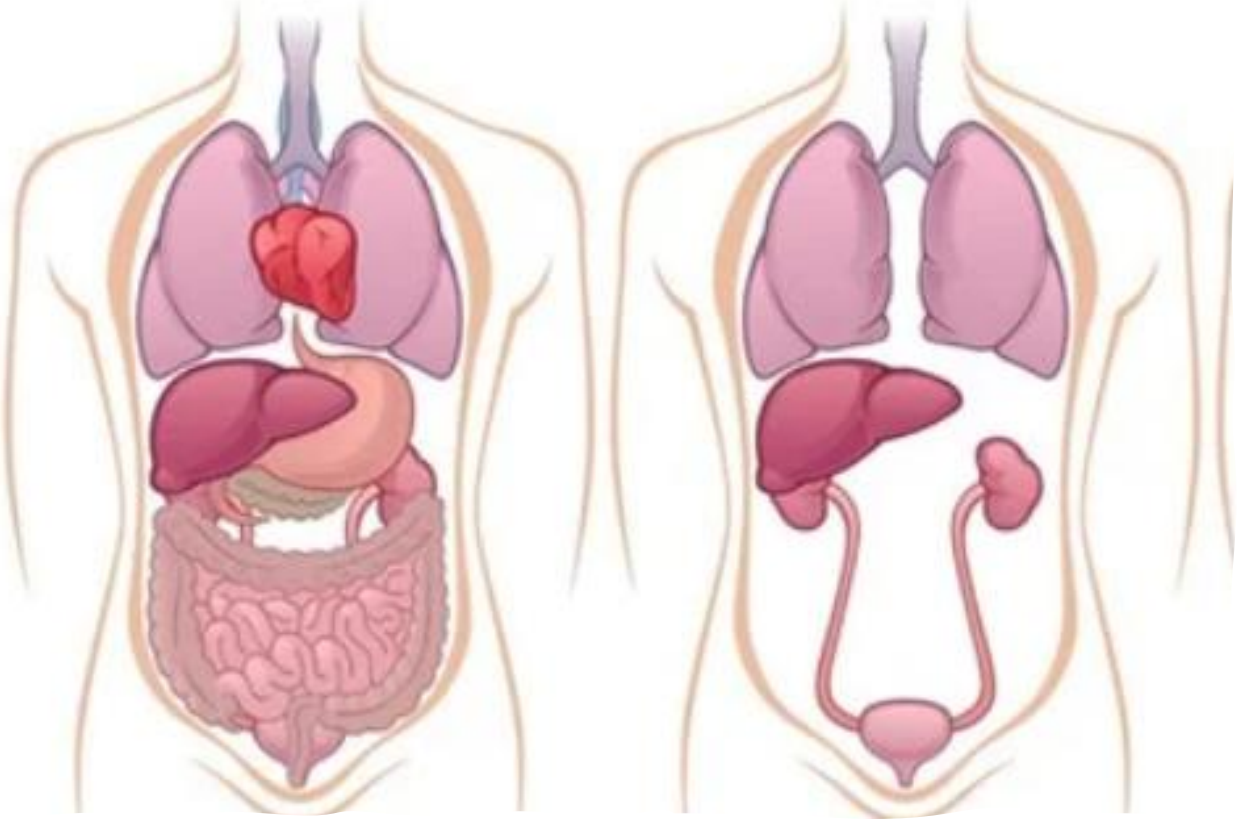
Cirrhosis affects approximately 2.2 million adults in the United States

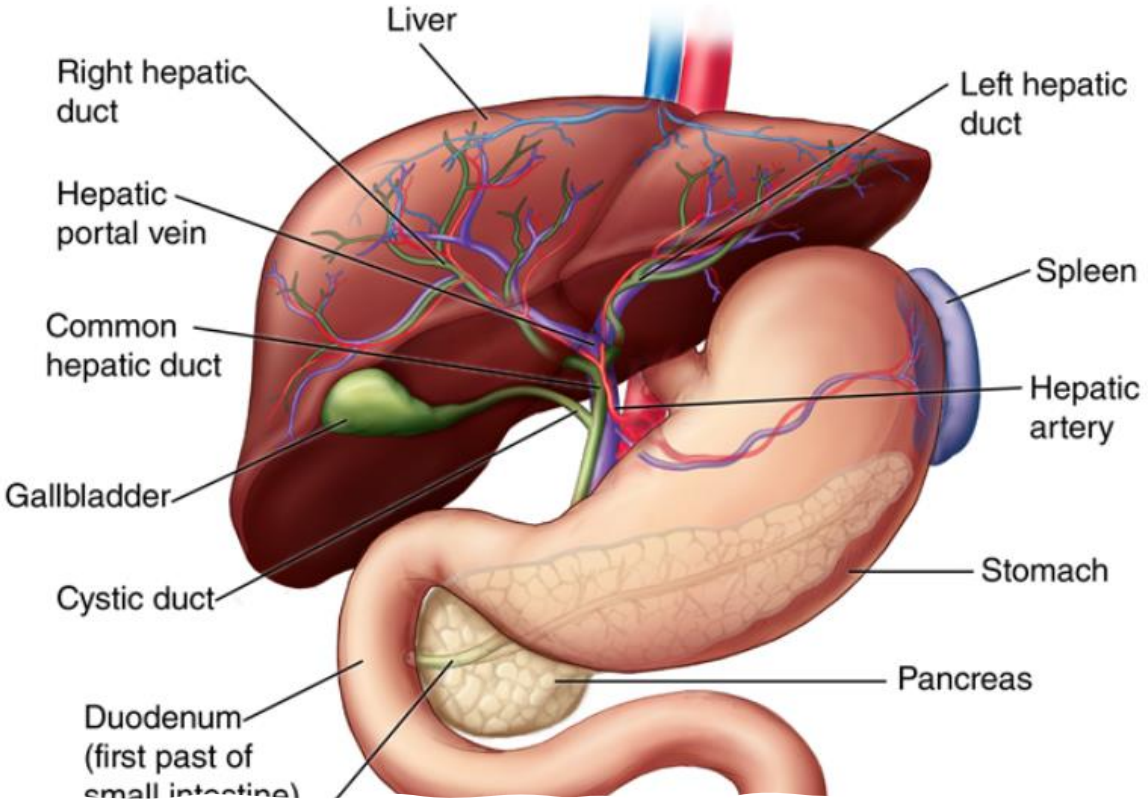
From 2010 to 2021, the annual age-adjusted mortality due to cirrhosis increased from 1.49 per to 21.9 per 100,000

Cirrhosis is now the 10th leading cause of death in the United States, and one of the leading causes of death in patients aged 25 – 44 years

https://www.cdc.gov/nchs/fastats/leading-causes-of-death.htm

Tapper EB, Parikh ND. Diagnosis and Management of Cirrhosis and Its Complications: A Review. JAMA. 2023 May 9;329(18):1589-1602





Anatomy

- The liver is located in the upper right-hand portion of the abdominal cavity, beneath the diaphragm, and on top of the stomach, right kidney, and intestines.

Detoxification:
- Urea (Ammonia)
- Environmental toxins

Coagulation:
- Synthesis of clotting factors: (fibrinogen, prothrombin, V, VII, VIII, IX, X, XI, XII, XIII)

Lipid metabolism:
- Synthesis of cholesterol
- Production of triglycerides

Drug Metabolism:
- Phase I: oxidation, reduction, hydrolysis (CYP450)
- Phase II: Conjugation

Glucose homeostasis:
- Gluconeogenesis
- Synthesizes and stores glycogen from glucose

Digestion:
- Bile production

Hormone regulation:
- Deiodination T4 to T3
- Metabolism of estrogen, testosterone, steroids
- Thrombopoeitin production (regulates platelet production)

Vitamin Storage:
- Store and metabolize fat-soluble vitamins A,D,E,K

Bilirubin metabolism:
- Heme broken down to unconjugated bilirubin, conjugated in liver and secreted into bile

Chronic Liver Failure: Etiology

• Alcoholic liver disease (most common)
• Viral (hepatitis B and C, Epstein-Barr)
• Nonalcoholic fatty liver disease (NASH)
• Autoimmune causes:
  • Primary biliary cirrhosis
  • Primary sclerosing cholangitis
  • Autoimmune hepatitis
	• Budd-Chiari (venoocclussive)
	• Medication induced (acetaminophen, isoniazid, methotrexate, amiodarone, statins, certain antibiotics)
	• Hemochromatosis (Wilson's disease)
	• Alpha-1 antitrypsin deficiency
	• Cystic fibrosis

Smith A, Baumgartner K, Bositis C. Cirrhosis: Diagnosis and Management. Am Fam Physician. 2019 Dec 15;100(12):759-770.

Normal vs. Cirrhosis

- Persistent inflammation and wound healing resulting in hepatic parenchymal fibrosis
- Images represent progressive, diffuse, fibrosing, nodular condition disrupting the entire normal liver architecture
- Approximately 80 – 90% of the liver parenchyma is destroyed before liver failure is manifested clinically

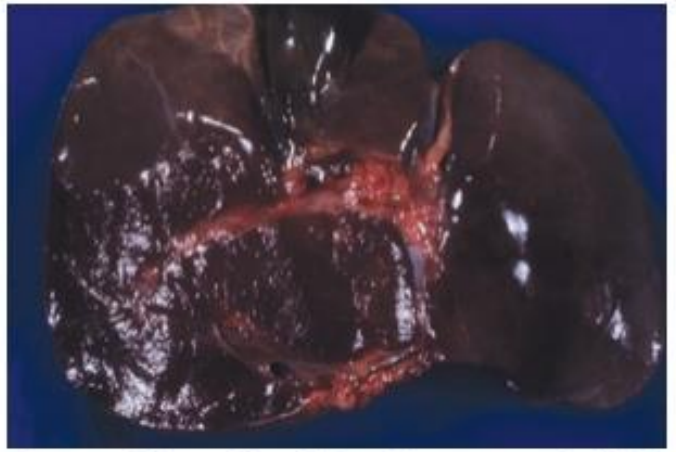


Figure 2. Inferior surface of liver, biliary tree, and gallbladder (gross) revealing normal hepatic tissue and structure.

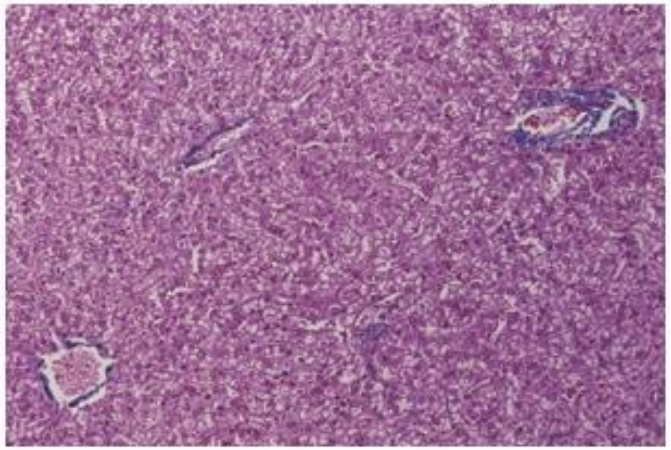


Figure 4A. Normal hepatic tissue (microscopic, 10X, trichrome stain).

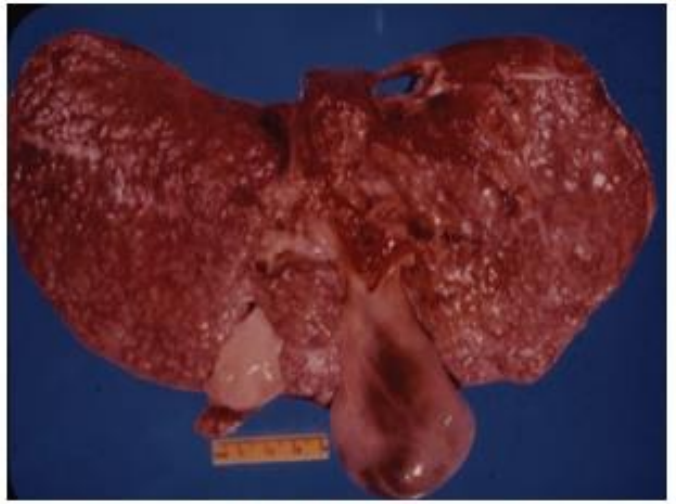


Figure 3. Inferior surface of liver and gallbladder (gross) revealing cirrhotic liver.

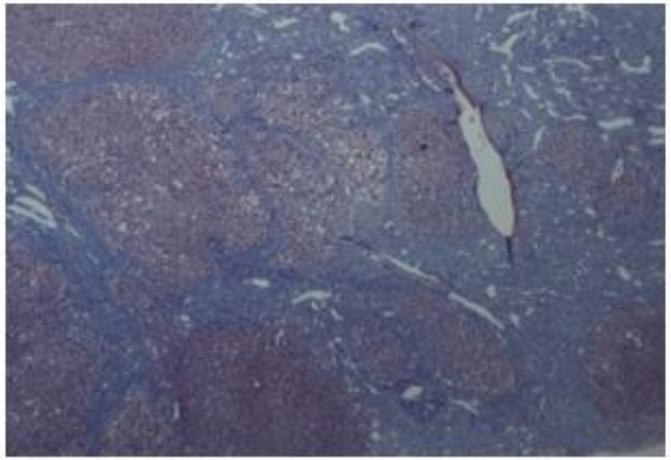
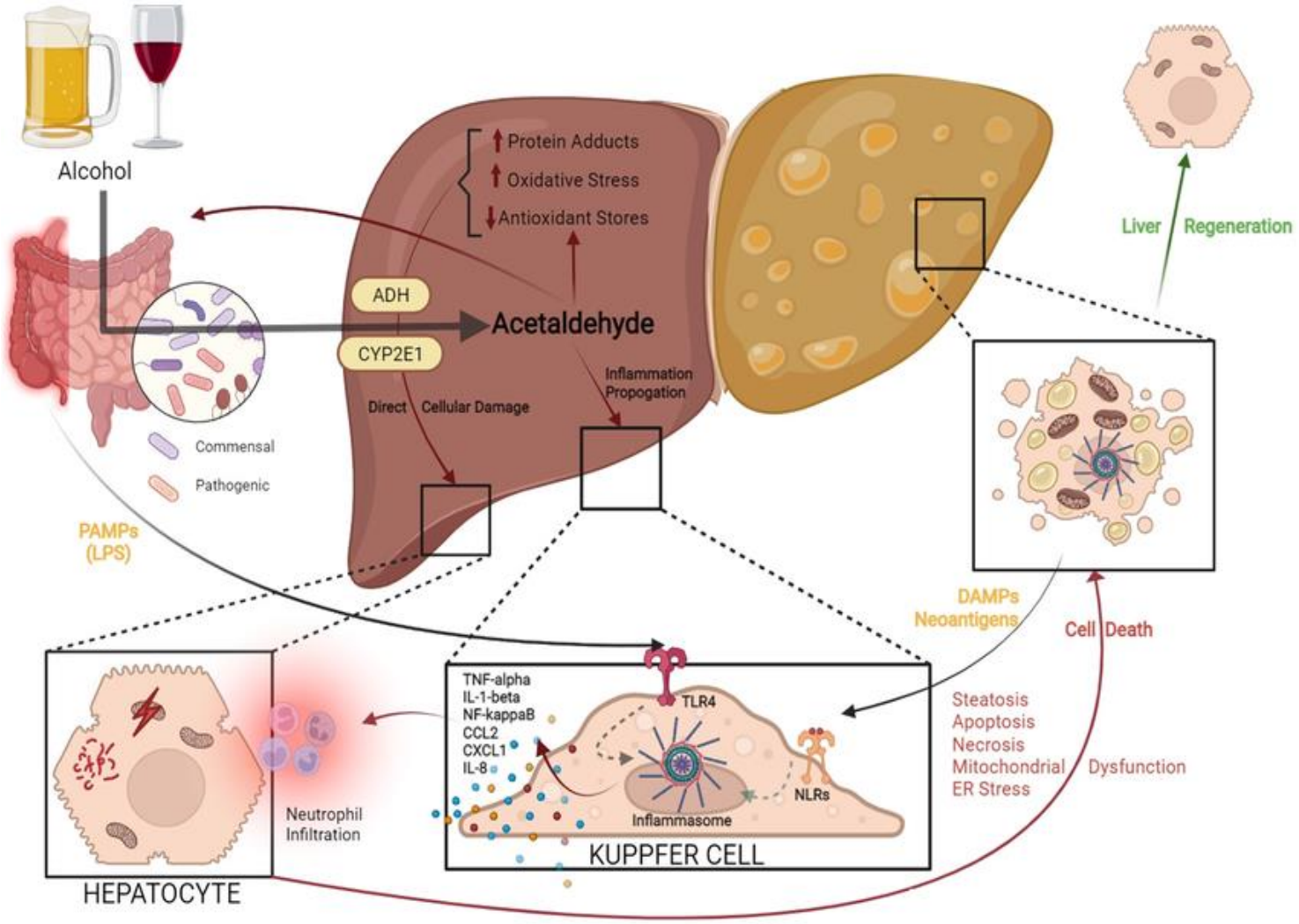


Figure 4B. Cirrhosis (microscopic, 10X, trichrome stain).

Photographs courtesy of Henry D. Appelman, M.D., Professor, Department of Pathology, University of Michigan Medical School, Ann Arbor, Mich.

How Does Alcohol Cause Cirrhosis?

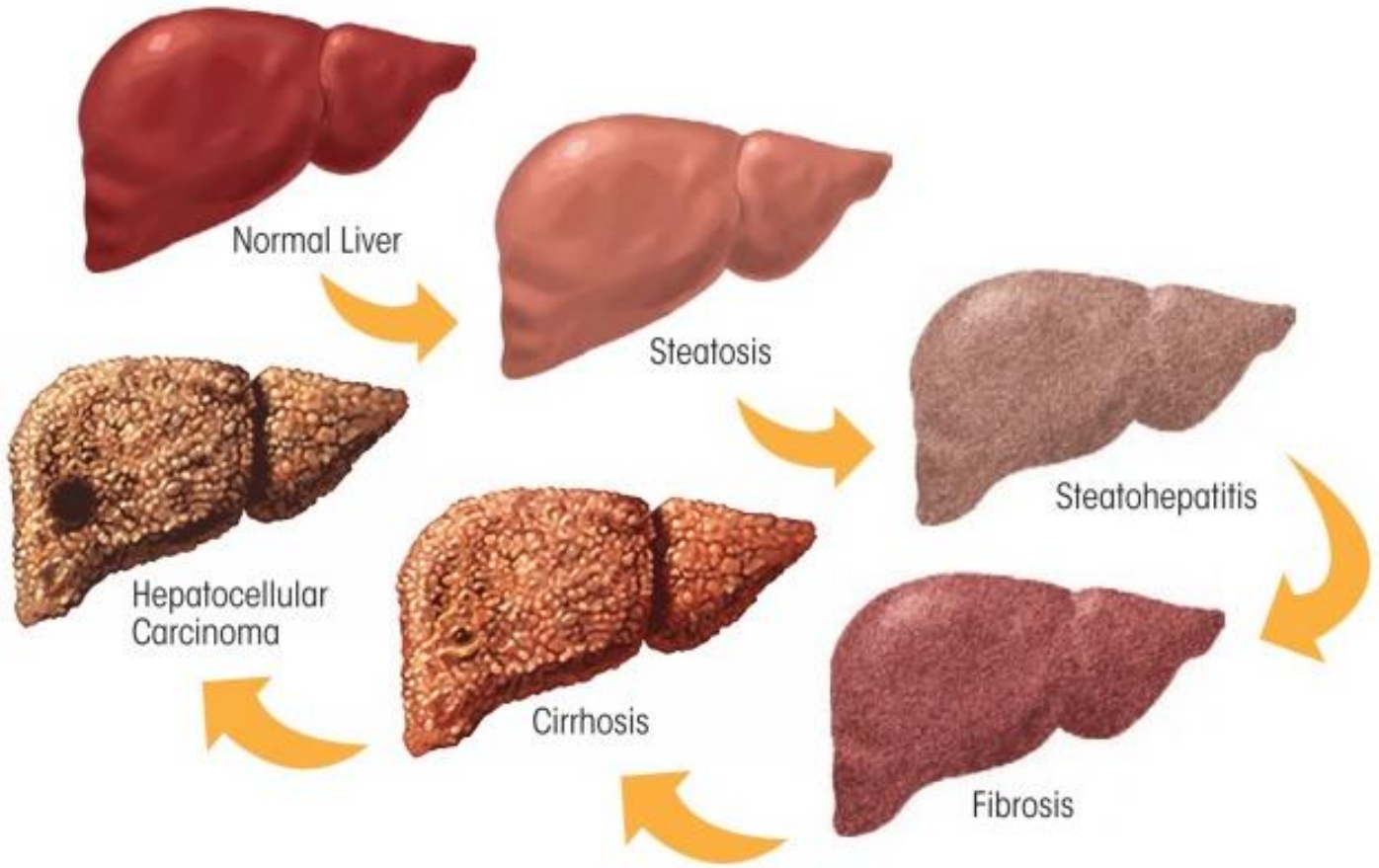
- Ethanol is metabolized in the liver by hepatocytes by alcohol dehydrogenase and CYP2E1 into acetaldehyde
  - Acetaldehyde in excess can cause inflammation, lipid accumulation, fibrosis, and carcinogenesis
- CYP2E1 induces reactive oxygen species (ROS) overproduction which causes oxidant stress and cellular damage to DNA and proteins



Osna NA, Donohue TM, Kharbanda KK. Alcoholic Liver Disease: Pathogenesis and Current Management. Alcohol Res. 2017;38(2):147-161.

Spectrum of Alcoholic Liver Disease

- Heavy alcohol use first leads to steatosis characterized by deposition of fat in the hepatocytes
- Presence of fat leads to greater lipid peroxidation and even further oxidative damage
- Acetaldehyde causes direct oxidative stress and hepatocyte damage leading to fibrosis
- Fibrosis progresses to cirrhosis in the late state of hepatic scarring



Osna NA, Donohue TM, Kharbanda KK. Alcoholic Liver Disease: Pathogenesis and Current Management. Alcohol Res. 2017;38(2):147-161.

Alcohol Use Disorder

ALCOHOLISM SCREENING

"CAGE"

	DESCRIPTION	QUESTION
C	CONCERN by the person that there is a problem	Have you ever felt that you should CUT down on your drinking?
A	APPARENT to others that there is a problem	Have you ever become ANNOYED by criticisms of your drinking?
G	GRAVE consequences	Have you ever felt GUILTY about your drinking?
E	EVIDENCE of dependence or tolerance	Have you ever had a morning EYE OPENER to get rid of a hangover?

Pharmacotherapy: Alcohol Use Disorder

TABLE 4. Relapse Prevention Medications in Alcoholic Liver Disease

Medication	Dosing	Metabolism (M) and Excretion (E)	Mechanism of Action	ALD Considerations
Naltrexone*	50 mg/d orally or 380 mg monthly sq	M: Hepatic E: Mostly renal, fecal 2%-3%	Opioid receptor antagonist	Not studied in patients with ALD Hepatotoxicity concerns
Acamprosate*	666 mg tid	M: None E: Renal	NMDA receptor antagonist	Not studied in patients with ALD No reported instances of hepatotoxicity
Gabapentin	600-1,800 mg/d	M: None E: Renal 75%, fecal 25%	Modulates GABA activity through action at presynaptic calcium channels	Not studied in patients with ALD Monitor closely for renal dysfunction and worsening mental status/sedation
Baclofen	30-60 mg/d	M: Hepatic, limited E: Renal	GABA-B receptor agonist	Single RCT in patients with ALD showed benefit
Topiramate	75-400 mg/d	M: Not extensively metabolized E: Renal	GABA action augmentation, glutamate antagonism	Not studied in patients with ALD

Note: Adapted from Winder et al.[237]
*FDA-approved for AUD treatment. Disulfiram is not included on this list because it is not recommended for use in patients with ALD.
Abbreviations: GABA, gamma-aminobutyric acid; NMDA, *N*-methyl-D-aspartate; sq, subcutaneous; and tid, 3 times per day.

Crabb DW, et al. Diagnosis and Treatment of Alcohol-Associated Liver Diseases: 2019 Practice Guidance From the American Association for the Study of Liver Diseases. Hepatology. 2020 Jan;71(1):306-333.

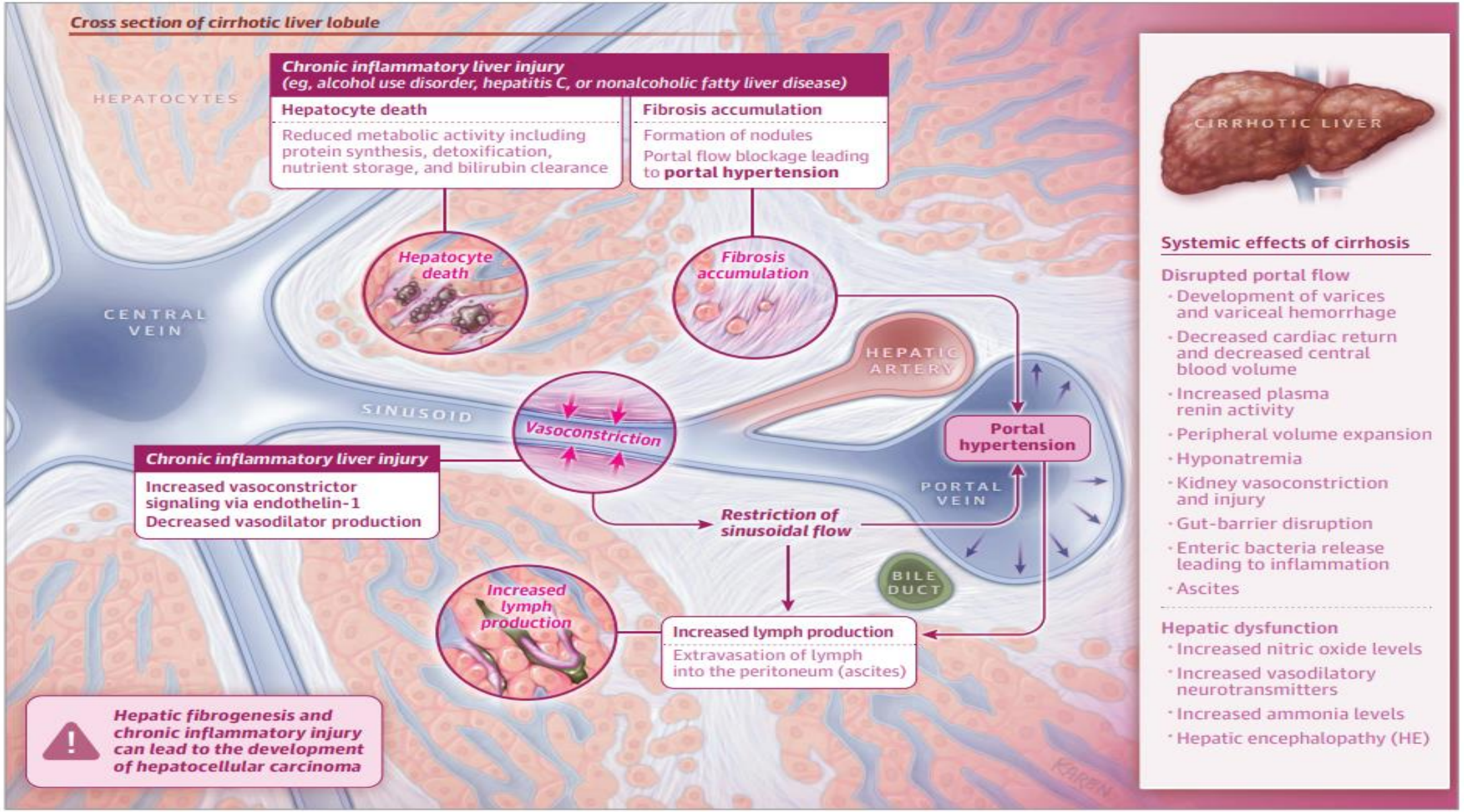
Chronic Liver Disease: Pathophysiology

- Chronic liver disease is a progressive and continuous process of inflammation, destruction, and regeneration of liver parenchyma, which leads to fibrosis and portal hypertension
  - Chronic inflammatory liver injury leads to fibrosis:
    - Activation of hepatic myofibroblasts and macrophages, increased collagen accumulation (fibrosis) and increases in intrahepatic vascular tone
      - Impedes portal inflow (mechanical and dynamic resistance mechanisms)
      - Eventual hepatocyte death reducing liver metabolic functional capacity
  - Portal hypertension (due mostly to increased resistance of flow secondary to fibrosis) leads to:
    - Compensatory splanchnic* vasodilation which causes decreased systemic vascular resistance
      - Decreased SVR leads to increased cardiac output
    - Increased portal pressure forces blood from extracellular space into peritoneum (ascites) leading to ‘effective” decreased blood volume
      - Activates renin system to increase aldosterone leading to further fluid retention
      - Increased antidiuretic hormone (promotes free water retention and leads to hyponatremia)

**Splanchnic circulation* refers to gastric, intestinal, pancreatic, hepatic and splenic circulation

World J Gastroenterol. 2014 Mar 14;20(10):2555-2563

Figure 1. Impact of Portal Hypertension and Hepatic Insufficiency on Cirrhosis Pathophysiology



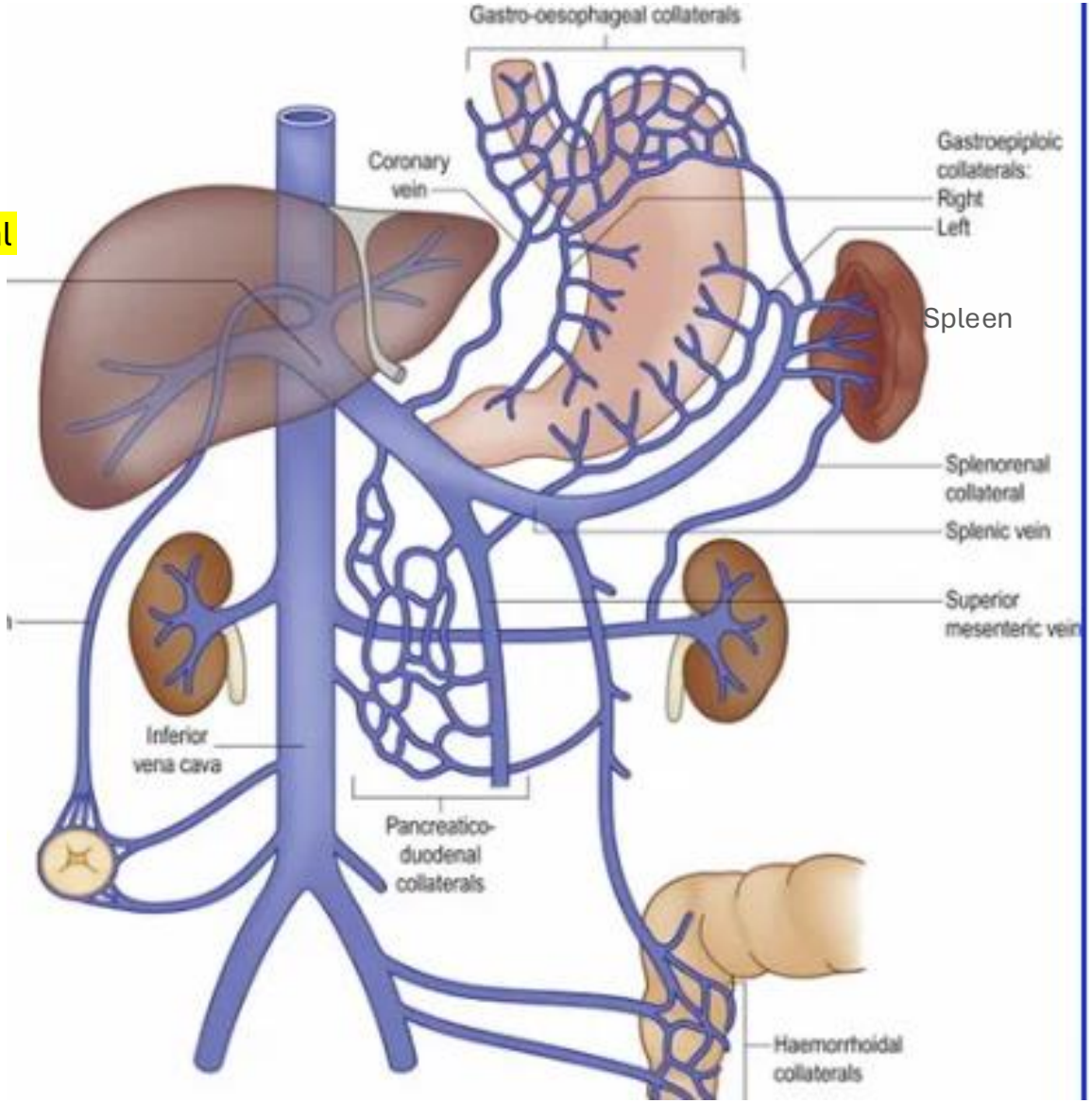
Cirrhosis leads to intrahepatic resistance, which causes portal hypertension and, at later stages, hepatic insufficiency, which disrupts the liver's normal metabolic functions. Together these features cause gut-barrier disruption and portosystemic shunting, resulting in the multisystem complications of cirrhosis, eg, hepatic encephalopathy, sarcopenia, ascites, and kidney injury.

Tapper EB, Parikh ND. Diagnosis and Management of Cirrhosis and Its Complications: A Review. JAMA. 2023 May 9;329(18):1589-1602

Anatomy: Hepatic Circulation

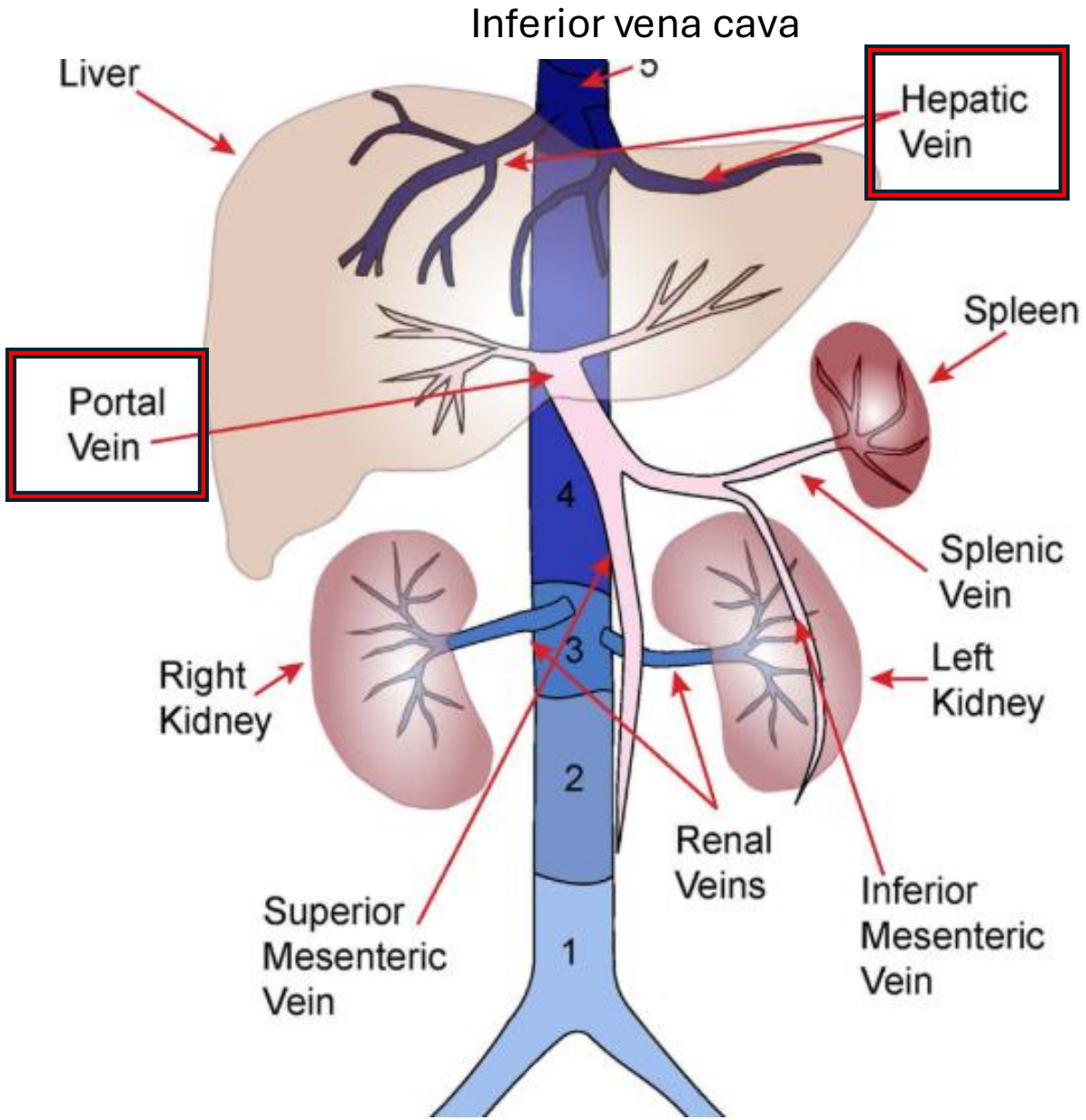
- Hepatic arteries supply oxygenated blood to the liver
  - Liver receives 25% of cardiac output
- Hepatic portal vein carries deoxygenated blood from gastrointestinal tract to the liver, delivering nutrients
  - Liver blood flow through sinusoids, absorbing nutrients
  - Then blood flows through hepatic vein into inferior vena cava
  - When there is resistance of blood flow through liver due to cirrhosis, fluid backs up into spleen, stomach, esophagus, intestines, pancreas, and colon

Portal Vein



Portal Hypertension

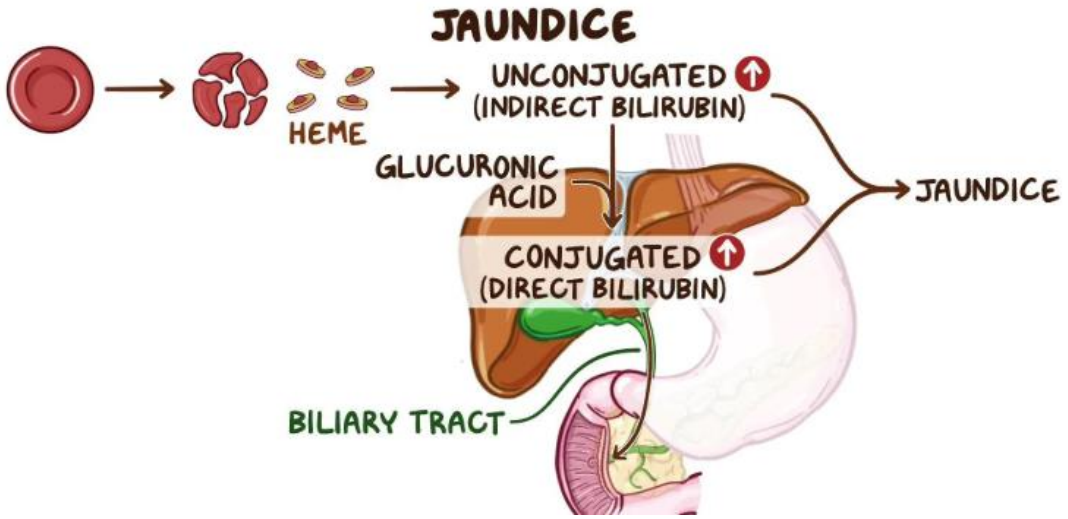
- Definition: increased pressure within the portal venous system
- Measurement of hepatic venous pressure gradient (HVPG): can be measure indirectly using ultrasound imaging to determine the difference in pressure between portal venous pressure and pressure within the inferior vena cava or hepatic vein
  - Pressure gradient normally < 5 mmHg
  - Portal hypertension when gradient ≥ 6 mmHg
  - Clinically significant portal hypertension > 10 mmHg

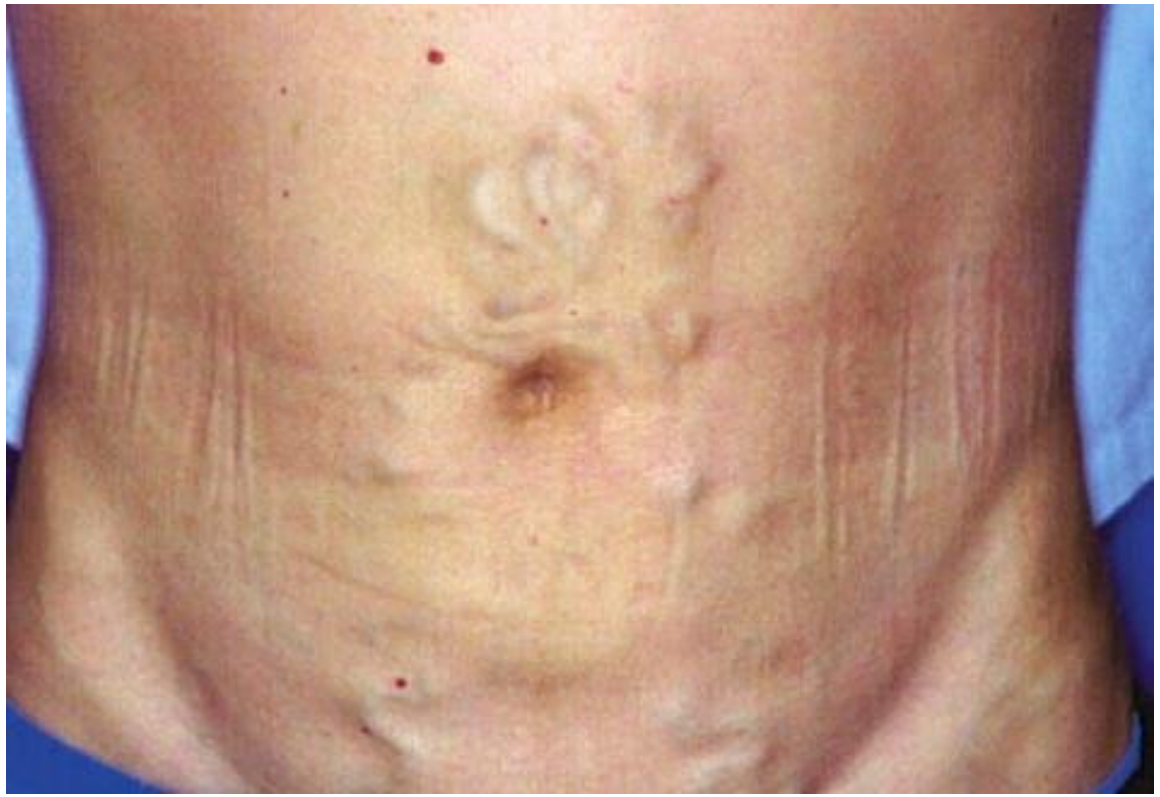


Clinical Signs and Symptoms of Liver Disease

- Jaundice: yellowing of skin
- Icteric conjunctivae/Scleral icterus: yellowing of the whites of the eyes
- Pruritis: itching due to accumulation of bile salts under the skin

- Mechanism: Jaundice and scleral icterus are caused by hyperbilirubinemia
  - Breakdown of red blood cells releases hemoglobin which is broken down into heme which releases bilirubin (yellow in color)
    - Dysfunction of hepatocytes leads to increased levels of unconjugated bilirubin
  - Unconjugated bilirubin is transported to liver and conjugated to become water soluble in bile where it is excreted into the biliary system, stored in the gallbladder, ultimately released into duodenum to break down fatty acids



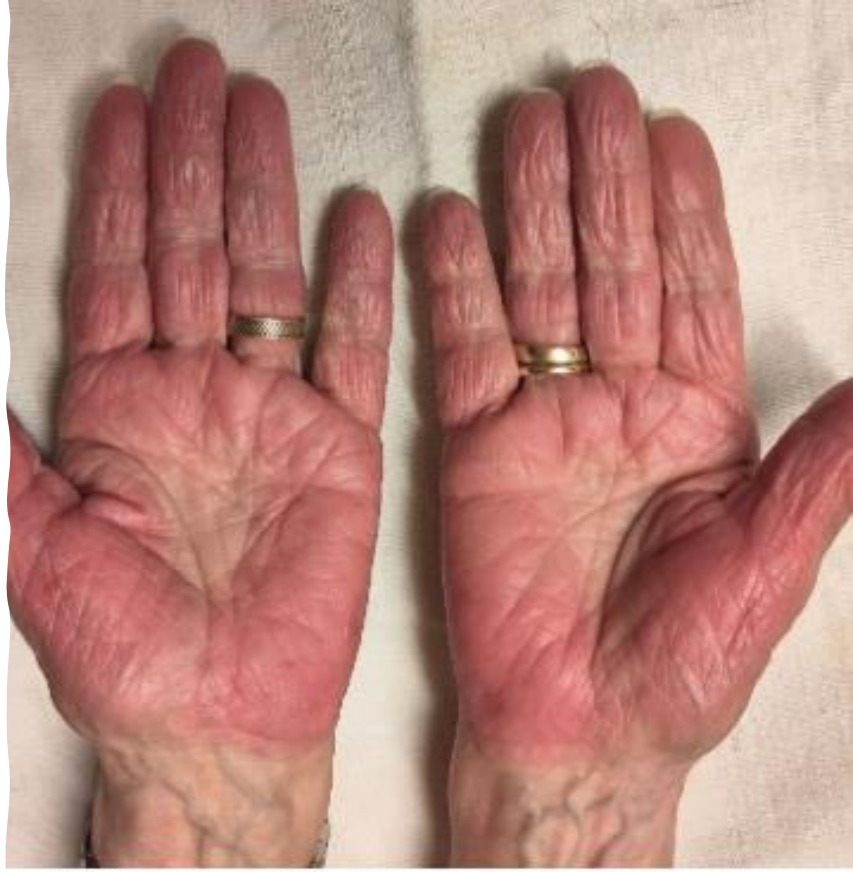


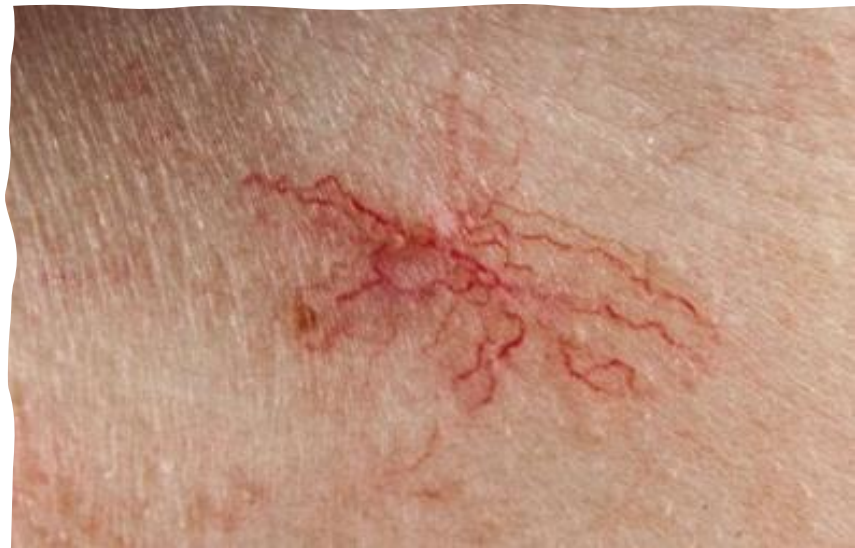
Clinical Signs and Symptoms

- Ascites: excessive abdominal fluid accumulation (between peritoneum and abdominal organs)
- Caput medusae: engorged portal vein pushes blood into smaller veins around umbilicus, creating a network of dilated veins
- Splenomegaly: enlarged spleen due to portal congestion
- Hemorrhoids: swollen and inflamed veins in rectum and anus due to porto-systemic venous anastomosis

Clinical Signs and Symptoms

- Gynecomastia: enlargement of breast tissue in males
- Palmar erythema: non-tender, blanching, symmetric redness of both palms
  - Mechanism: increased free estrogen levels which leads to vasodilation of surface capillaries of the hands
- Spider angiomas (spider nevi): small dilated blood vessels
  - When pressure is applied, the central arteriole is compressed, causing the lesion to blanch
  - When pressure is released, lesion refills from central arteriole
  - Mechanism: excess estrogen due to impaired liver metabolism leading to vasodilation and increased angiogenesis

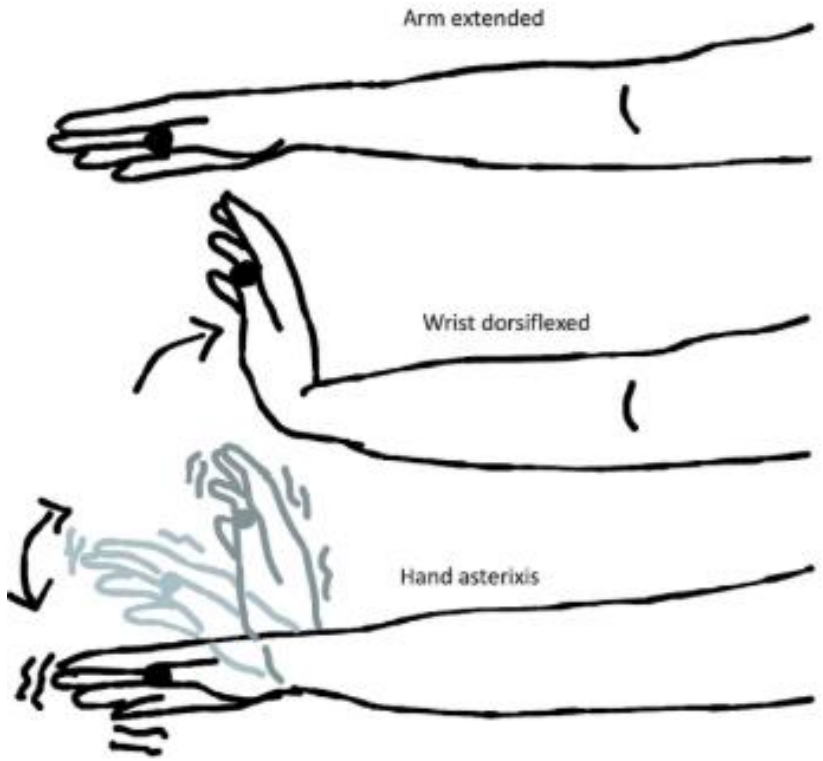




Clinical Signs and Symptoms

- Confusion: hepatic encephalopathy due to hyperammonemia

- Asterixis: “flapping tremor” a neurological sign characterized by involuntary, brief and irregular jerking movements of the hands
  - Patient is asked to extend arms and hyperextend of wrists to observe for involuntary flapping motion
  - Negative myoclonus consisting of loss of postural tone



AASLD. J Hepatol. 2014 Sep;61(3):642-59.

Laboratory Testing

- "Liver function tests" – a misnomer since these tests do not reflect liver function, but may reflect hepatocyte inflammation or injury
  - Aminotransferases: Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST)
    - AST/ALT ratio > 2 suggestive of alcoholic cirrhosis
- Bilirubin (total bilirubin, conjugated vs unconjugated)
  - Determines etiology of hyperbilirubinemia (i.e. pre-hepatic, intrahepatic vs posthepatic biliary blockage)
- Albumin: expect hypoalbuminemia due to decreased hepatic synthesis
- Coagulation tests: PT/INR
  - Elevated INR due to decreased liver production of clotting factors
- Platelet count
  - Thrombocytopenia due to sequestration of platelets in the spleen and decreased thrombopoietin production
- Ammonia level (if confusion): assess for hepatic encephalopathy
  - Elevated ammonia due to decreased capacity of liver to convert to urea
- Serum sodium
  - Hyponatremia due to increased ADH and free water retention
- Serum creatinine (SCr)
  - Assess for prerenal AKI and hepatorenal syndrome

Prognosis

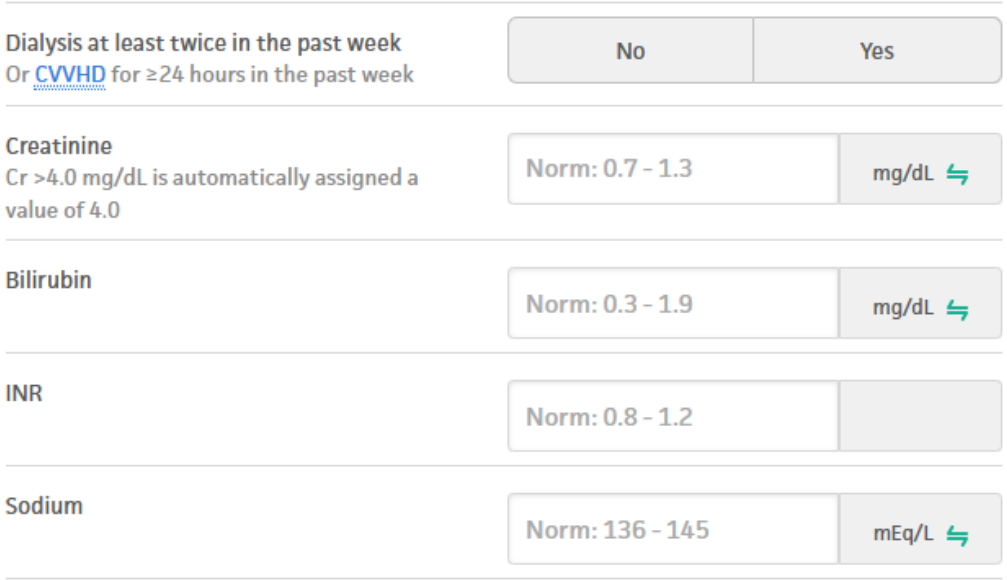
MELD(i) = 0.957 × ln(Cr) + 0.378 × ln(bilirubin) + 1.120 × ln(INR) + 0.643

Then, round to the tenth decimal place and multiply by 10.

If MELD(i) > 11, perform additional MELD calculation as follows:

MELD = MELD(i) + 1.32 × (137 – Na) – [0.033 × MELD(i) × (137 – Na)]

- Prognosis of cirrhosis is highly variable depending on if patient has evidence of decompensation (complication of cirrhosis such as variceal hemorrhage, SBP, hepatorenal syndrome, etc)
- Model for End-State Liver (MELD) is a model to predict prognosis based on bilirubin, creatinine, and INR
  - Newer model incorporates serum sodium



https://www.mdcalc.com/calc/78/meld-score-model-end-stage-liver-disease-12-older

Example: MELD-Na Calculation

	CHEM PROFILE
132	Sodium
4.1	Potassium
96	Chloride
21	CO2
15	Anion Gap
118	Glucose
32	BUN
1.66	Creatinine
41	Calculated GFR
19.3	BUN/Creatinine Ratio
9.0	Calcium
	Phosphorus
213	AST (SGOT)
94	ALT (SGPT)
128	Alkaline Phosphatase
6.0	Total Protein
3.2	Albumin
38.7	Total Bilirubin
2.0	Magnesium
70	Lipase
115	Ammonia

	ROUTINE COAGULATION
38.8	Prothrombin Time
3.9	INR

MELD Na (UNOS/OPTN)

Quantifies end-stage liver disease for transplant planning with sodium.

IMPORTANT

We've updated and combined our MELD scores into one page. Clinicians can choose the formula that best fits their needs: the original MELD score; the current MELD-Na used by UNOS/OPTN, and the 2022 MELD 3.0 score. Click here to view.

INSTRUCTIONS

Use in patients ≥12 years old. Note: As of January 2016, calculation of the MELD has changed. It now includes serum sodium level. See OPTN's announcement.

When to Use | Pearls/Pitfalls | Why Use

Dialysis at least twice in the past week
Or CVVHD for ≥24 hours in the past week — No | Yes

Creatinine
Cr >4.0 mg/dL is automatically assigned a value of 4.0 — 1.66 mg/dL

Bilirubin — 38.7 mg/dL

Very high double-check.

INR — 3.9

Sodium — 132 mEq/L

40 points
MELD Score (2016)*

71.3%
Estimated 3-Month Mortality

Copy Results | Next Steps

Interpretation:

MELD Score	Mortality
≤9	1.9%
10–19	6.0%
20–29	19.6%
30–39	52.6%
≥40	71.3%

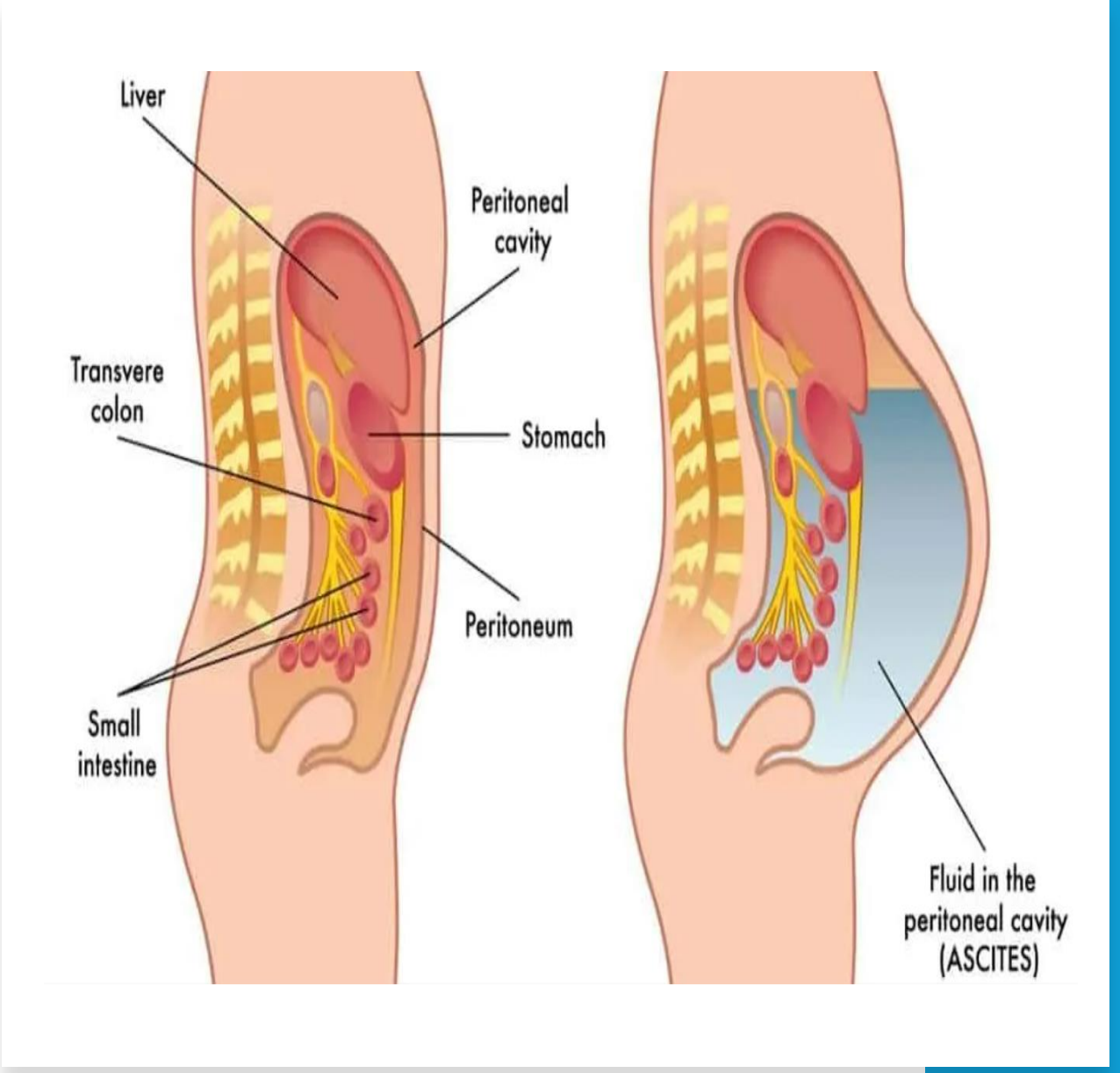
Acute Decompensated Liver Failure

Roadmap

- Ascites
- Spontaneous bacterial peritonitis (SBP)
- Esophageal variceal hemorrhage
- Hepatic encephalopathy
- Acute alcoholic hepatitis
- Hepatorenal syndrome (HRS)

Ascites

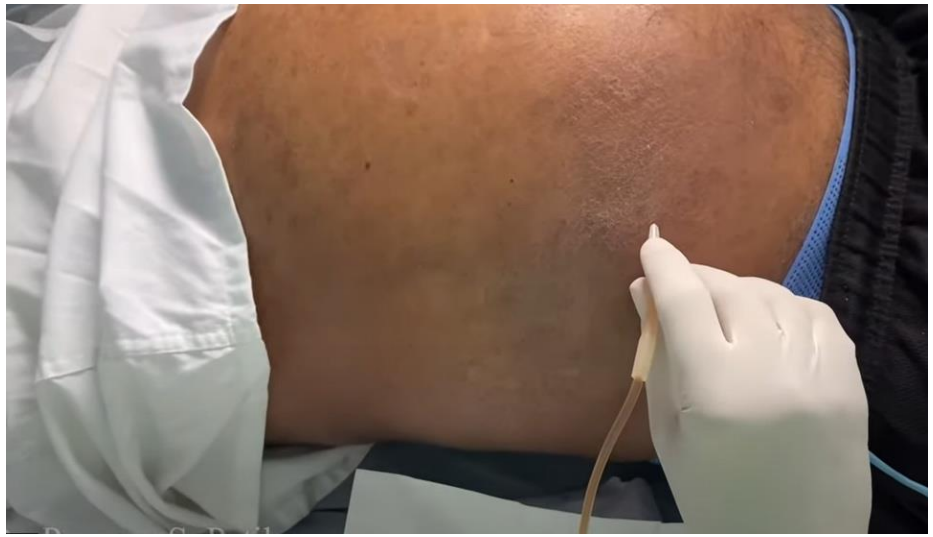
- Ascites is the pathological accumulation of fluid within the peritoneal cavity
- Ascites is commonly the first decompensation-defining event
  - 5 – 10% of patients with compensated cirrhosis develop ascites per year
    - Present in 50% of patients with decompensated cirrhosis within 10 years
  - Development of ascites is associated with reduction in 5-year survival from 80% to 30%
- Pathophysiology: portal pressure increases above critical threshold causing fluid leak from vessels into the peritoneal cavity
  - Other mechanisms: aldosterone hypersecretion, hypoalbuminemia, splanchnic vasodilation



Khan S, et al. Cleve Clin J Med. 2023 Apr 3;90(4):209-213

Paracentesis

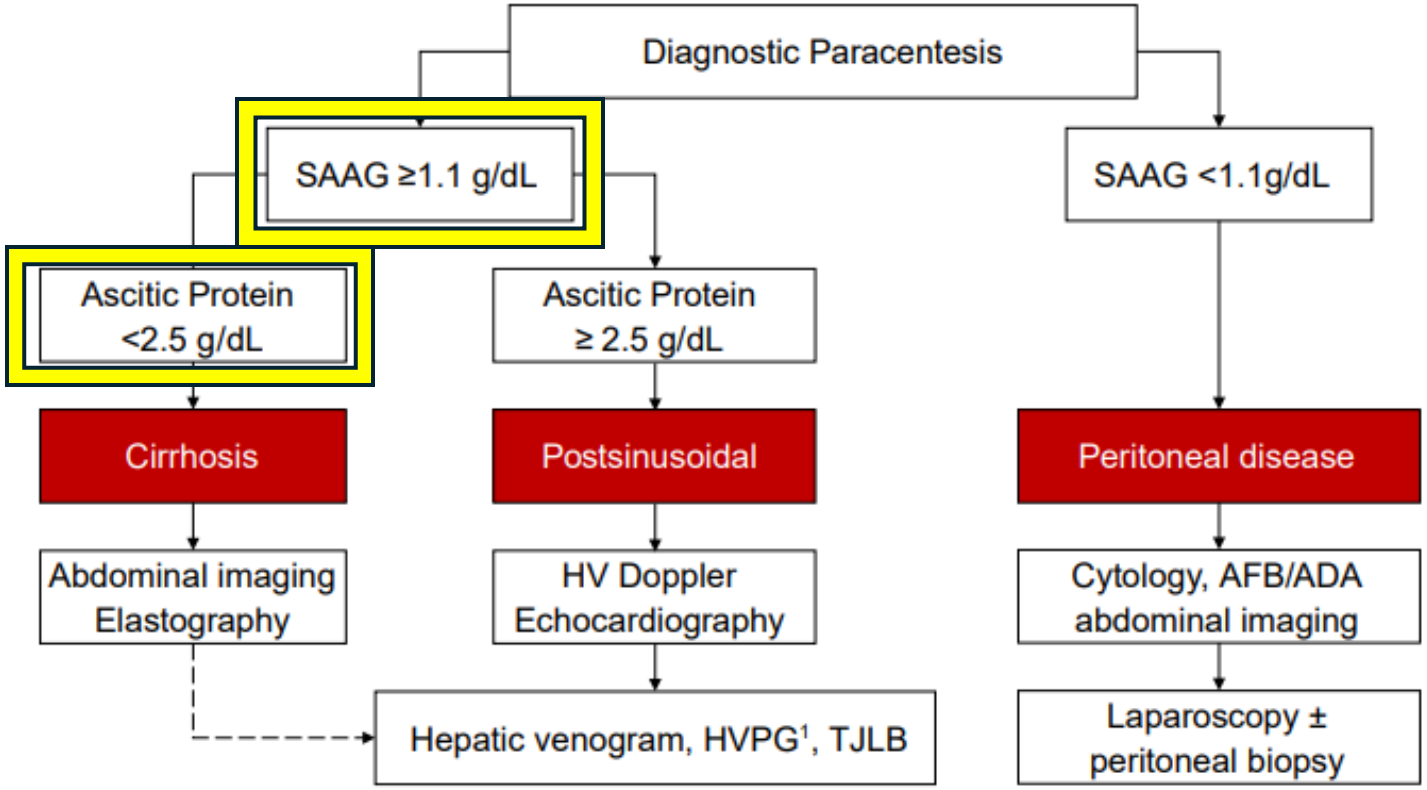
- Diagnostic paracentesis should be performed on any patient promptly if any suspicion of infection
- Perform diagnostic paracentesis and test fluid for the following:
    - SAAG (serum ascites albumin gradient)
    - PMN count
    - Culture
    - Ascites protein concentration, glucose, LDH if secondary bacterial peritonitis suspected
- Therapeutic paracentesis may be performed to remove large amounts of fluid in patients with tense ascites
    - Remove enough fluid to relieve intra-abdominal pressure for patient comfort
    - Large volume paracentesis (LVP) defined as removal of > 5 L
        - For LVP: replace albumin 6 – 8 g for every liter of ascites removed to prevent post paracentesis circulatory dysfunction (PPCD)



Diagnostic Paracentesis

Serum-ascites albumin gradient (SAAG) ≥ 1.1 g/dL suggestive of portal hypertension or right heart failure

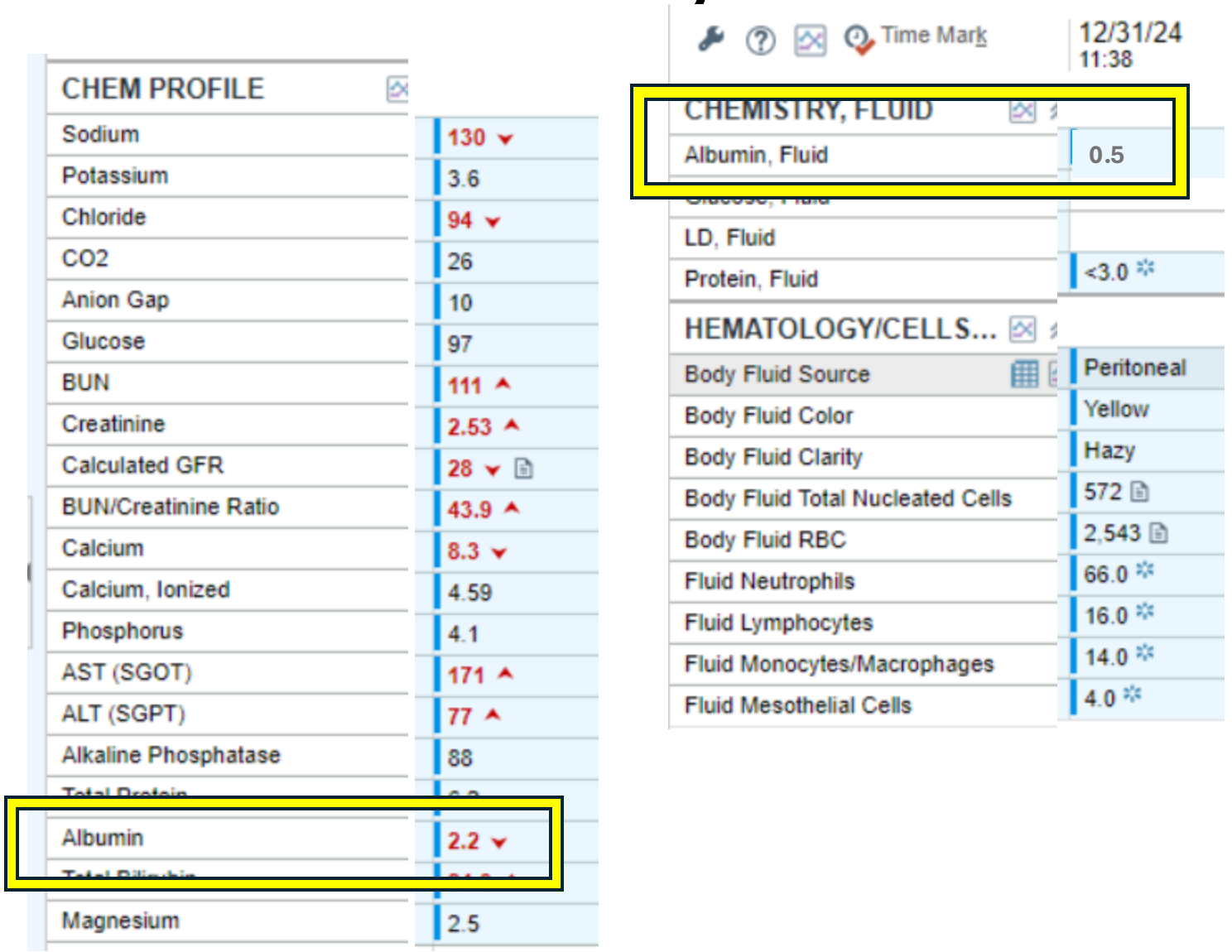
When portal pressure increases, it forces fluid out of the blood vessels into the peritoneal cavity, but large proteins, such as albumin, cannot pass through vessel walls



Hepatology. 2021 Aug;74(2):1014-1048

Example Paracentesis Fluid Analysis

- SAAG = serum albumin – ascites albumin
- SAAG ≥ 1.1 suggests portal hypertension or heart failure
- 2.2 – 0.5 = 1.7 → portal hypertension
- Serum albumin < 2.5 g/dL suggests cirrhosis as cause of portal hypertension



CHEM PROFILE	
Sodium	130 ↓
Potassium	3.6
Chloride	94 ↓
CO2	26
Anion Gap	10
Glucose	97
BUN	111 ↑
Creatinine	2.53 ↑
Calculated GFR	28 ↓
BUN/Creatinine Ratio	43.9 ↑
Calcium	8.3 ↓
Calcium, Ionized	4.59
Phosphorus	4.1
AST (SGOT)	171 ↑
ALT (SGPT)	77 ↑
Alkaline Phosphatase	88
Albumin	2.2 ↓
Magnesium	2.5

Time Mark 12/31/24 11:38

CHEMISTRY, FLUID	
Albumin, Fluid	0.5
LD, Fluid	
Protein, Fluid	<3.0
HEMATOLOGY/CELLS...	
Body Fluid Source	Peritoneal
Body Fluid Color	Yellow
Body Fluid Clarity	Hazy
Body Fluid Total Nucleated Cells	572
Body Fluid RBC	2,543
Fluid Neutrophils	66.0
Fluid Lymphocytes	16.0
Fluid Monocytes/Macrophages	14.0
Fluid Mesothelial Cells	4.0

Classification of Ascites

- Classification of ascites Grade 1 – 3 based on fluid accumulation and response to treatment

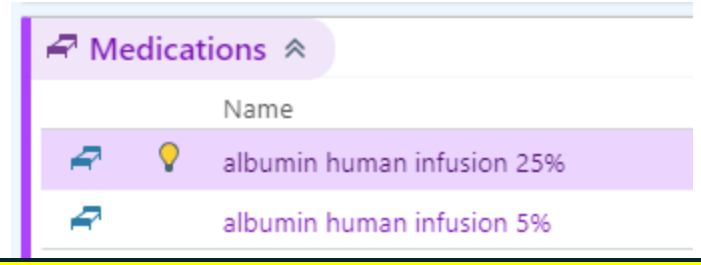
TABLE 5. Classification of Ascites

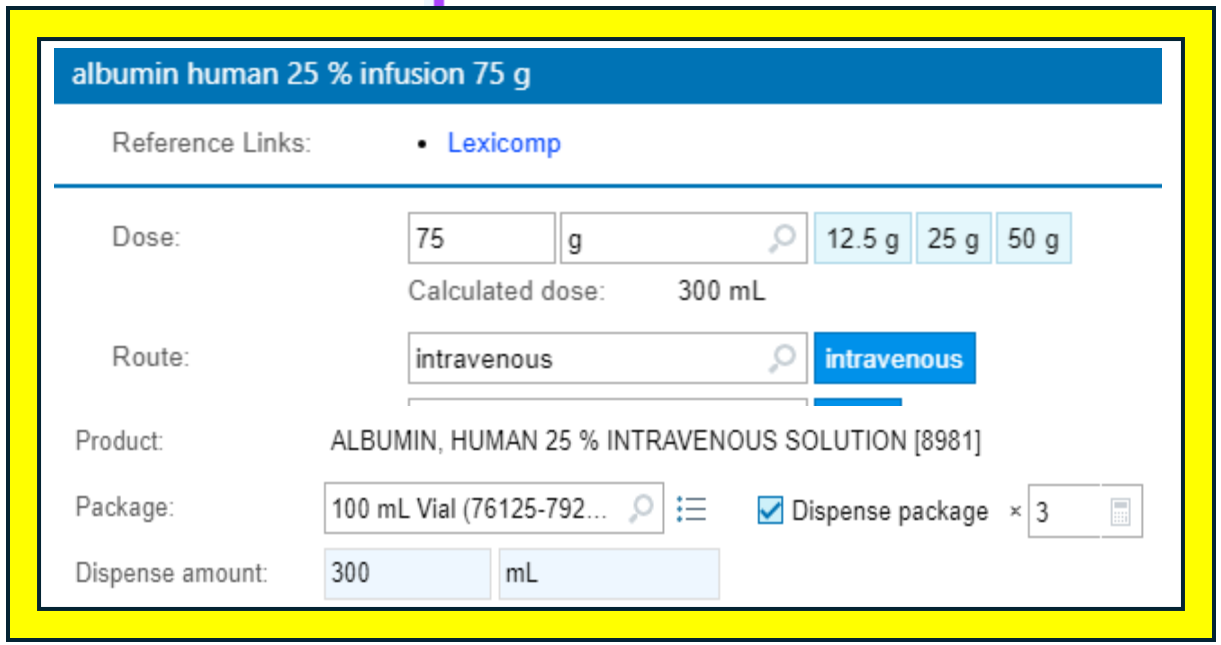
According to Amount of Fluid Accumulation		According to the Response to Treatment	
Grade 1. Mild ascites	Only detected by ultrasound	Responsive ascites	Ascites that can be fully mobilized or limited to grade 1 with diuretic therapy associated or not to moderate dietary sodium restriction
Grade 2. Moderate ascites	Moderate symmetric distension of abdomen	Recurrent ascites	Ascites that recurs on at least 3 occasions within a 12-month period despite dietary sodium restriction and adequate diuretic dosage
Grade 3. Large or gross ascites	Marked distension of the abdomen	Refractory Ascites	Ascites that cannot be mobilized or the early recurrence of which (i.e., after LVP) cannot be satisfactorily prevented by medical therapy

Hepatology. 2021 Aug;74(2):1014-1048

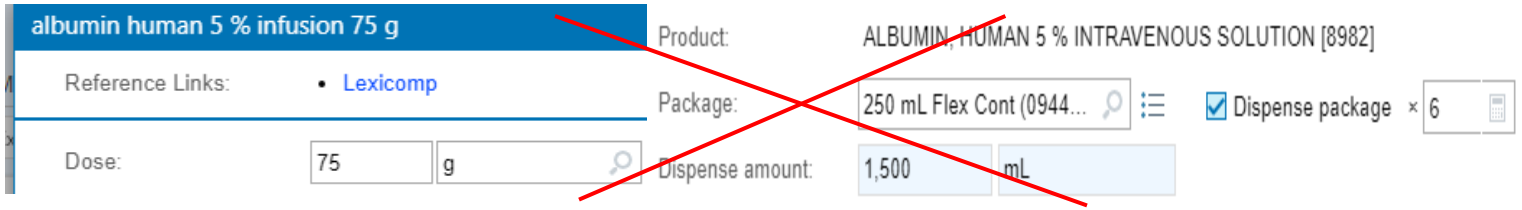
Albumin Dose for LVP

- For LVP > 5 L replace albumin 6 – 8 g/L removed to prevent hypotension (albumin increases oncotic pressure in the intravascular space)
- Example: 10 L removed during large volume paracentesis
- 6 – 8 g/L = 60 – 80 grams albumin
- Order albumin 25% 75 g IV once over 2 hours





DO NOT use albumin 5% → only contains 5 g albumin per 100 mL → 75 g of 5% albumin would be 1,500 mL !!



Treatment of Ascites: Sodium Restriction

- Moderate dietary sodium restriction
  - 2 g = 2000 mg or 88 mmol/day of sodium to achieve negative sodium balance and net fluid loss
- DO not fluid restrict unless profound hyponatremia
- Sodium restriction counseling
- Dietary sodium restriction alone is insufficient in most patients with cirrhosis presenting with ascites
  - Peritoneal membrane's ability to reabsorb ascites from the abdominal cavity is limited to 500 mL per day

2 servings per container: 760 mg per serving = 1,520 mg per package

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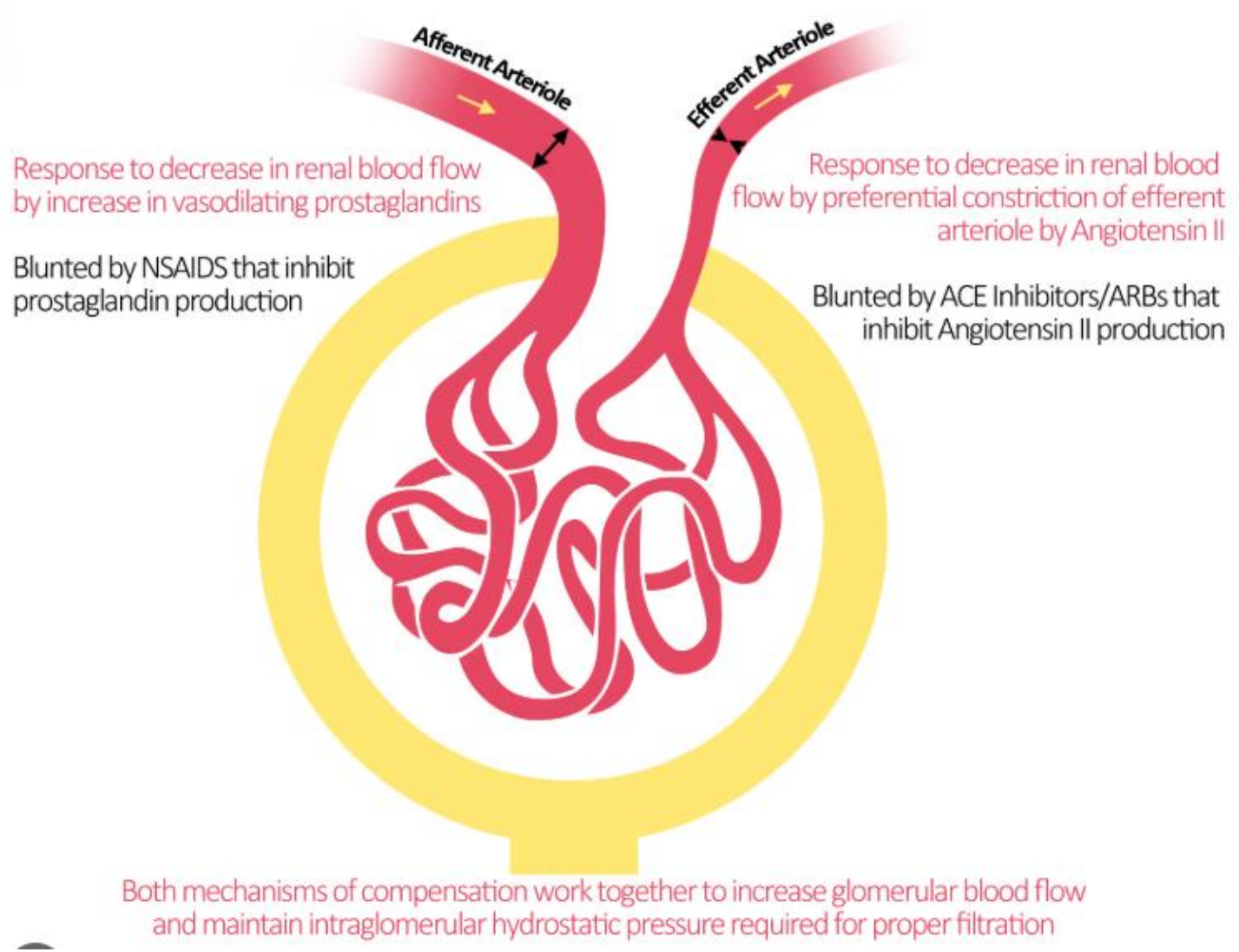
Medications to AVOID

- AVOID NSDAIDs: non-steroidal anti-inflammatory drugs inhibit prostaglandins, leading to decreased renal perfusion (by preventing vasodilation at the afferent arteriole) which increases risk for hepatorenal syndrome
    - NSAIDs also inhibit thromboxane A2 production which increases bleeding risk
- AVOID ACEI: angiotensin converting enzyme inhibitor prevent efferent arteriole vasoconstriction which may decrease renal blood flow



Treatment: Diuretics

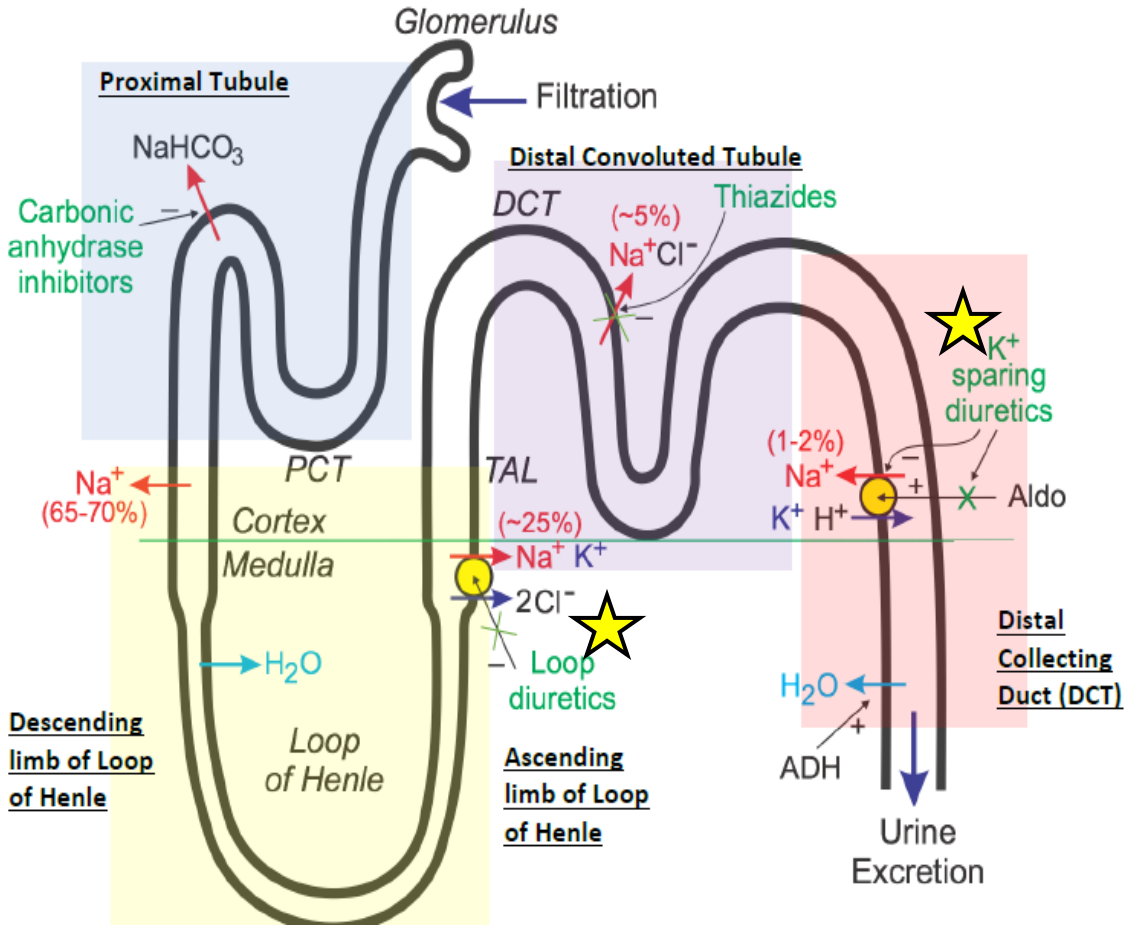
Loop diuretic comparison:

	Furosemide	Torsemide	Bumetanide
Relative intravenous potency (mg)	40	20	1
Oral : intravenous dosing	1 : 2	1 : 1	1 : 1
Bioavailability (%)	10–100	80–100	80–100
Drug half-life (h)	1.5–2.0	3–4	1.0–1.5
Duration of effect (h)	6–8	6–16	4–6

If suboptimal response to furosemide, may switch to torsemide or bumetanide to improve natriuresis

- Aldosterone antagonist (potassium sparing diuretic) in combination with loop diuretic in 2.5:1 ratio for first episode of ascites
  - INITIAL doses:
    - Spironolactone 100 mg PO (titrated to max 400 mg/day) daily PLUS furosemide 40 mg PO daily (titrated to max 160 mg/day)
    - *Preferred combination to achieve rapid natriuresis while maintaining normokalemia*
      - Loop diuretics inhibit sodium (and water) reabsorption in the loop of Henle → causing natriuresis
      - But there is still a possibility to reabsorbsodium and water distally, especially in cirrhosis with hyperaldosterone state
      - Aldosterone antagonists inhibit sodium (and water) reabsorption in the distal convoluted tubule (DCT) and collecting duct → increases sodium and water excretion while conserving potassium

Mechanism of Action of Diuretics



DIURETICS	MECHANISM OF ACTION
Thiazide diuretics: Hydrochlorothiazide, Chlorothiazide **Thiazide-related diuretics**: Chlorthalidone, metolazone, indapamide	Inhibits sodium reabsorption (by inhibiting the Na/Cl symporter) in the distal collecting tubule causing increased excretion of sodium and water as well as potassium and hydrogen ions
Loop diuretic: Furosemide, Bumetanide, Torsemide, ethacrynic acid	Primarily inhibits reabsorption of sodium and chloride (by inhibiting the Na/K/2Cl symporter) in the thick segment of the ascending loop of Henle and proximal and distal renal tubules, interfering with the chloride-binding cotransport system, thus causing its natriuretic effect
Potassium sparing diuretic and Aldosterone receptor antagonist: Spironolactone, eplerenone **Potassium sparing diuretic**: Triamterene, amiloride	Competes with aldosterone for receptor sites in the distal renal tubule, increasing sodium chloride and water excretion while conserving potassium and hydrogen ions; may block the effect of aldosterone on arteriolar smooth muscle. Block epithelial sodium channels in late distal convoluted tubule and collecting duct which inhibits sodium reabsorption from the lumen reducing intracellular sodium, decreasing the function of the Na/K/ATPase, leading to K retention and decreased Ca, Mg, H+ excretion. As sodium uptake capacity in the DCT is limited, the natriuretic and diuretic effect are weak.

Combination Diuretic in Ascites: Balancing Act

Diuretic	Spironolactone	Furosemide
Mechanism of Action	Aldosterone Antagonist	Loop Diuretic
Effect on Potassium	Potassium sparing	Potassium wasting
Dosing in Ascites*	Starting ratio of 20mg of furosemide for every 50mg of spironolactone (2:5 ratio). Dose can be adjusted depending on response and surveillance labs. Alternative loop diuretics, including torsemide or bumetanide, may improve natriuresis in patients who do not respond to furosemide.	
Adverse effects	Hyperkalemia, gynecomastia, acute kidney injury	Hypokalemia, hyponatremia, muscle cramps, acute kidney injury

* Uptitration of diuretic doses in patients with cirrhosis is frequently limited by the development of electrolyte derangements and/or acute kidney injury.

Diuretic Resistance

- Refractory ascites occurs in approximately 5 – 10% of all patients and is associated with poor survival of 50% at 6 months
- Diuretic resistance:
  - Inability to mobilize ascites despite confirmed sodium restriction and maximum tolerated diuretics
  - Rapid re-accumulation of fluid after therapeutic paracentesis despite adherence to sodium restricted diet
  - Diuretic-related complications such as azotemia, hepatic encephalopathy, or progressive electrolyte disturbances

TABLE 7. Characteristics of RA

Diuretic-resistant ascites
- Ascites that cannot be mobilized
- Early recurrence of which cannot be prevented

Because of the lack of response to dietary sodium restriction and maximal doses of diuretics

Diuretic-intractable ascites
- Ascites that cannot be mobilized
- Early recurrence that cannot be prevented

Because of the development of diuretic-induced complications* that precludes the use of effective doses of diuretics

Fails sodium restriction
- 88 mmol or 2,000 mg/day

Fails maximum doses of diuretics
- Spironolactone 400 mg/day or amiloride 30 mg/day
- Furosemide 160 mg/day

Both for at least 1 week

Lack of treatment response
- Mean weight loss of <0.8 Kg over 4 days
- Urinary sodium less than sodium intake

Early recurrence of ascites
- Reappearance of grade 2 or grade 3 ascites within 4 weeks of initial mobilization

***Diuretic-induced complications**
- Renal impairment: increase in serum creatinine by >100% to a value >2.0 mg/dL
- Hyponatremia with a decrease of >10 mmol/L or an absolute value of <125 mmol/L
- Hypo- or hyperkalemia of <3 mmol/L or >6 mmol/L
- Hepatic encephalopathy

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Titration and Monitoring of Diuretics

- Reminder: initial combination diuretics for first episode of ascites = spironolactone 100 mg PO once daily PLUS furosemide 40 mg per day
- Titration maintains ratio 2.5:1 → example increase to spironolactone 150 mg PO once daily PLUS furosemide 60 mg PO once daily
    - Titrate to maximum spironolactone 400 mg PLUS maximum furosemide 160 mg as tolerated
- Adverse effects of diuretic therapy may occur in 20 – 40% of patients with cirrhosis and ascites
    - AKI, hyponatremia, hyperkalemia, gynecomastia, muscle cramps, worsening hepatic encephalopathy
- Monitor serum sodium, potassium, SCr

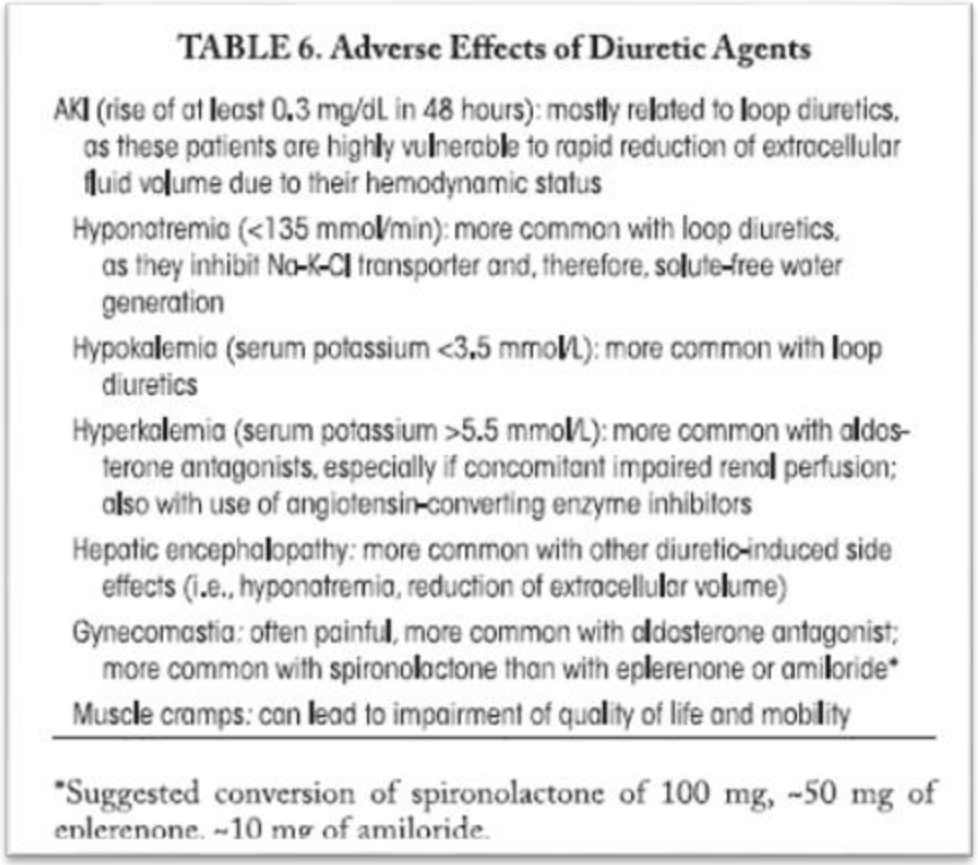

TABLE 6. Adverse Effects of Diuretic Agents

AKI (rise of at least 0.3 mg/dL in 48 hours): mostly related to loop diuretics, as these patients are highly vulnerable to rapid reduction of extracellular fluid volume due to their hemodynamic status

Hyponatremia (<135 mmol/min): more common with loop diuretics, as they inhibit Na-K-Cl transporter and, therefore, solute-free water generation

Hypokalemia (serum potassium <3.5 mmol/L): more common with loop diuretics

Hyperkalemia (serum potassium >5.5 mmol/L): more common with aldosterone antagonists, especially if concomitant impaired renal perfusion; also with use of angiotensin-converting enzyme inhibitors

Hepatic encephalopathy: more common with other diuretic-induced side effects (i.e., hyponatremia, reduction of extracellular volume)

Gynecomastia: often painful, more common with aldosterone antagonist; more common with spironolactone than with eplerenone or amiloride*

Muscle cramps: can lead to impairment of quality of life and mobility

*Suggested conversion of spironolactone of 100 mg, ~50 mg of eplerenone, ~10 mg of amiloride.

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Roadmap

Ascites

Spontaneous bacterial peritonitis (SBP)

Esophageal variceal hemorrhage

Hepatic encephalopathy

Acute alcoholic hepatitis

Hepatorenal syndrome (HRS)

Spontaneous Bacterial Peritonitis (SBP)

- SBP defined as ascitic fluid infection without another source
  - Documented by positive ascitic bacterial culture and elevated ascites fluid absolute polymorphonuclear leukocyte (PMN) count ≥ 250 cells/mm^3
- Bacterial translocation (passage of bacteria from the gut into the bloodstream)
- Risk factors for SBP:
  - Variceal hemorrhage
  - Malnutrition
  - Use of proton pump inhibitors (PPIs)
  - Ascitic fluid total protein concentration < 1 g/dL

Bacteria organism	% of isolates
Eschericia coli	43%
Klebsiella pneumoniae	11%
Streptococcus pneumoniae	9%
Other strep species	19%
Other Enterobacteriaceae (Enterobacter, Citrobacter, Proteus, Serratia)	4%
Staphylococcus	3%
Pseudomonas	1%
Other (including Enterococcus)	10%

Spontaneous Bacterial Peritonitis

- Signs/Symptoms: abdominal pain, tenderness on palpation, altered mental status, fever, ileus, hypotension
  - Presentation is highly variable including asymptomatic
    - Since delay in initiation of antibiotics may increase mortality, diagnostic paracentesis should be performed on any patient hospitalized emergently with cirrhosis and ascites
- Diagnosis established with diagnostic paracentesis and fluid analysis
  - Absolute nucleated cell count ≥ 250/mm^3
  - Positive ascitic fluid bacterial culture (or positive blood culture)

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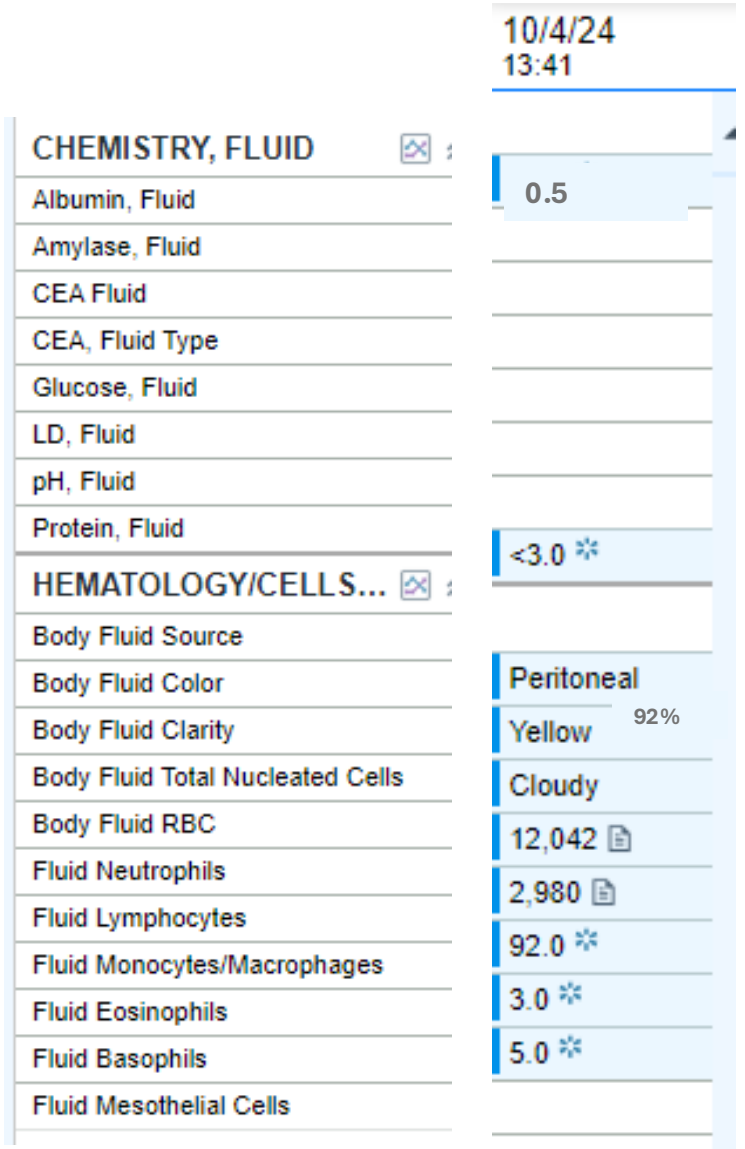
ExampleA Case: SBP

- 61/M (70 kg) with history of ETOH abuse and cirrhosis presents with worsening abdominal distension and tenderness
  - Patient has frequent paracentesis every 2 – 3 weeks and is currently receiving furosemide 80 mg PO daily and spironolactone 200 mg PO daily
  - Diagnostic paracentesis performed
    - Total nucleated cells 12,042/mm^3 x 92% neutrophils = 11,078/mm^3 PMNs
    - Ascites fluid sent for culture/susceptibility testing



	10/4/24 13:41
CHEMISTRY, FLUID	
Albumin, Fluid	0.5
Amylase, Fluid	
CEA Fluid	
CEA, Fluid Type	
Glucose, Fluid	
LD, Fluid	
pH, Fluid	
Protein, Fluid	<3.0
HEMATOLOGY/CELLS...	
Body Fluid Source	Peritoneal
Body Fluid Color	Yellow
Body Fluid Clarity	Cloudy
Body Fluid Total Nucleated Cells	12,042
Body Fluid RBC	2,980
Fluid Neutrophils	92.0
Fluid Lymphocytes	3.0
Fluid Monocytes/Macrophages	5.0
Fluid Eosinophils	
Fluid Basophils	
Fluid Mesothelial Cells	

92%

Treatment SBP

- Empiric antibiotics: third generation cephalosporin for 5 days:
  - Cefotaxime 2 g IV every 8 hours x 5 days
  - Ceftriaxone 1 g IV q24 hours x 5 days

- Bacterial infections are a common precipitant of acute deterioration leading to multiorgan failure, especially AKI → albumin is an intravascular volume expander
  - IV albumin improved survival by preventing progression of AKI in randomized trials in select patient
    - Albumin 1.5 g/kg IV on DAY 1 and 1 g/kg IV on DAY 3 if any of the following:
      - Renal dysfunction: SCr > 1 mg/dL or BUN > 30 mg/dL
      - Severe hepatic decompensation: Bilirubin > 5 mg/dL

Example Case:

- Empiric ceftriaxone 1 g IV q24 hr x 5 days initially started
- Both SCr > 1 and bilirubin > 5 → indications for albumin
  - 1.5 g/kg x 70 kg = albumin 100 g IV on DAY 1 followed by 1 g/kg = albumin 70 grams IV on DAY 3

10/6/24 04:49

CHEM PROFILE	
Sodium	129
Potassium	4.0
Chloride	93
CO2	25
Anion Gap	11
Glucose	89
BUN	30
Creatinine	1.57
Calculated GFR	50
BUN/Creatinine Ratio	19.1
Calcium	9.0

AST (SGOT)	38
ALT (SGPT)	7
Alkaline Phosphatase	47
Total Protein	6.0
Albumin	3.9
Total Bilirubin	6.3
Bilirubin, Direct	3.0
Bilirubin, Indirect	3.3

Culture body fluid with gram stain Order: 118852154

Collected 10/4/2024 13:41 Status: Final result Visible to patient: No (inaccessible in MyChart)

Specimen Information: Peritoneal Cavity; Peritoneal Fluid

0 Result Notes

Fluid Culture: Rare Serratia marcescens !

Performed on MCCLB-VITEK2-3
The organism value for this result has been updated. These results have been appended to the previously preliminary verified report.

Gram Stain Result: Moderate Polymorphonuclear leukocytes
This is an appended report. These results have been appended to a previously preliminary verified report.
No Epithelial cells
This is an appended report. These results have been appended to a previously preliminary verified report.
No organisms seen
This is an appended report. These results have been appended to a previously preliminary verified report.

Resulting Agency: MCCLB

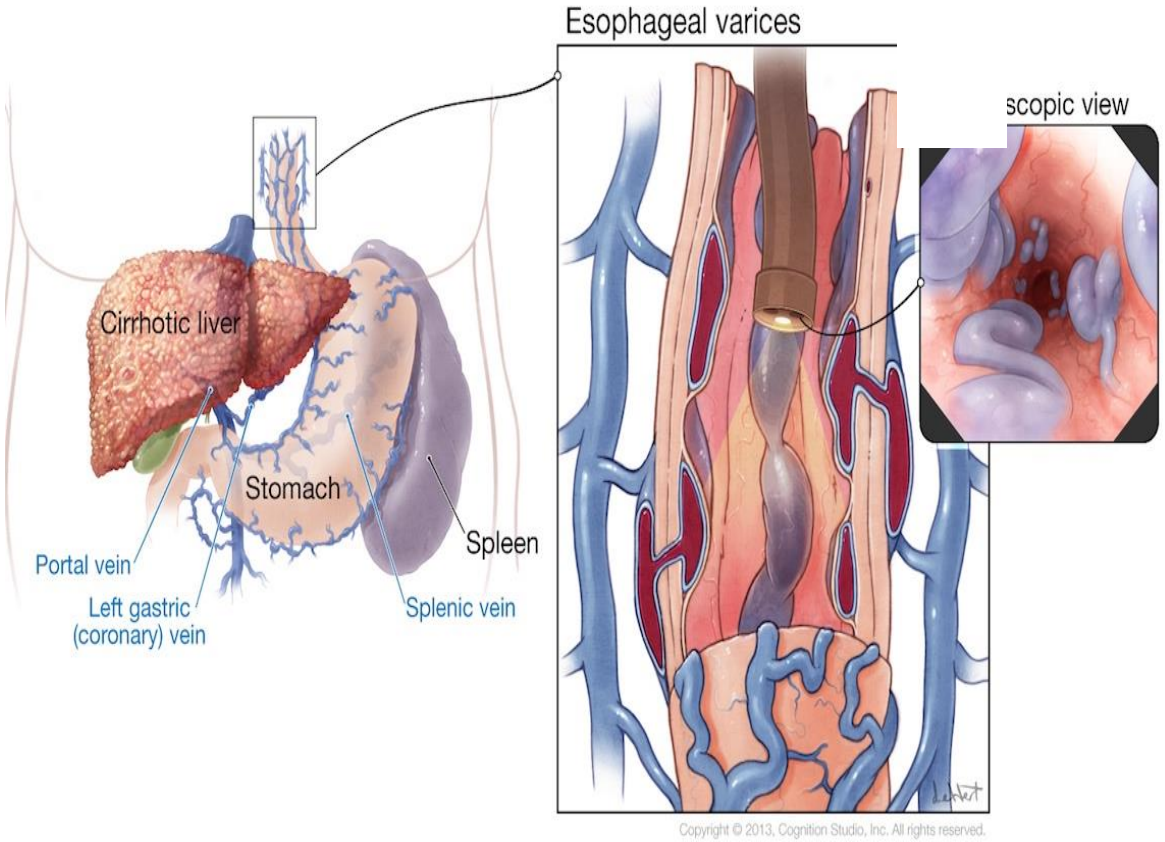
Susceptibility

	Serratia marcescens MIC	
$ Cefazolin	>=32 ug/ml	Resistant
$$ Cefepime	<=0.12 ug/ml	Susceptible *
$$ Ceftazidime	<=0.5 ug/ml	Susceptible *
$$ Ceftriaxone	<=0.25 ug/ml	Susceptible
$ Ciprofloxacin	<=0.06 ug/ml	Susceptible
$$$$ Ertapenem	<=0.12 ug/ml	Susceptible *
$ Gentamicin	<=1 ug/ml	Susceptible
$$$ Levofloxacin	<=0.12 ug/ml	Susceptible *
$$$ Meropenem	<=0.25 ug/ml	Susceptible *
$ Trimethoprim/Sulfamethoxazole	<=20 ug/ml	Susceptible

Roadmap

- Ascites
- Spontaneous bacterial peritonitis (SBP)
- Esophageal variceal hemorrhage
- Hepatic encephalopathy
- Acute alcoholic hepatitis
- Hepatorenal syndrome (HRS)

Esophageal Varices



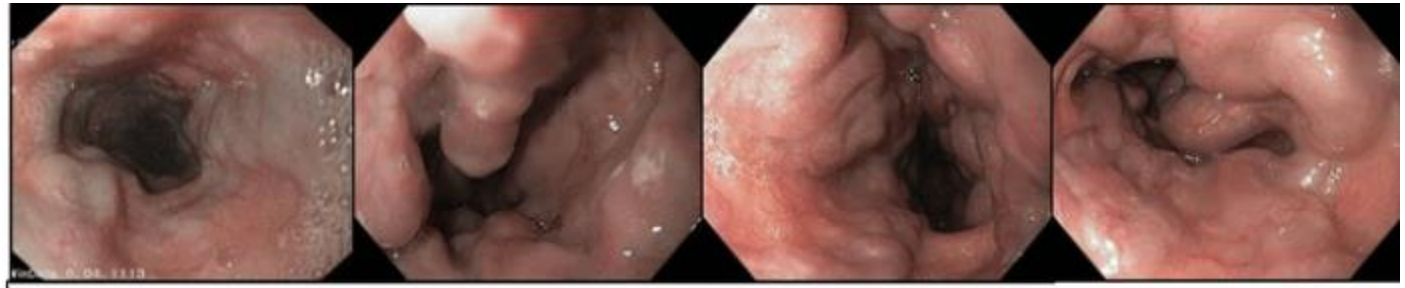
- Pathophysiology: resistance to hepatic flow to due cirrhosis causes splanchnic vasodilation to compensate and hyperdynamic state (increased cardiac output) and varices develop to decompress the portal venous system
- Rate of progression of varices:
  - In the presence of clinically significant portal hypertension (HVPG ≥ 10), new varices develop in 5% of patients at year 1, and 28% at year 3
  - Small varices progress in size at a rate of 12% per year

Merli M, Nicolini G, Angeloni S, et al. Incidence and natural history of small esophageal varices in cirrhotic patients. J Hepatol. 2003 Mar;38(3):266-72.

Endoscopy Findings

- Various grading systems evaluating size and evidence of high-risk features

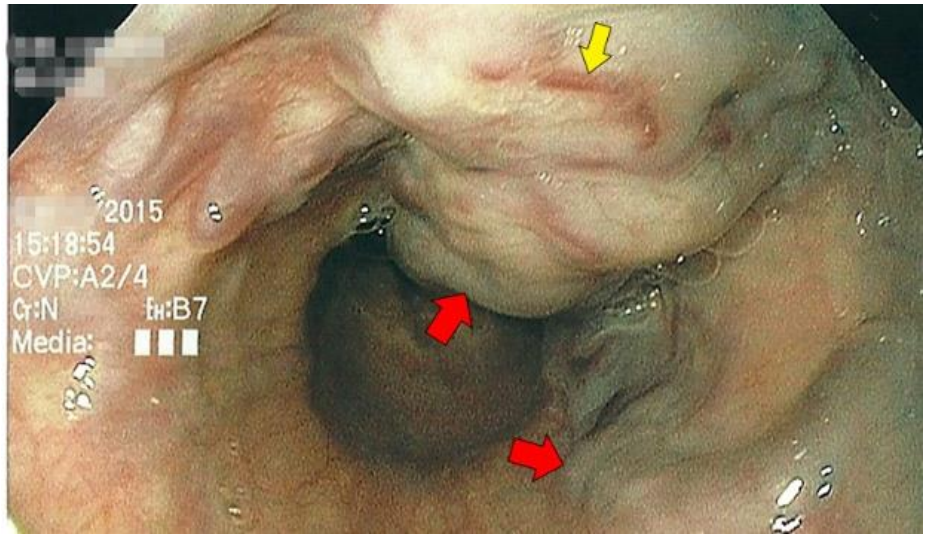
Size	Description
Small	Minimally elevated varices above the esophageal mucosa surface
Medium	Tortuous varices occupying less than 1/3 of the esophageal surface
Large	Varices that occupy more than 1/3 of the esophageal surface



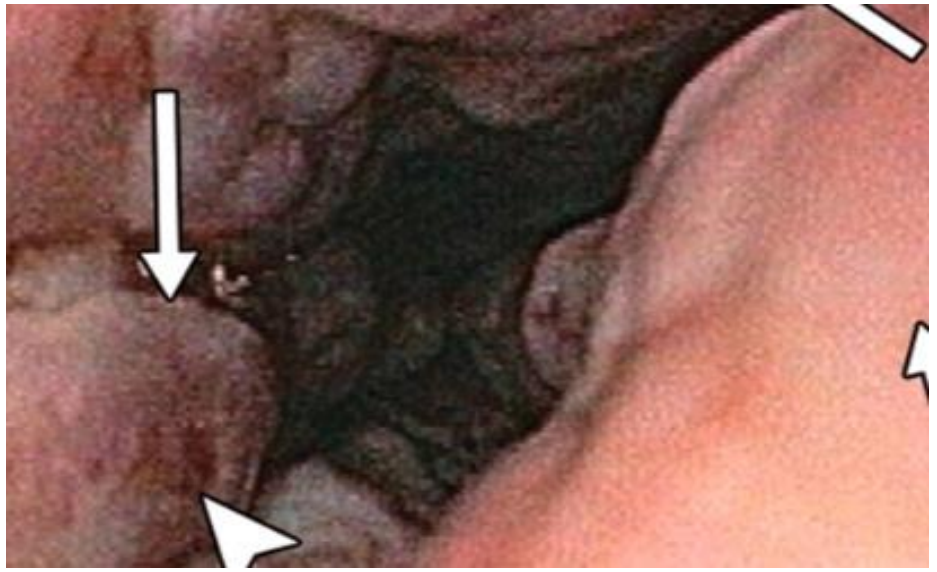
Grade	Endoscopic findings
0	Absence of esophageal varices
I	Microvessels that sketch varicose strings located in the esophagogastric transition or in the distal esophagus
II	One or two fine-caliber varices (smaller than 3 mm diameter) located in the distal esophagus
III	Medium caliber varices (between 3 or 6 mm diameter) or more than varices up to 3 mm that may reach up to a third medium third of the esophagus.
IV	Thick caliber varices, larger than 6 mm diameter, in any part of the esophagus.

Endoscopy Findings

- Protruding vessels (varices)



- Red wale marks: longitudinal red streaks on varices (yellow arrow) that resemble red corduroy wales



- Cherry red spots: discrete red cherry-colored flat spots that overlie varices

Primary Prophylaxis: Prevention of Variceal Hemorrhage in Select Patients

- Traditionally, screening all patients with evidence of portal hypertension for evidence of esophageal varices
- Patients with nonbleeding esophageal varices risk stratified based on risk of hemorrhage
- Consensus among grading systems: indication for primary prevention of variceal hemorrhage in patients with medium-large varices or any high-risk features (wale marks, cherry red spots)
- Paradigm shift to considering primary prevention with non-selective beta blockers (NSBB) to prevent decompensation of cirrhosis in *any* patient with clinically significant portal hypertension regardless of presence of varices
  - PREDESCI trial: 631 patients with HVPG ≥ 10 mmHg randomized to NSBB or placebo
    - Significant reduction in decompensation (development of ascites, hemorrhage, or overt encephalopathy) or death: 16% NSBB group vs 27% placebo (HR 0.51, 95% CI 0.26 – 0.97, p = 0.041)

Villanueva C, et al. β blockers to prevent decompensation of cirrhosis in patients with clinically significant portal hypertension (PREDESCI): a randomized, double-blind, placebo-controlled, multicentre trial. Lancet. 2019 Apr 20;393(10181):1597-1608.

Non-selective Beta Blockers

- Non-selective beta blockers (such as carvedilol, propranolol, and nadalol) block beta-1 receptors and beta-2 receptors
  - *Beta-1* blockade decreases cardiac output and slows heart rate
  - *Beta-2* blockade will vasoconstrict splanchnic blood vessels to decrease portal blood flow (thus reducing pressure on the varices and decreasing the risk of rupture and hemorrhage)
  - Carvedilol additionally blocks *alpha-1-adrenergic activity* and may facilitate the release of nitric oxide intra-hepatically to decrease portal pressure

Non-Selective Beta Blockers

BOX 3 Contraindications to nonselective beta-blockers

Absolute contraindications

- Asthma
- 2nd and 3rd degree atrioventricular block (in absence of implanted pacemaker)
- Sick sinus syndrome
- Extreme bradycardia (<50 bpm)

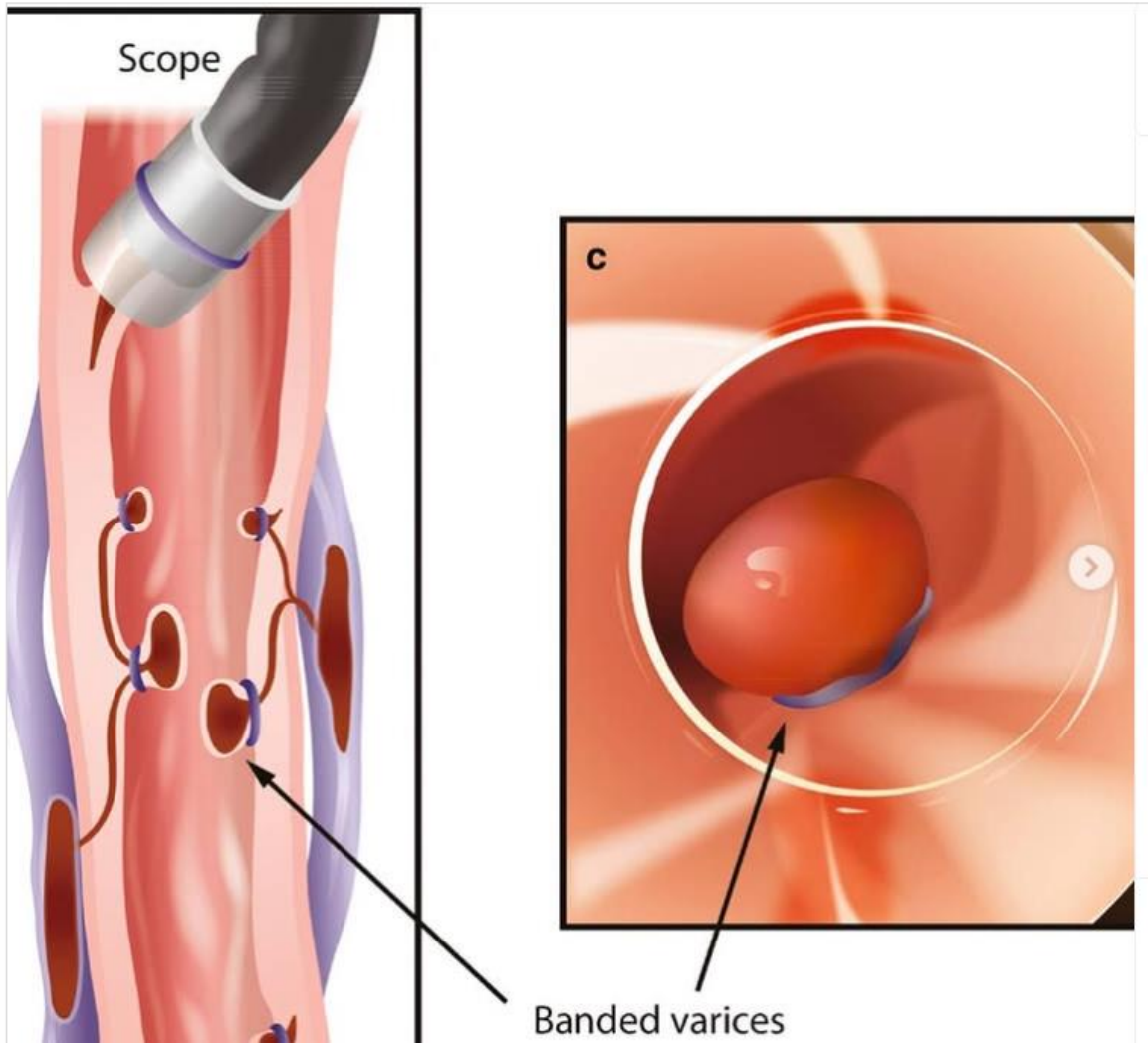
TABLE 3 Nonselective beta-blockers used in portal hypertension

Therapy	Mechanism of action	Starting dose	Titration	Maximal dose	Goal	Common adverse effects	Maintenance
Propranolol	Decreased cardiac output; caused by decreased heart rate and contractility from beta-1 adrenergic blockade, plus	20–40 mg twice daily	Increase the dose every 2–3 d until treatment goal	Without ascites: 320 mg/day; with ascites: 160 mg/day	HR of 55–60 bpm if tolerated; SBP should be maintained ≥90 mm Hg	Fatigue, bradycardia, dyspnea, orthostasis, hypotension, constipation	Indefinitely or until TIPS or liver transplant. No indication for routine upper endoscopy
Nadolol	Splanchnic arterial vasoconstriction; caused by beta-2 blockade leading to unopposed alfa-adrenergic vasoconstriction	20–40 mg at bedtime		Without ascites: 160 mg/day; with ascites: 80 mg/day			
Carvedilol	Above plus decreased intrahepatic vascular resistance; caused by anti-alpha-adrenergic activity	6.25 mg once daily	Increase to 6.25 mg twice daily after 3 d	12.5 mg/day (higher doses could be considered for nonhepatic indications)	No HR goal; SBP should be maintained ≥90 mm Hg		

Kaplan DE, et al. AASLD Practice Guidance on risk stratification and management of portal hypertension and varices in cirrhosis. Hepatology. 2024 May 1;79(5):1180-1211.

Endoscopic Variceal Ligation (EVL)

- EVL is an alternative preventative strategy that may be performed during screening endoscopy
- Device loaded with rubber bands attached to tip of endoscope, varix is suctioned into the device and rubber band is deployed around the base, resulting in occulsion



Acute Variceal Hemorrhage: Goals of Therapy

Protect Airway	Hemodynamic Stability	Control Bleeding	Prevent Infection
• NPO • Closely monitor airway and low threshold for intubation	• Volume resuscitation/ RBC transfusion • Vasoconstriction to reduce blood flow to site of hemorrhage (esophageal varices)	• Endoscopy with possible ligation • Balloon tamponade if uncontrolled bleeding as temporizing measure • FFP not routinely recommended to correct INR • May consider vitamin K IV	• Prophylactic IV antibiotics to prevent bacterial infection after translocation of gut bacteria

Acute Variceal Hemorrhage: Medical Management

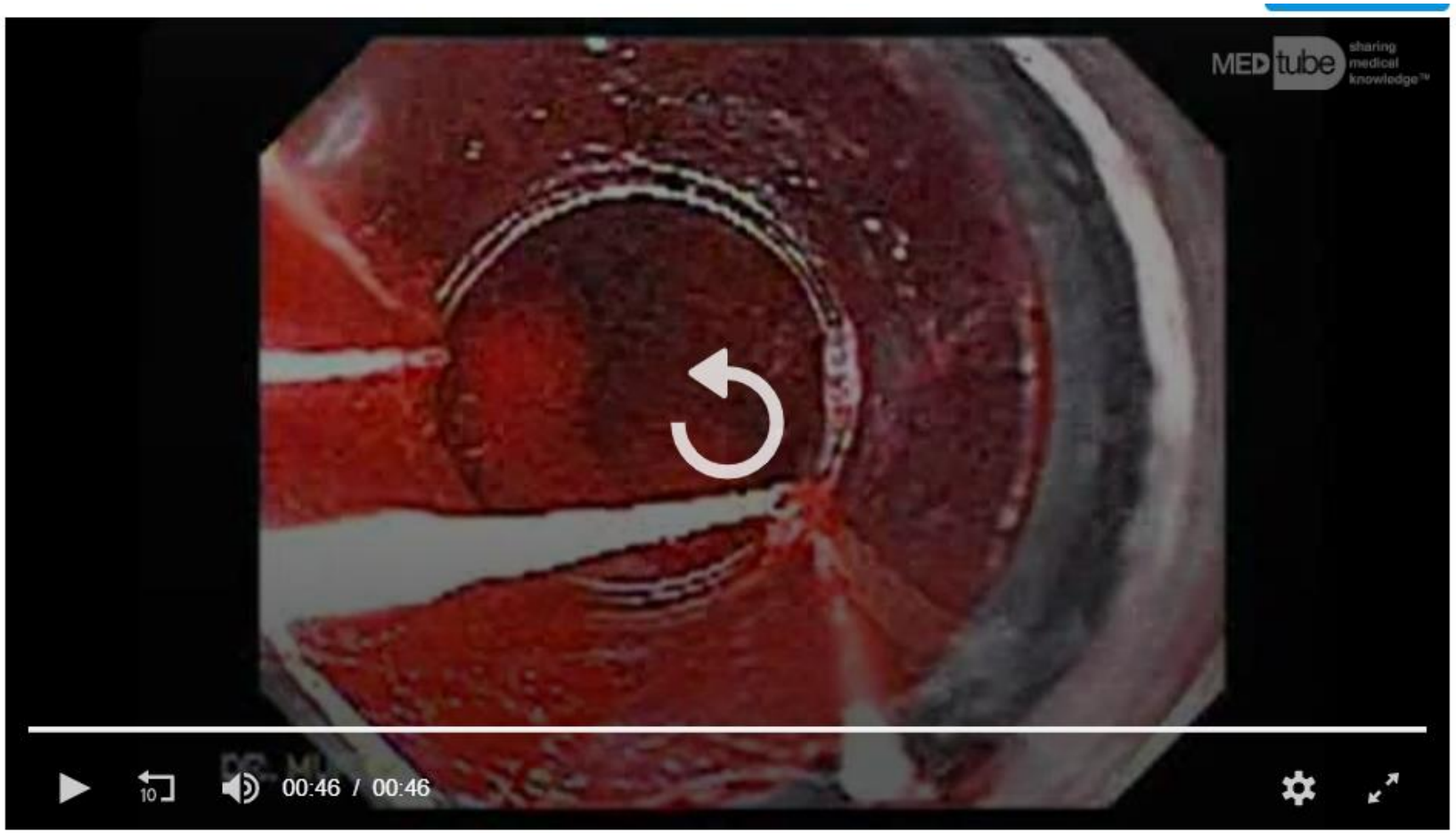
- Transfusion RBCs to target Hgb ~ 7 g/dL
  - DO NOT OVER-resuscitate → may increase portal pressure and worsen bleeding
- Proton-pump inhibitors: pantoprazole 80 mg IV x 1, if endoscopy not performed within 12 hours start 40 mg IV q12 hr until procedure
  - Reduce gastric acid secretion which may prevent clotting and reduce risk of early rebleeding after EVL
  - PPIs should be stopped after endoscopy once hemostasis has been achieved if no other indication
- Vasoactive agents to decrease portal blood flow
  - Octreotide: 50 mcg IV once followed by continuous infusion 25 – 50 mcg/hour x 2 – 5 days
- Short-course prophylactic antibiotics: ceftriaxone 1 g IV q24hr x 5 days

Prophylactic Antibiotics in Acute Variceal Hemorrhage

- Choice of antibiotic: ceftriaxone 1 g IV q24 hr for up to 5 days
  - May be discontinued sooner once bleeding is controlled in absence of active infection
  - *Fluoroquinolones no longer recommended due to high rates of resistance*
- Evidence: meta-analysis of twelve trials including 1,241 patients evaluating prophylactic antibiotics vs placebo in cirrhotic patients with gastrointestinal bleeding
  - Reduced mortality RR 0.79, 95% CI = 0.63 -0.98
  - Reduced bacterial infections RR 0.35, 95% CI 0.26 – 0.47
  - Reduced rebleeding: RR 0.53, 95% CI 0.38 – 0.74

Aliment Pharmacol Ther. 2011 Sep;34(5):509-18.

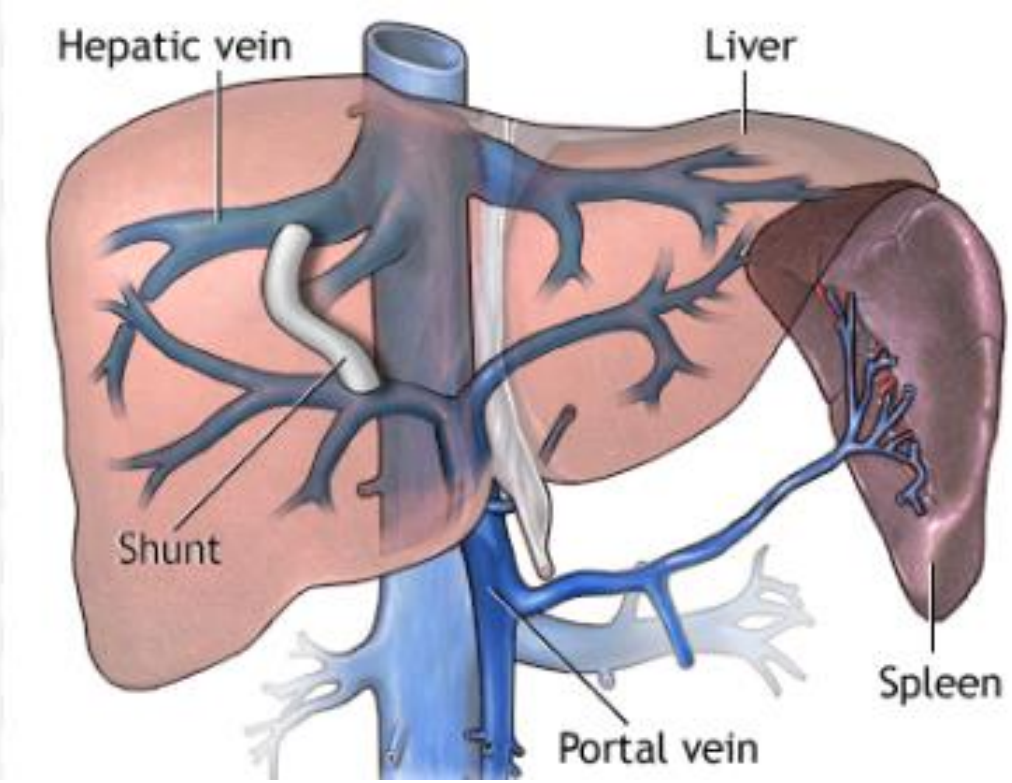
Acute Variceal Hemorrhage: Endoscopic Banding



Esophageal Varix - Banding of Two Bleeding Varices • Video • MEDtube.net

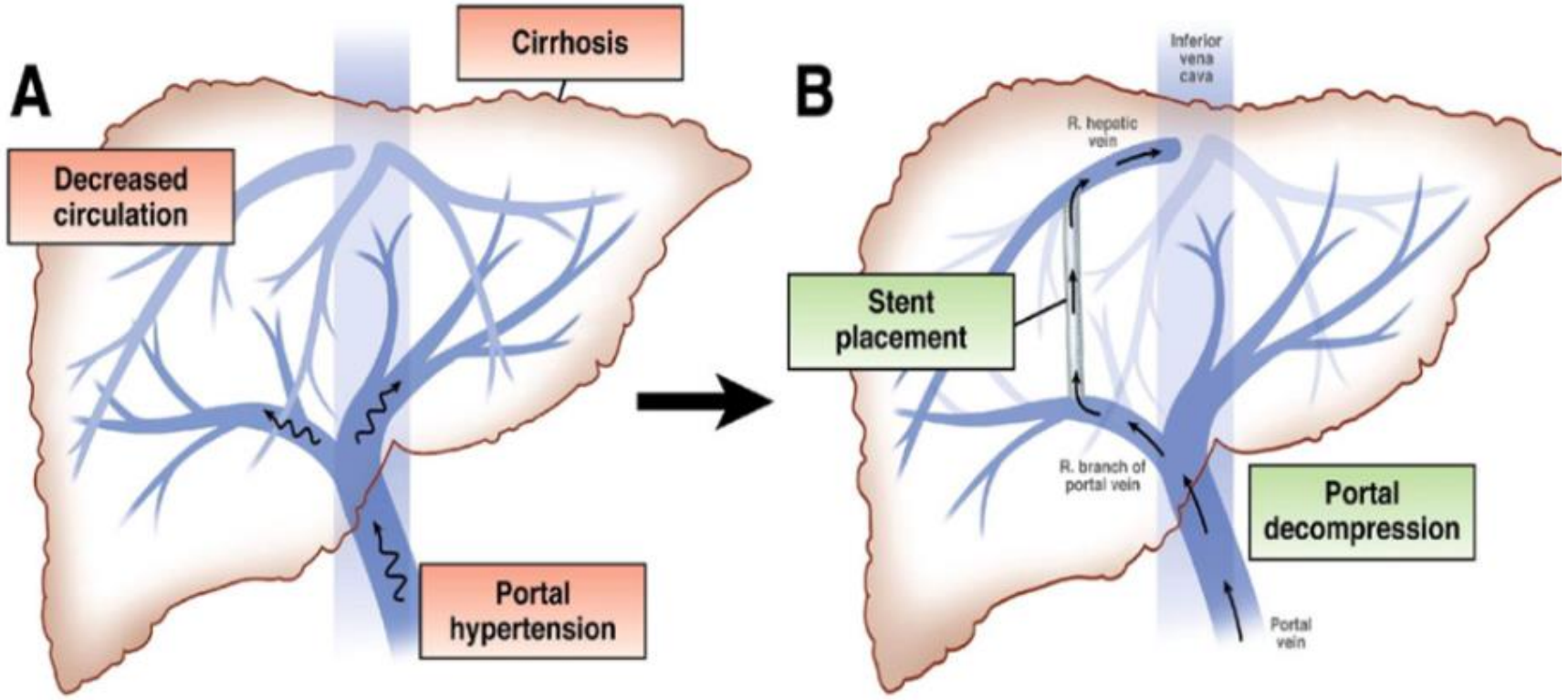
Transjugular Intrahepatic Portosystemic Shunt (TIPS)

- Minimally invasive procedure to treat esophageal varices by creating a low-resistance channel within the liver that diverts blood flow away from the portal vein, reducing pressure and preventing bleeding
- Indications may include active bleeding of esophageal varices who fail initial therapy to prevent recurrence
    - May also be considered in refractory ascites

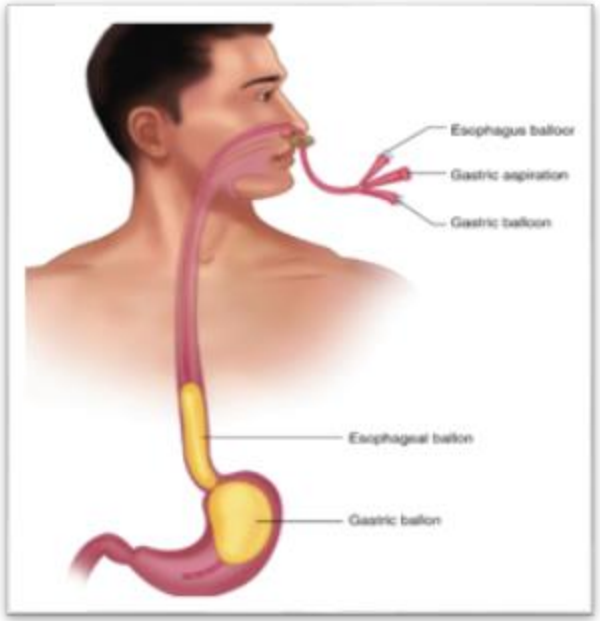


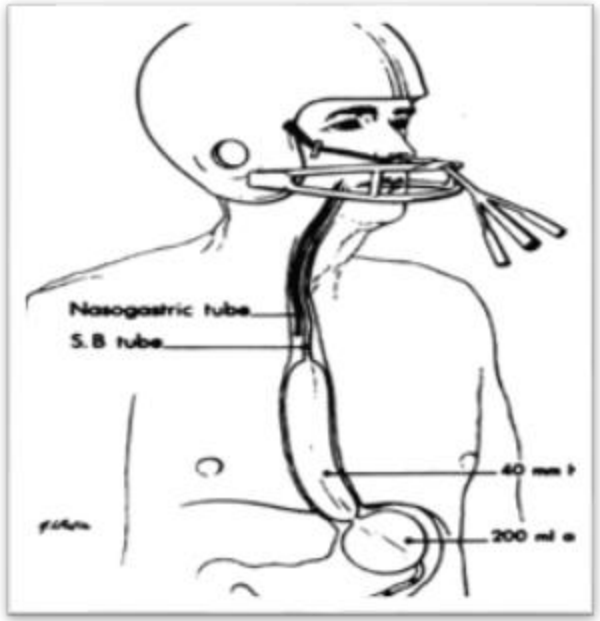
Post-TIPS Hepatic Encephalopathy

- Bypassing the liver decreases first-pass clearance of neurotoxins such as ammonia which may precipitate hepatic encephalopathy
- Decreasing hepatic resistance also results in increased splanchnic blood flow that may enhance systemic delivery of ammonia to the brain

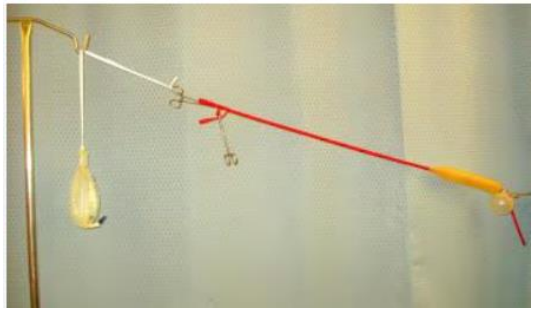


Why does hepatic encephalopathy develop after transjugular intrahepatic portosystemic (TIPS) shunt? | AASLD





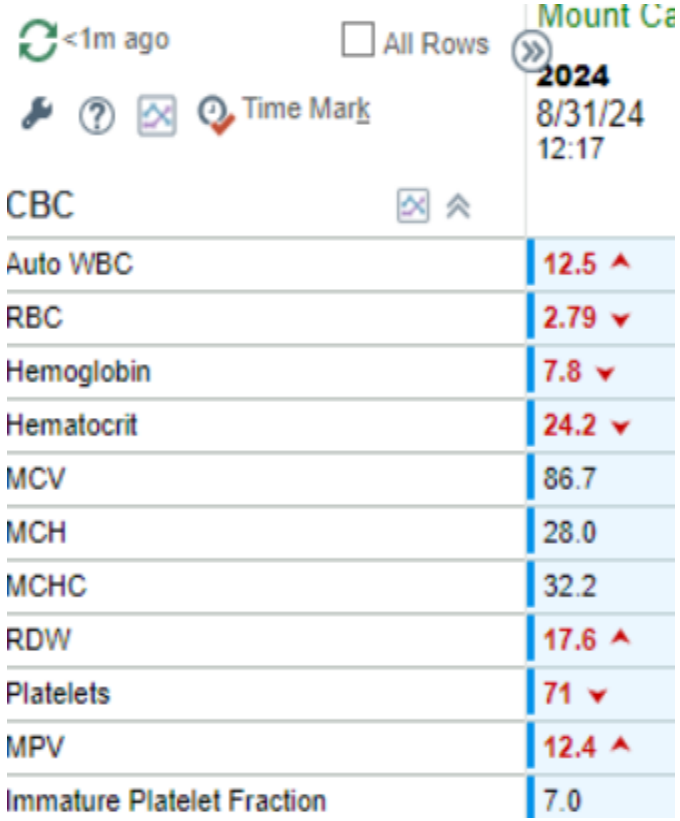
Balloon Tamponade

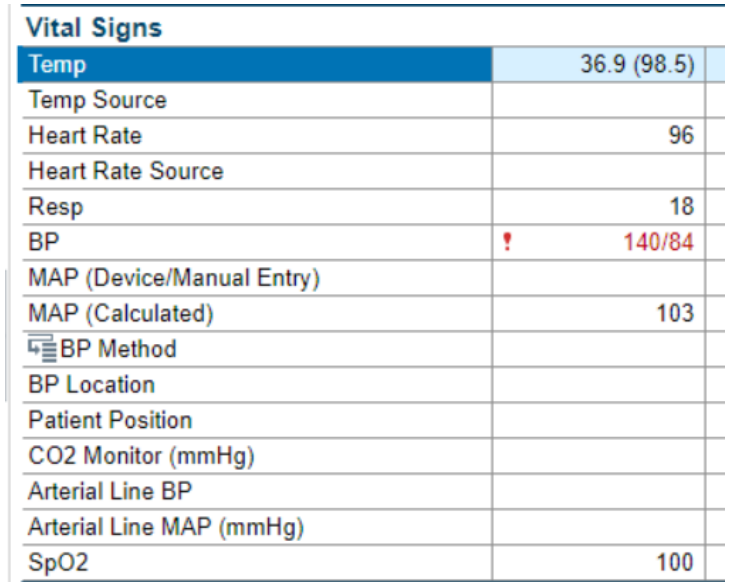


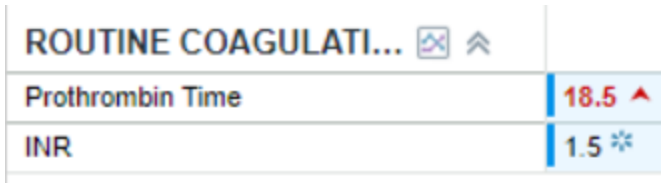
- In life-threatening uncontrolled esophageal hemorrhage, balloon tamponade is an effective way to achieve short-term hemostasis
- Sengstaken-Blakemore: 250 mL gastric ballon, esphageal balloon, and gastric suction port

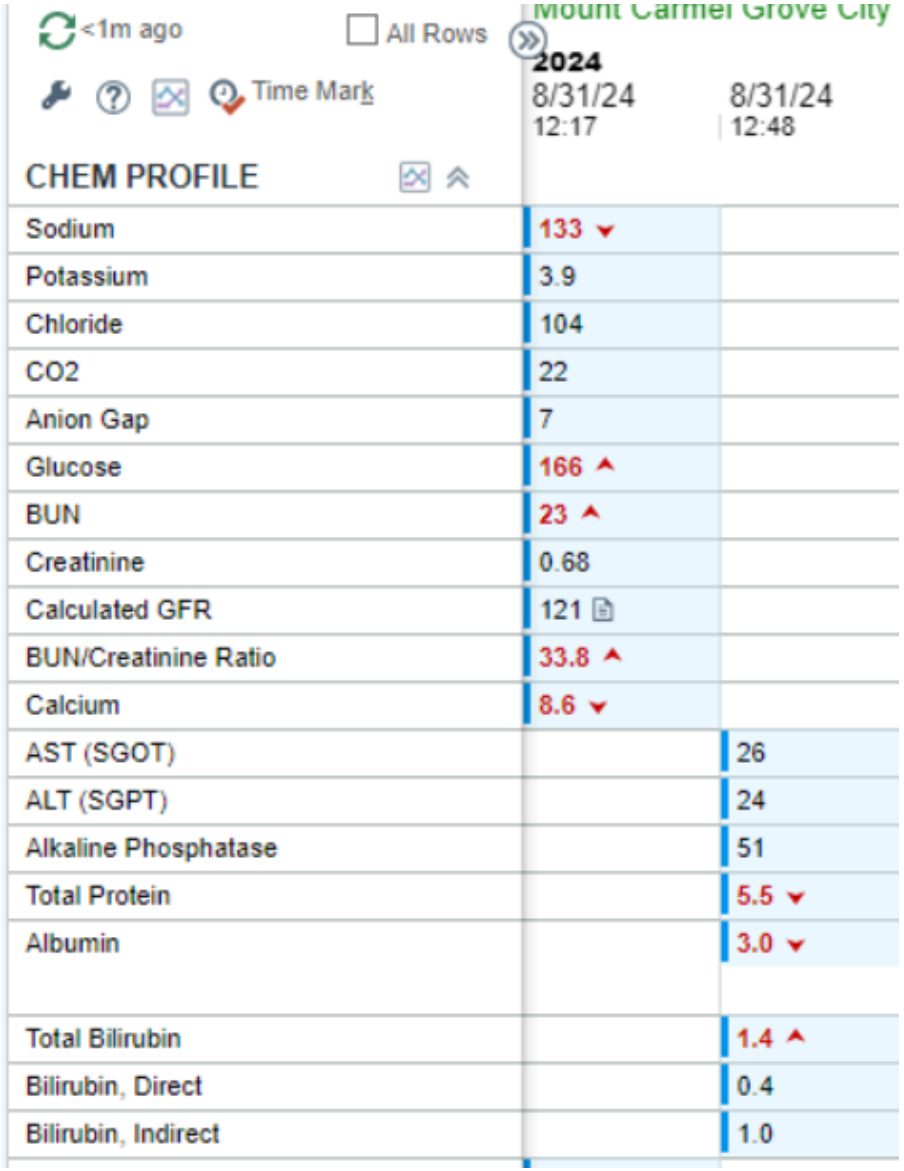
Example Case

- 39/M patient with history of alcohol abuse and cirrhosis presented vomiting blood









Example Case:

- Initiate:
  - Hemodynamically stable, do not need to fluid resuscitate
  - Hgb > 7 mg/dL, repeat Hgb in 6 hours and transfuse only if Hgb < 7 g/dL
  - Start vasoconstrictor octreotide 50 mcg IV x 1 followed by infusion 50 mcg/hr x 2 – 5 days
  - Start PPI protonix 80 mg IV x 1, then 40 IV BID until EGD
- EGD: EVL with banding x 5 to control bleeding

Findings:

Three columns of grade III varices with no stigmata of recent bleeding were found in the lower third of the esophagus. They were medium in size. Red wale signs were present. Five bands were successfully placed with incomplete eradication of varices. There was no bleeding during and at the end of the procedure.

Moderate portal hypertensive gastropathy was found in the gastric fundus and in the gastric body.

The examined duodenum was normal.

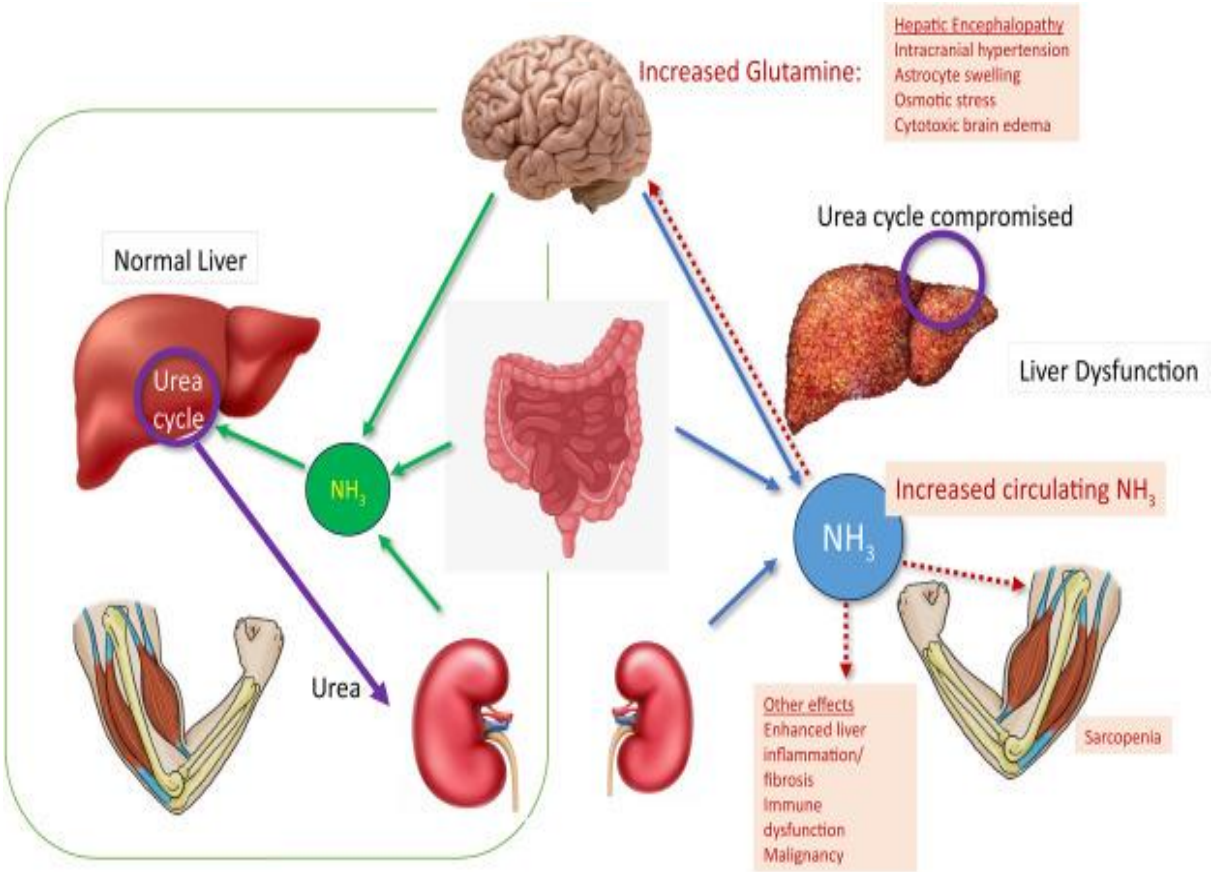
- Prevention of rebleeding: next day initiate propranolol 10 mg PO qhs to target HR 55 – 60 bpm

Roadmap

- Ascites
- Spontaneous bacterial peritonitis (SBP)
- Esophageal variceal hemorrhage
- Hepatic encephalopathy
- Acute alcoholic hepatitis
- Hepatorenal syndrome (HRS)

Mechanism Hepatic Encephalopathy

- Bacteria in the gut breakdown dietary proteins to form ammonia which is usually detoxified in the liver by urea cycle → accumulates in liver failure
- Ammonia crosses the blood brain barrier and acts as a neurotoxin (impairs neurotransmission, causes oxidative stress, and inflammation)
- Ammonia is converted to glutamate then to glutamine, an osmol, causing cerebral edema, intracranial hypertension, and in severe cases brain herniation



J Clin Exp Hepatol. 2024 Jul-Aug;14(4):101361.

Hepatic Encephalopathy

- AASLD definition: hepatic encephalopathy is a brain dysfunction caused by liver insufficiency or portosystemic shunting; it manifests as a wide spectrum of neurological or psychiatric abnormalities ranging from subclinical alterations to coma
- Risk for first episode of overt hepatic encephalopathy (OHE) is 5 – 25% within 5 years after cirrhosis diagnosis
- After TIPS procedure, median cumulative 1-year incidence of OHE is 10 – 50%
- Symptoms: apathy, irritability, sleep-wake disturbances, progressive disorientation to time and space, acute confusional state, agitation, somnolence, stupor, and in severe cases coma
    - Motor symptoms abnormalities in non-comatose patients: hypertonia, hyperreflexia, positive Babinski sign, asterixis

AASLD. J Hepatol. 2014 Sep;61(3):642-59.

Grading Encephalopathy: West Haven Criteria

Note: high blood ammonia levels alone do not add any diagnostic, staging, or prognostic value in patients with chronic liver disease

Table 2. WHC and Clinical Description

WHC Including MHE	ISHEN	Description	Suggested Operative Criteria	Comment
Unimpaired		No encephalopathy at all, no history of HE	Tested and proved to be normal	
Minimal	Covert	Psychometric or neuropsychological alterations of tests exploring psychomotor speed/executive functions or neurophysiological alterations without clinical evidence of mental change	Abnormal results of established psychometric or neuropsychological tests without clinical manifestations	No universal criteria for d Local standards and expe required
Grade I		• Trivial lack of awareness • Euphoria or anxiety • Shortened attention span • Impairment of addition or subtraction • Altered sleep rhythm	Despite oriented in time and space (see below), the patient appears to have some cognitive/behavioral decay with respect to his or her standard on clinical examination or to the caregivers	Clinical findings usually n reproducible
Grade II	Overt	• Lethargy or apathy • Disorientation for time • Obvious personality change • Inappropriate behavior • Dyspraxia • Asterixis	Disoriented for time (at least three of the followings are wrong: day of the month, day of the week, month, season, or year) ± the other mentioned symptoms	Clinical findings variable, reproducible to some exte
Grade III		• Somnolence to semistupor • Responsive to stimuli • Confused • Gross disorientation • Bizarre behavior	Disoriented also for space (at least three of the following wrongly reported: country, state [or region], city, or place) ± the other mentioned symptoms	Clinical findings reproduc some extent
Grade IV		Coma	Does not respond even to painful stimuli	Comatose state usually reproducible

All conditions are required to be related to liver insufficiency and/or PSS

AASLD. J Hepatol. 2014 Sep;61(3):642-59.

Treatment: Differential Diagnosis and Identification of Precipitating Cause

- Alternative causes of altered mental status should be considered, ruled out, or treated
  - Hypoglycemia, ketosis, alcohol intoxication, alcohol withdrawal, Wernicke encephalopathy, neuroinfection, hyponatremia, nonconvulsive epilepsy, intracranial hemorrhage, obstructive sleep apnea, brain lesion, normal pressure hydrocephalus
- Identify potential precipitating cause and correct

Table 3. Precipitating Factors for OHE by Decreasing Frequency

Episodic	Recurrent
Infections*	Electrolyte disorder
GI bleeding	Infections
Diuretic overdose	Unidentified
Electrolyte disorder	Constipation
Constipation	Diuretic overdose
Unidentified	GI bleeding

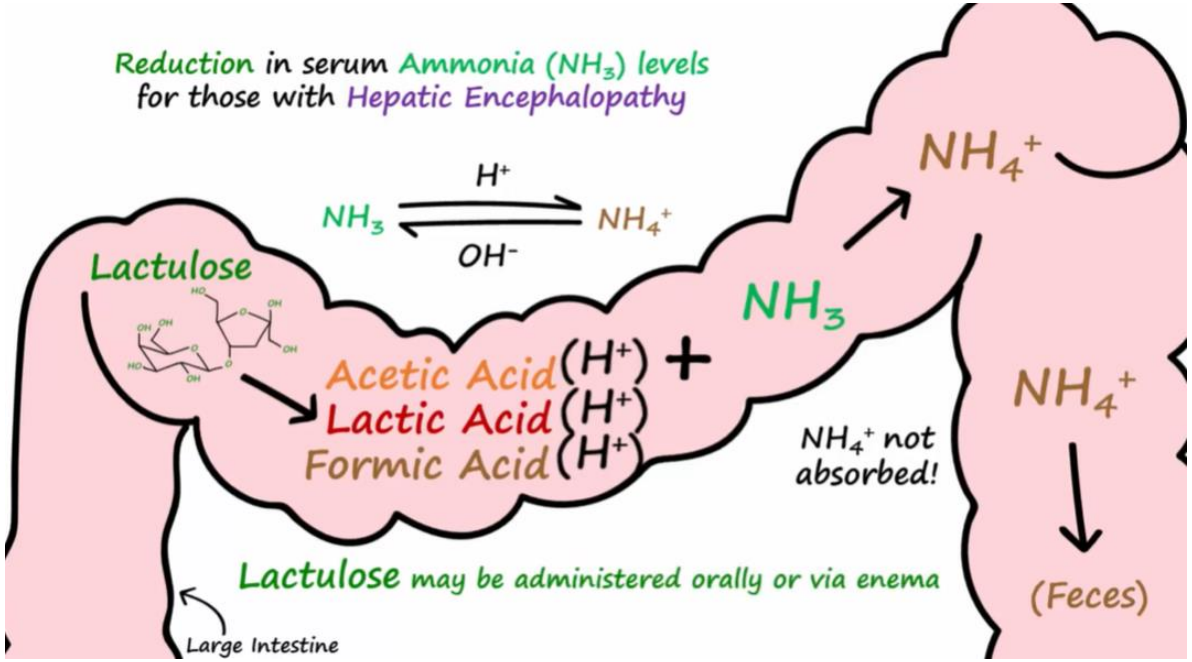
Modified from Strauss E, da Costa MF. The importance of bacterial infections as precipitating factors of chronic hepatic encephalopathy in cirrhosis. Hepato-gastroenterology 1998;45:900-904.

*More recent unpublished case series confirm the dominant role of infections.

AASLD. J Hepatol. 2014 Sep;61(3):642-59.

Treatment

- Lactulose: nonabsorbable disaccharide
  - Preferred initial treatment
    - Mechanisms:
      - Nondigestible prebiotic promoting growth of beneficial microorganisms in the intestines
      - Bacterial degradation of lactulose into lactic acid, acetic acid, and formic acid to acidify gut (lower pH)
        - Converts ammonia (NH3) into ammonium (NH4+) and due to charge cannot cross intestinal membrane and is trapped
      - Osmotic effect pulling water into intestines causing diarrhea to remove trapped NH4+

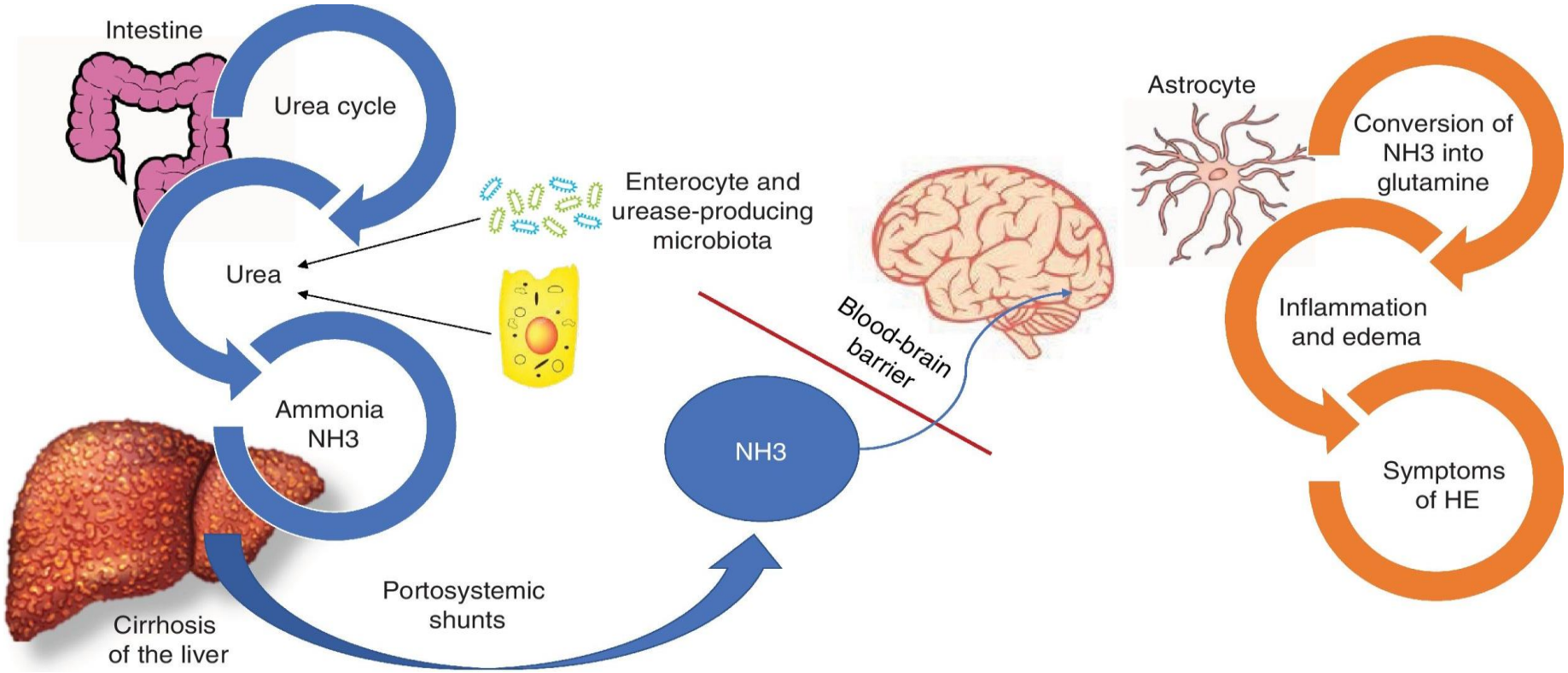


Lactulose Dosing

- **Treatment** of hepatic encephalopathy
  - Initial lactulose 20 – 30 g (30 – 45 mL) every 1 – 2 hours to induce ~2 soft stools/day, then reduce to 20 – 30 g 2 – 4 times daily to achieve 2 – 3 soft stools/day
  - If patient is unable to take PO:
    - Rectal administration: Retention enema 200 g (300 mL) in 700 mL of NS or water, retain for 30 – 60 minutes; may repeat every 4 – 8 hours as needed
- **Prevention** of hepatic encephalopathy
  - 20 – 30 g 2 – 4 times daily, may adjust dose every 1 – 2 days to achieve 2 – 3 soft stools/day

Treatment: Rifaximin

- Effective add-on to lactulose
- Dose: 550 mg BID or 400 mg TID
- Mechanism: inhibits intestinal bacteria (blocks RNA polymerase) to reduce ammonia production



Examples:

Ammonia

Collected:	07/11/24 0739
Result status:	Final
Resulting lab:	MOUNT CARMEL
Reference range:	11 - 60 mcmol/L
Value:	73 ^

60/F patient admitted for jaundice. Alert and oriented. Ammonia level found to be 73 mmol/L. Not currently receiving treatment for HE.

→ No need to treat laboratory elevation when no clinical symptoms of HE

Collected:	09/08/24 0507
Result status:	Final
Resulting lab:	MOUNT CARMEL
Reference range:	11 - 60 mcmol/L
Value:	106 ^

55/M patient admitted with confusion. History of hepatic encephalopathy on lactulose 30g TID and patient having 1 loose BM daily. Ammonia level found to be 106 mmol/L.

→ Increase lactulose interval to every 2 hours until 2 loose BMs then schedule dose QID. Add rifaximin 500 mg TID to regimen

Collected:	11/07/24 2328
Result status:	Final
Resulting lab:	MOUNT CARMEL
Reference range:	11 - 60 mcmol/L
Value:	270 ^

45/F patient admitted with confusion. History of hepatic encephalopathy on lactulose 30. Ammonia 270 mmol/L. Patient unable to take PO, not able to reliably swallow and does not have NG due to history of esophageal varices.

→ Lactulose enema enema 200 g (300 mL) in 700 mL of NS, retain for 30 – 60 minutes

Roadmap

Ascites

Spontaneous bacterial peritonitis (SBP)

Esophageal variceal hemorrhage

Hepatic encephalopathy

Acute alcoholic hepatitis

Hepatorenal syndrome (HRS)

Acute Alcoholic Hepatitis

Alcoholic hepatitis is rapid onset of jaundice and liver enzyme abnormalities in the setting of long-term heavy alcohol consumption

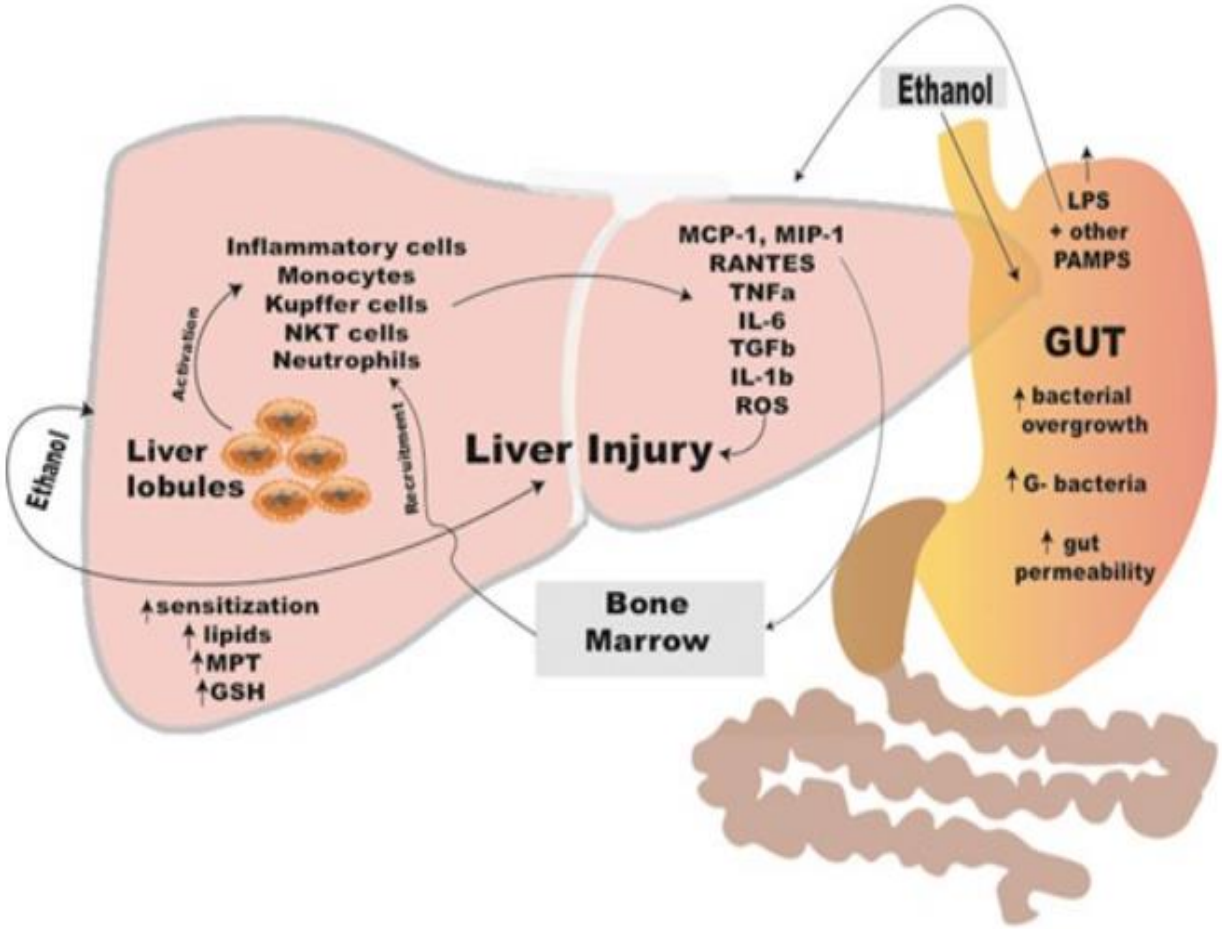
Risk factors: prolonged heavy alcohol use, younger age, female sex, obesity, underlying cirrhosis, genetic predisposition

High 28-day mortality rate 16 – 30%, and 56% 1-year mortality

Jophlin LL. Am J Gastroenterol. 2024 Jan 1;119(1):30-54.

Alcoholic Hepatitis Pathophyisology

- Alcohol oxidative metabolic pathway leads to reduced levels of nicotinamide adenine dinucleotide (NAD) converted to NADH which promotes lipogenesis by inhibiting oxidation of triglycerides
- Translocation of lipopolysaccharides into hepatocytes bind to CD 14 and toll-like receptor 4 to release reactive oxygen species (ROS) activating cytokines → diffuse inflammation



Hisseubu Nm Shor J, Szabo G. Alcoholic Hepatitis: A Review. Alcohol 2019 Jul 1;54(4):408-416.

National Institute of Alcoholism and Alcohol Abuse (NIAAA) Criteria for Alcoholic Hepatitis

Definition	Criteria
Definite alcoholic hepatitis	Histological confirmation of features of alcohol-associated hepatitis (biopsy-proven)
Probable alcoholic hepatitis	- Onset of jaundice within 60 days of heavy alcohol use (more than 50 g/day) for a minimum of 6 months - Serum bilirubin ≥ 3 mg/dL - Elevated AST (50 – 400 U/L) - AST:ALT ratio of 1.5 - No other cause of acute hepatitis
Possible alcoholic hepatitis	Clinical diagnosis uncertain due to another confounding etiology of liver disease or unclear history on alcohol consumption

Jophlin LL, et al. ACG Clinical Guideline: Alcohol-Associated Liver Disease. Am J Gastroenterol. 2024 Jan 1;119(1):30-54.

Example: Acute Alcoholic Hepatitis Diagnostic Criteria

101	Ammonia
2.1	Lactate

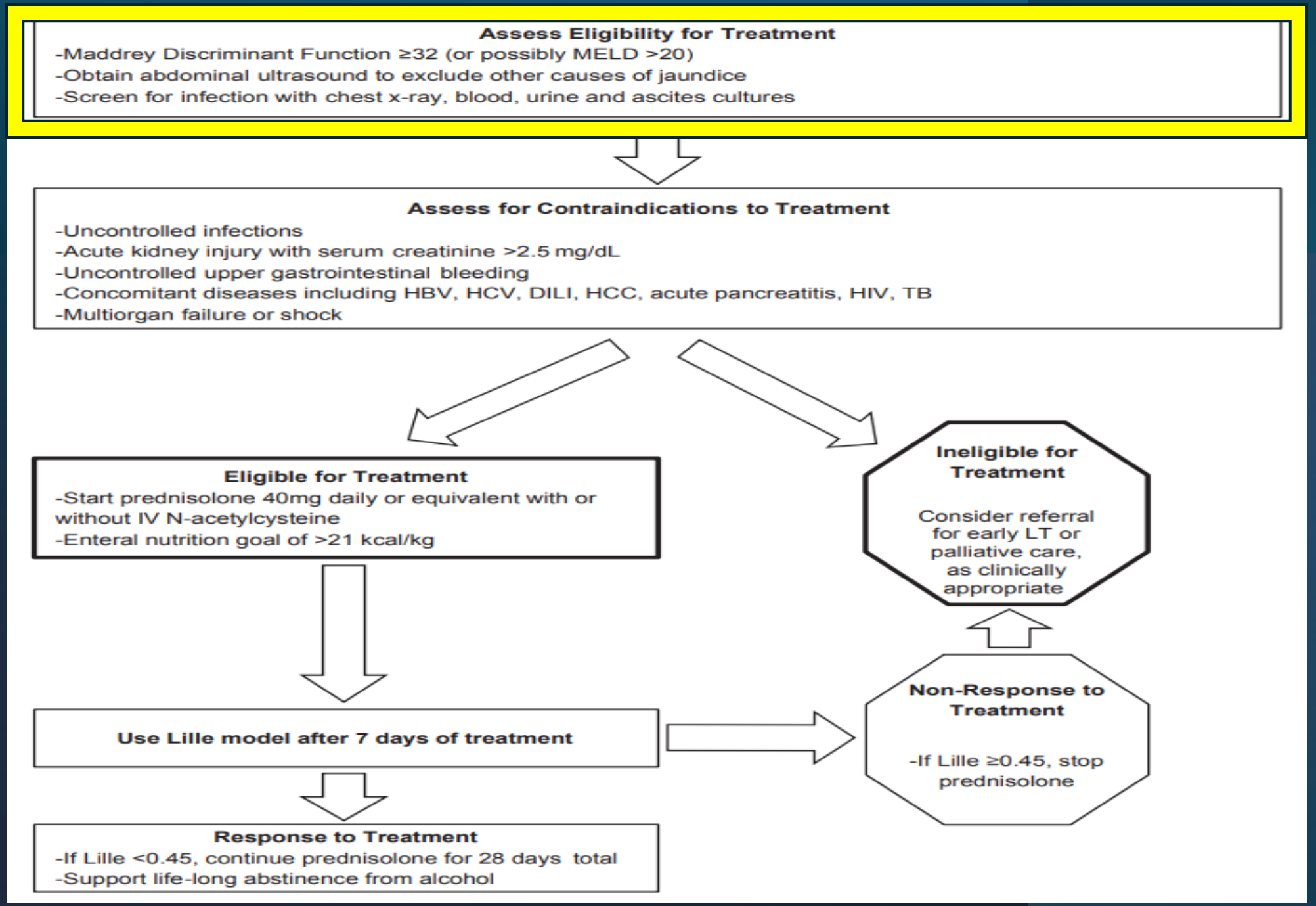
1/15/25 10:04	CHEM PROFILE
132	Sodium
4.1	Potassium
96	Chloride
21	CO2
15	Anion Gap
118	Glucose
32	BUN
1.66	Creatinine
41	Calculated GFR
19.3	BUN/Creatinine Ratio
9.0	Calcium
	Phosphorus
213	AST (SGOT)
94	ALT (SGPT)
128	Alkaline Phosphatase
6.0	Total Protein
3.2	Albumin
38.7	Total Bilirubin
2.0	Magnesium
70	Lipase
115	Ammonia

- 34/F presented 1/5/2025 with confusion and yellowing of skin
  - HPI: patient with history of very heavy alcohol use (5-10 drinks per day of whiskey) but states she stopped drinking at the end of November
- PMH: alcohol abuse since COVID-19 pandemic 2020

AST > 50, AST:ALT ratio > 1.5
213:94→ ratio = 2.3

<u>Diagnostic criteria</u>:

- ☑ Heavy drinking for ≥ 6 months and if abstinent last drink within last 60 days
- ☑ Jaundice with bilirubin > 3 mg/dL
- ☑ AST > 50 IU/L, AST:ALT ratio > 1.5
- ☑ No other cause of acute hepatitis



Crabb DW, Iet al. Hepatology. 2020 Jan;71(1):306-333.

Risk Stratification to Determine Treatment

2024 ACG Guidelines for AH: MELD score is superior to the Maddrey Discriminate Function (MDF) to predict short term mortality associated with alcoholic hepatitis

TABLE 7. Characteristics of Lab-Based Prognostic Scores in Alcoholic Hepatitis

	Bili	PT/INR	Cr/BUN	Age	Alb	WBC	Stratification	Clinical Use
MDF	+	+	-	-	-	-	Severe: ≥32	Initiate corticosteroids
MELD	+	+	+	-	-	-	Severe: ≥21, but a continuous scale	Prognosis only
Lille	+	+	+	+	+	-	≥0.45: Nonresponse <0.45: Response	Day 7 cessation or continuation of corticosteroids

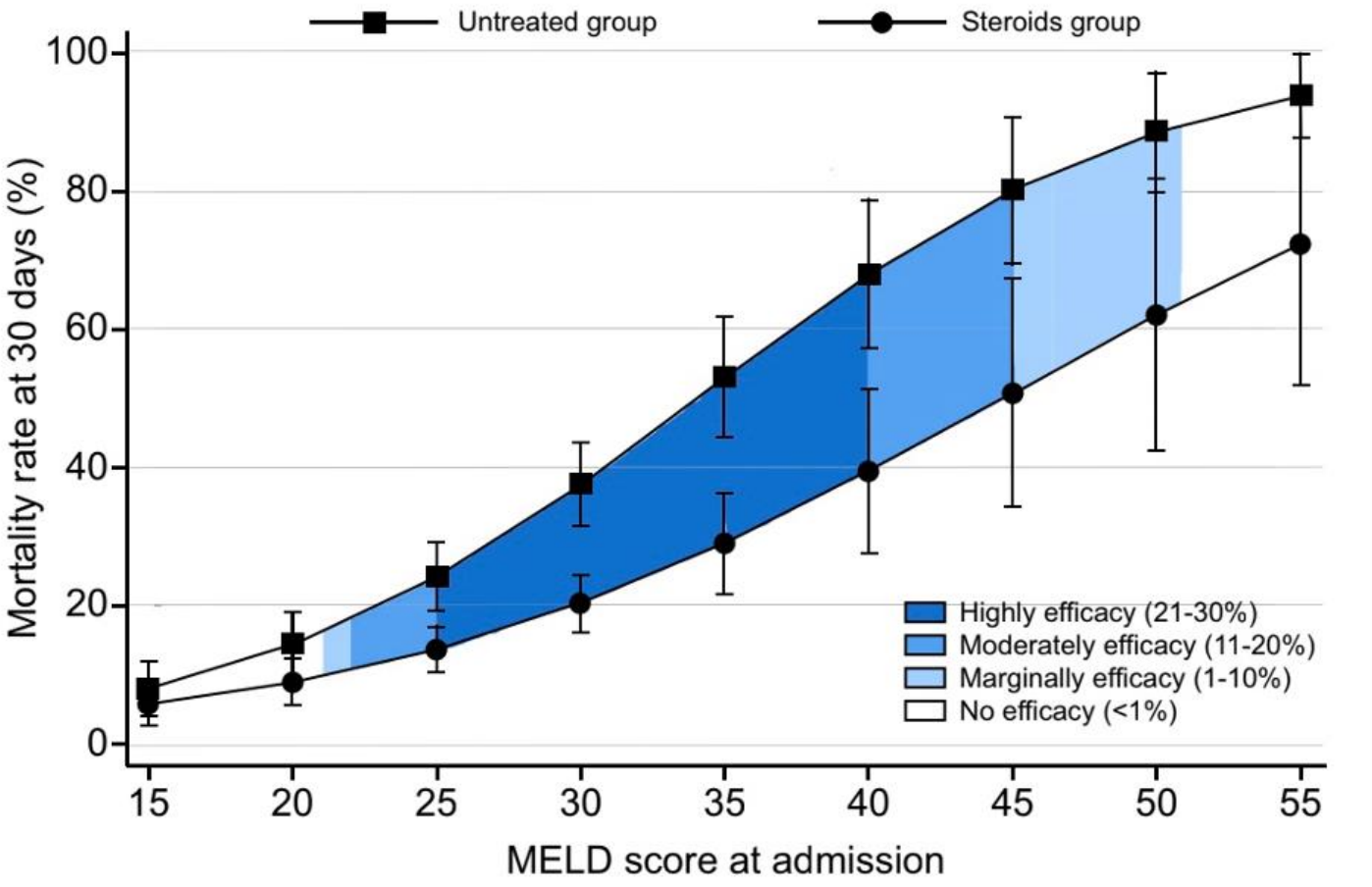
Abbreviations: Alb, serum albumin; Bili, serum total bilirubin; Cr/BUN, creatinine/blood urea nitrogen; PT/INR, prothrombin time/international normalized ratio; and WBC, white blood cell count.

Jophlin LL, et al Am J Gastroenterol. 2024 Jan 1;119(1):30-54.

Crabb DW, et al. Hepatology. 2020 Jan;71(1):306-333.

MELD Score to Define Optimal Use of Steroids for Alcoholic Hepatitis

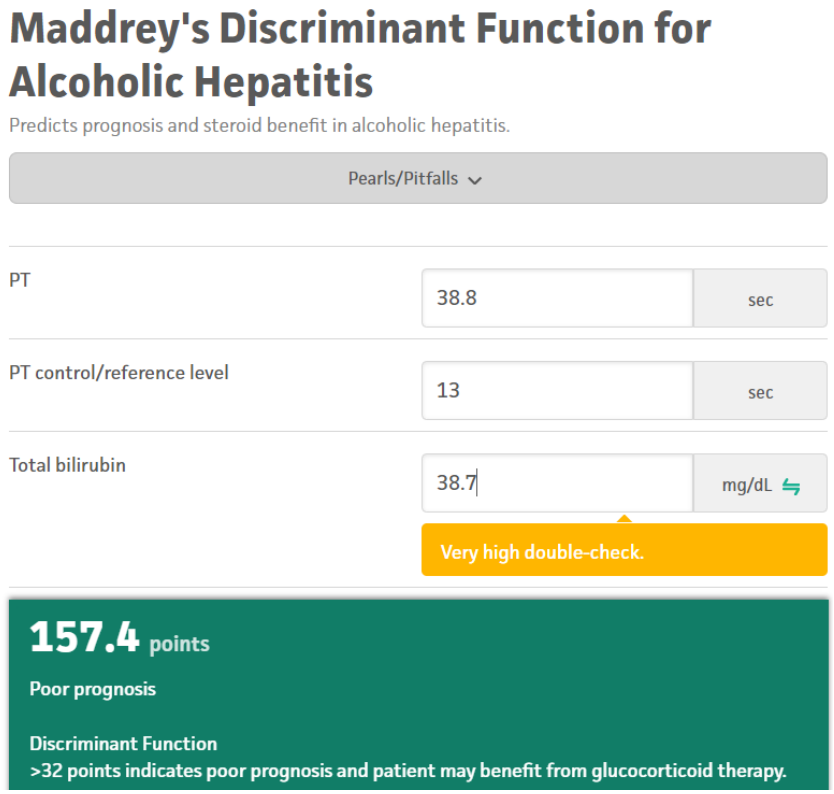
- International retrospective cohort including 3,380 adults with clinical or histological diagnosis of AH
- Steroids are indicated for patients with MELD score > 20 and associated with increased 30-day survival
- Maximum benefit seen in patients with MELD 25 – 39
- MELD > 51 can be used to define futility
- Note: in this study survival benefit was not sustained at 90 days



Arab JP, et al. J Hepatol. 2021 Nov;75(5):1026-1033.

Maddrey Discriminate Function (MDF)

- MDF ≥ 32 indicates poor prognosis and is indication for steroids to improve mortality
- Example case: MDF 157.4 based on elevated PT (38.8 seconds) and very elevated bilirubin (38.7)

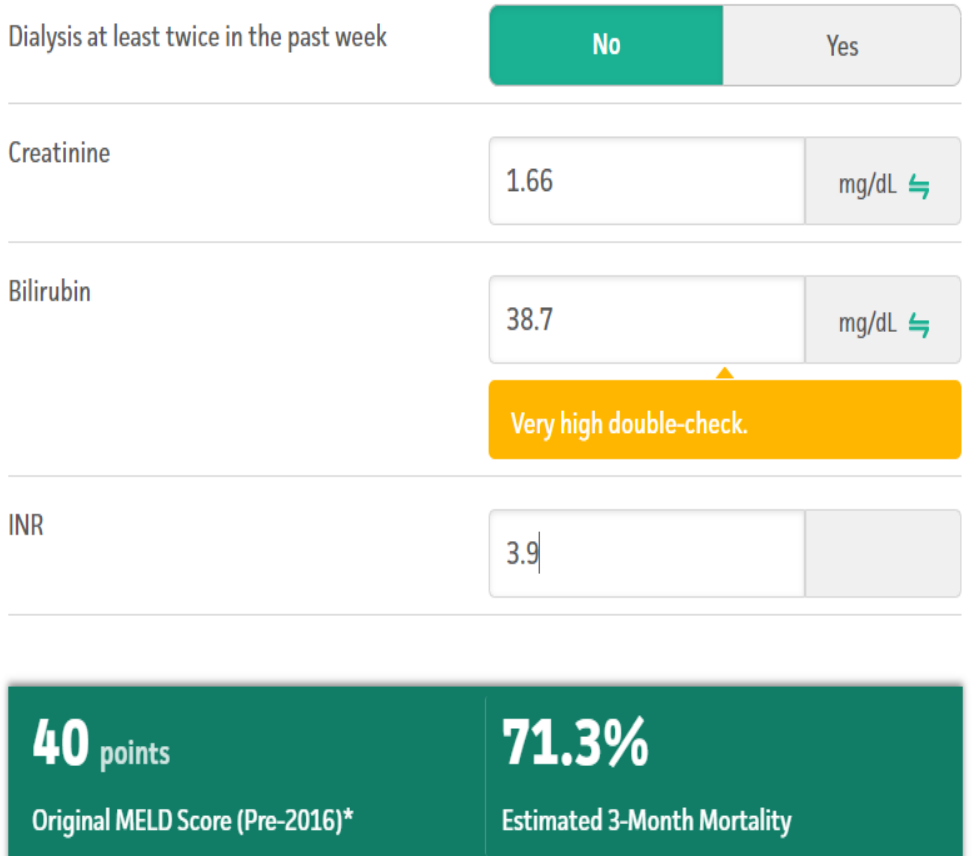


38.8	Prothrombin Time
3.9	INR

1/15/25 10:04	CHEM PROFILE
132	Sodium
4.1	Potassium
96	Chloride
21	CO2
15	Anion Gap
118	Glucose
32	BUN
1.66	Creatinine
41	Calculated GFR
19.3	BUN/Creatinine Ratio
9.0	Calcium
	Phosphorus
213	AST (SGOT)
94	ALT (SGPT)
128	Alkaline Phosphatase
6.0	Total Protein
3.2	Albumin
38.7	Total Bilirubin
2.0	Magnesium
70	Lipase
115	Ammonia

Example Case: MELD

- MELD > 20 indication for steroids to improve 30-day mortality
- MELD 25 – 39 maximum benefit from steroids
- Example case MELD score: 40 points



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1/15/25 10:04	CHEM PROFILE
132	Sodium
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15	Anion Gap
118	Glucose
32	BUN
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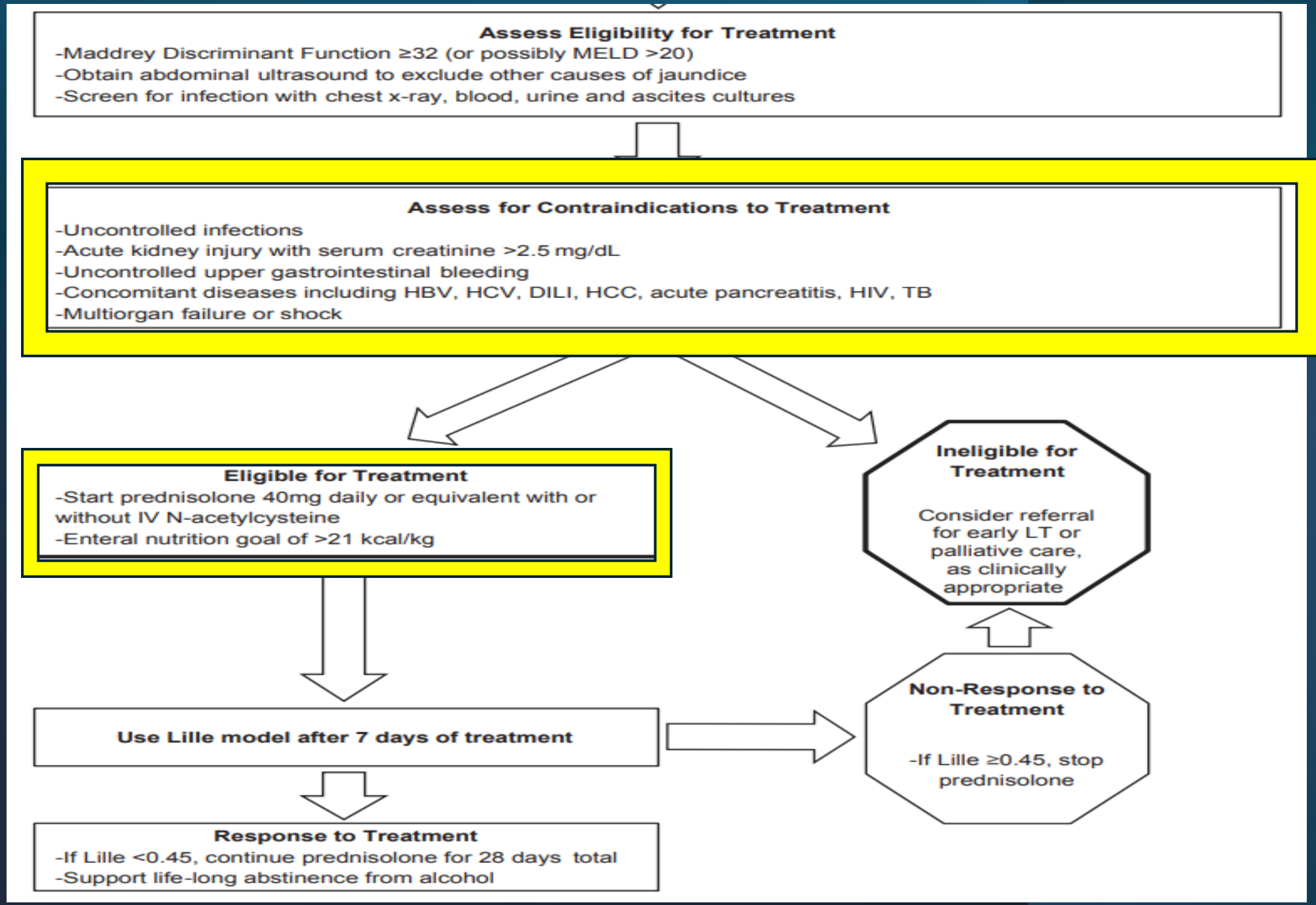
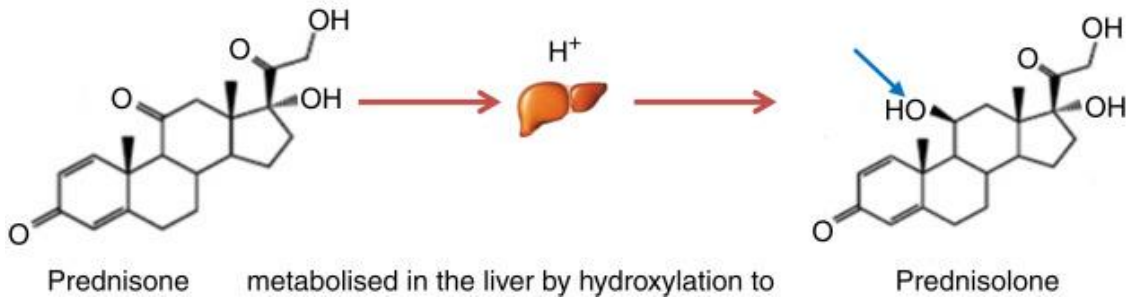


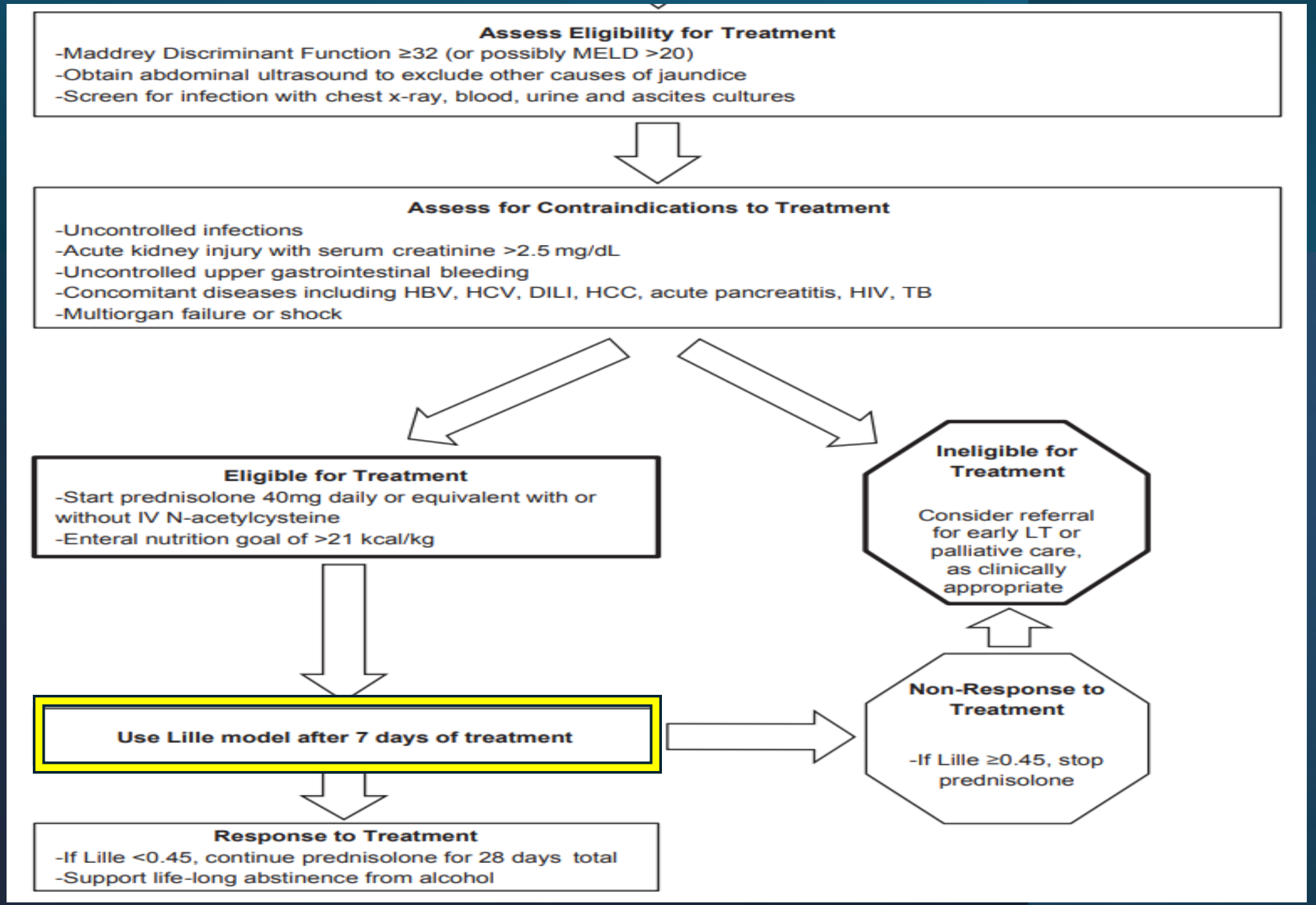
Crabb DW, Iet al. Hepatology. 2020 Jan;71(1):306-333.

Treatment: Prednisolone

- Corticosteroids (prednisolone or methylprednisolone) significantly decrease risk of death within 28 days compared to controls
  - 2,111 patients in 11 studies comparing steroids vs placebo or pentoxifylline
  - HR 0.64, 95% CI 0.48 – 0.86 (36% reduced risk of 28-day mortality)
- Dosing: If MDF ≥ 32 or MELD > 20: prednisolone 40 mg daily for 28 days, followed by a 2 – 4 week taper
  - Re-assess bilirubin at day 4 – 7 after initiation of steroids and if Lille model ≥ 0.45 stop steroids (no benefit)



Gastroenterology. 2018 Aug;155(2):458-468.



Crabb DW, Iet al. Hepatology. 2020 Jan;71(1):306-333.

Lille Model

Calculated on day 4 - 7 using initial labs and bilirubin response

Age	34	years
Albumin	3.2	g/dL
Bilirubin (initial)	38.7	mg/dL
	Very high double-check.	
Bilirubin (day 7)	33.3	mg/dL
	Very high double-check.	
Creatinine	1.66	mg/dL
PT	38.8	sec

0.249 points

INITIAL

1/15/25
10:04

	CHEM PROFILE
132	Sodium
4.1	Potassium
96	Chloride
21	CO2
15	Anion Gap
118	Glucose
32	BUN
1.66	Creatinine
41	Calculated GFR
19.3	BUN/Creatinine Ratio
9.0	Calcium
	Phosphorus
213	AST (SGOT)
94	ALT (SGPT)
128	Alkaline Phosphatase
6.0	Total Protein
3.2	Albumin
38.7	Total Bilirubin
2.0	Magnesium
70	Lipase
115	Ammonia
38.8	Prothrombin Time
3.9	INR

DAY 7

Component	01/22/2025
Albumin	2.9 ↓
Bilirubin Direct	18.6 ↑
Bilirubin Total	33.3 ↑
ALP	116
ALT	43
AST	131 ↑

Lille score < 0.45 → continue steroids for 28 days to improve survival

N-Acetylcysteine (NAC)

- ACG recommends NAC as adjunct to prednisolone

> 20. We recommend use of IV N-acetylcysteine as an adjuvant to corticosteroids in patients with severe AH (strong recommendation, moderate level of evidence).

- Mechanism: hepatoprotection as glutathione donor. Antioxidant. Improves microvascular tone to increase oxygen delivery to hepatic tissues
- Clinical evidence:
  - 2011 trial NEJM demonstrated reduced 1-month mortality combination glucocorticoids PLUS NAC in AH
  - 2020 trial of combination glucocorticoids PLUS NAC in AH did not demonstrate a survival advantage
- Current clinical practice NAC not routinely used for alcoholic hepatitis but may be considered in severe cases

Nguyen-Khac, et al. N Engl J Med. 2011 Nov 10;365(19):1782-9.

Amjad W, et al. Dig Dis Sci. 2020 Ded;65(12):3726-3733

Roadmap

Ascites

Spontaneous bacterial peritonitis (SBP)

Esophageal variceal hemorrhage

Hepatic encephalopathy

Acute alcoholic hepatitis

Hepatorenal syndrome (HRS)

Hepatorenal Syndrome

Hepatorenal syndrome is a late complication of cirrhosis

- Accounts for 3.2% of all hospital discharges related to cirrhosis
- Associated with high inpatient mortality ~46%

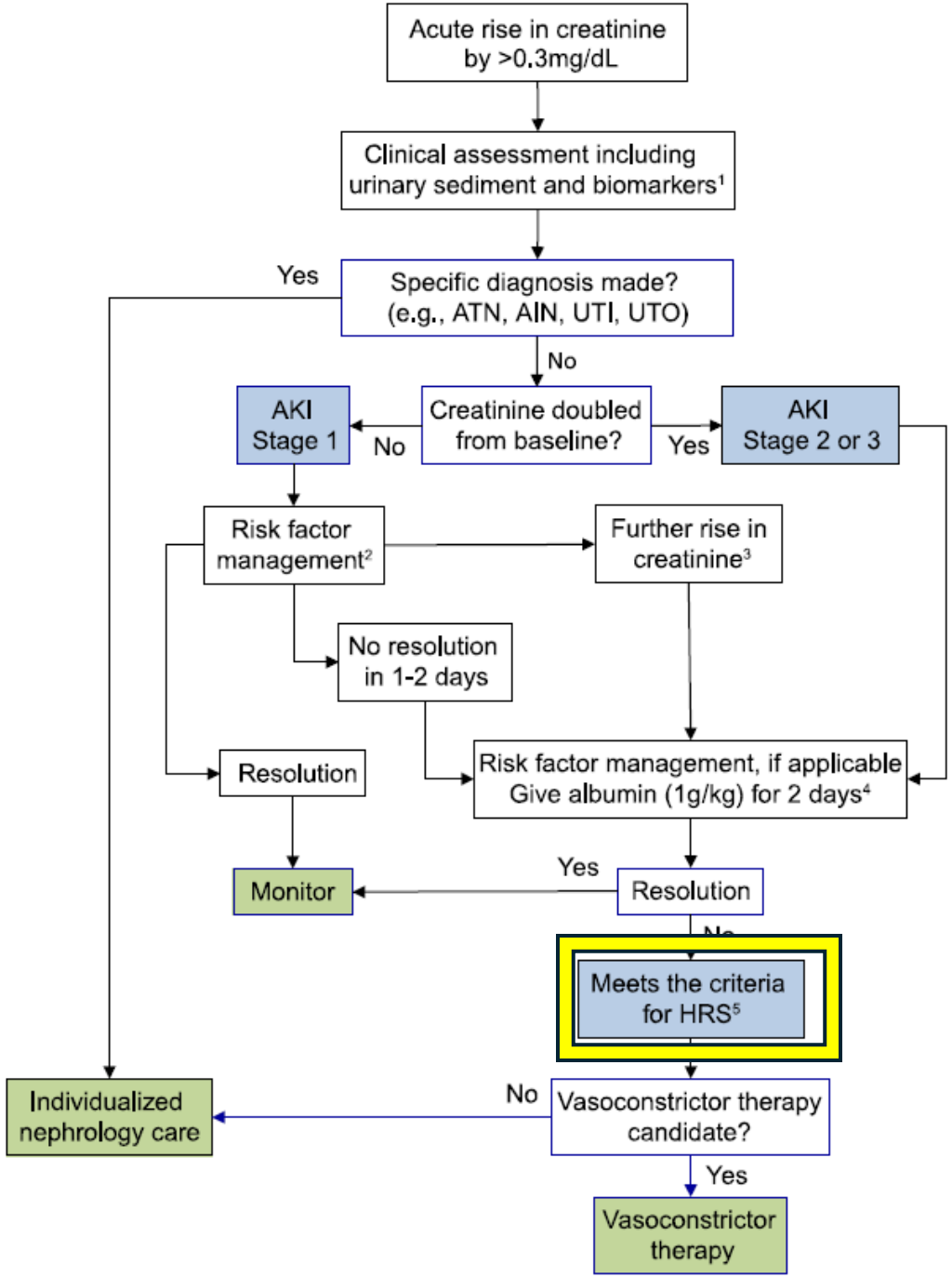
Mechanism: reduced renal perfusion. Portal hypertension leads to splanchnic vasodilation, sensed as decreased effective arterial blood volume, which releases various compensatory mediators

Biggins SW, et al Hepatology. 2021 Aug;74(2):1014-1048

Diagnosis and Management of AKI in Cirrhosis

AKI Stage	Description
Stage 1	Increase in SCr ≥ 0.3 mg/dL up to 2-fold of baseline
Stage 2	Increase in SCr 2-fold to 3-fold of baseline
Stage 3	Increase in SCr > 3-fold from baseline or SCr > 4 mg/dL or initiation of RRT

- Risk factor management: remove nephrotoxic drugs, reduce or discontinue diuretics, volume resuscitation (if depleted with albumin or balanced crystalloid (LR)



Biggins SW, et al Hepatology. 2021 Aug;74(2):1014-1048

Hepatorenal Diagnostic Criteria

- HRS-AKI diagnosis made after excluding hypovolemia, shock, nephrotoxic agents, and structural kidney disease
  - Retrospective cohort of 2,063 patients admitted with AKI and cirrhosis
    - Etiology: prerenal (44.3%), acute tubular necrosis (ATN) (30.4%), HRS-AKI (12.1%), other (6%), unable to be classified (7.2%)
- Diagnostic Criteria HRS-AKI:

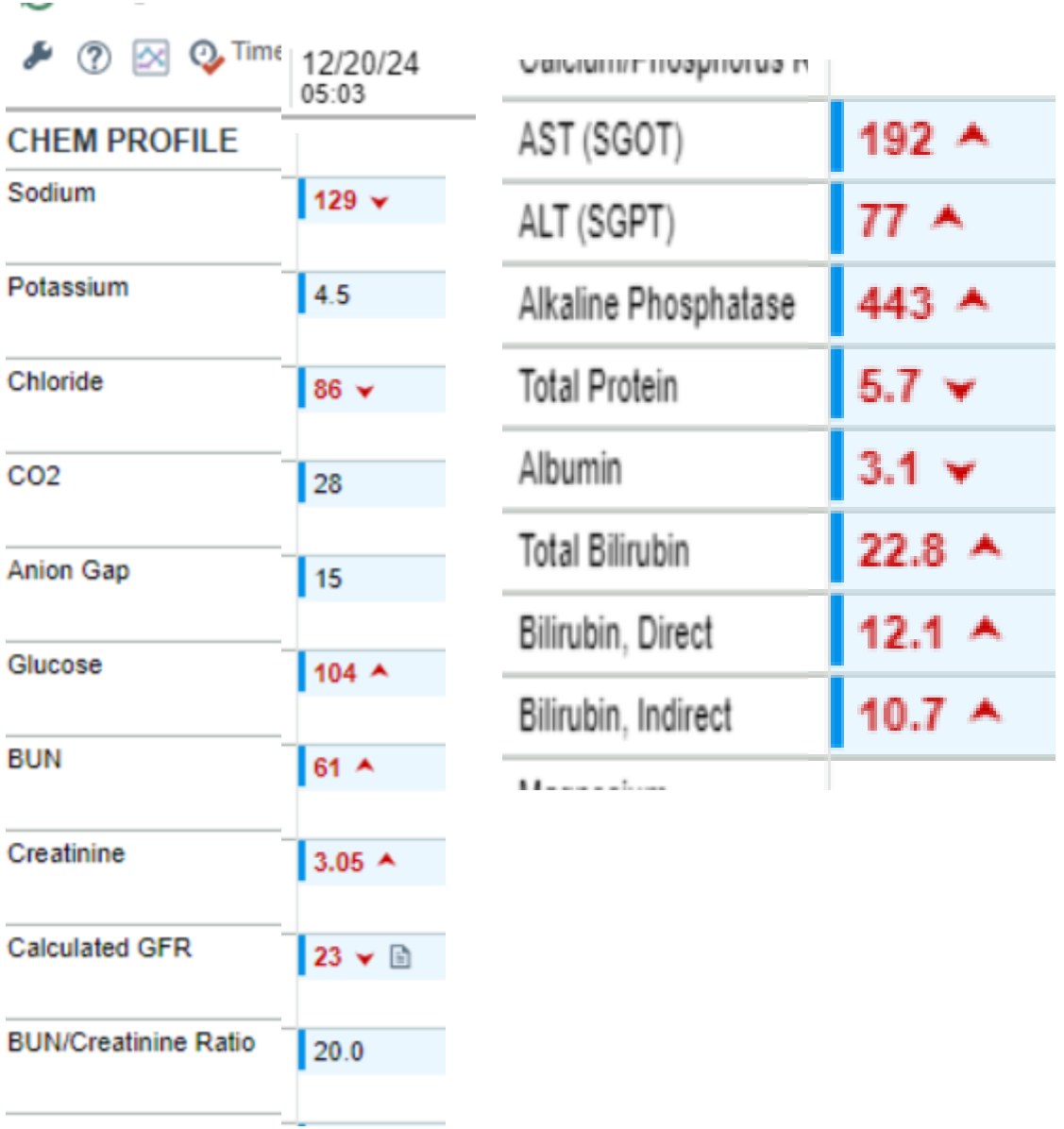
  - Cirrhosis with ascites
  - AKI: Scr increase by ≥ 0.3 mg/dL within 48 hours or 1.5 times baseline within 7 days
  - Absence of strong evidence for alternative cause of AKI
  - Lack of improvement in kidney function after 2 days after withholding diuretics and treatment with volume expansion (albumin 25% 1 g/kg (max 160 g/day))

Biggins SW, et al. Hepatology. 2021 Aug;74(2):1014-1048

Patidar KR, et al J Hepatol. 2023 Dec;79(6):1408-1417.

Example Case

- 57/M (90 kg) patient with history of alcohol abuse and recent binge drinking presented with yellowing of the skin
  - Lab confirmed hyperbilirubinemia (T.bili 22.8)
- Patient diagnosed with acute alcoholic hepatitis, steroids not initiated despite MDF ≥ 32 and MELD > 20 → contraindication AKI SCr > 2.5
  - SCr found to be 3.05 mg/dL
  - Baseline SCr 1.1 mg/dL
  - Suspect HRS-AKI



Treatment: HRS-AKI

- Albumin 25% PLUS vasoconstrictor therapy until creatinine returns to baseline up to 14 days
  - Albumin 25% 1 g/kg IV for 2 days therapy followed by 20 - 50 g/day
    - Mechanism: effective volume expansion to increase renal perfusion, may also have some anti-inflammatory, antioxidant, immune modulatory, and endothelial stabilizing properties
- Vasoconstrictor options:
    - ICU: Norepinephrine low dose continuous infusion (0.5 mg/hr) to achieve increase in MAP of at least 10 mmHg or increase in urine output > 200 mL/4 hours
    - NON-ICU: Midodrine PLUS octreotide
      - Midodrine 5 – 15 mg PO TID
      - Octreotide 100 – 200 mcg SC TID (or octreotide infusion 50 mcg/hr)
    - Terlipressin recently approved in US ($$$)
  - Consult nephrology
    - Renal replacement therapy per specialist if needed

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Mechanism

Norepinephrine

- Stimulates beta-1 and alpha-adrenergic receptors causing vasoconstriction, increasing systemic blood pressure

Midodrine

- Alpha-1 agonist increases arterial and venous tone to increase blood pressure to improve kidney perfusion pressure

Octreotide

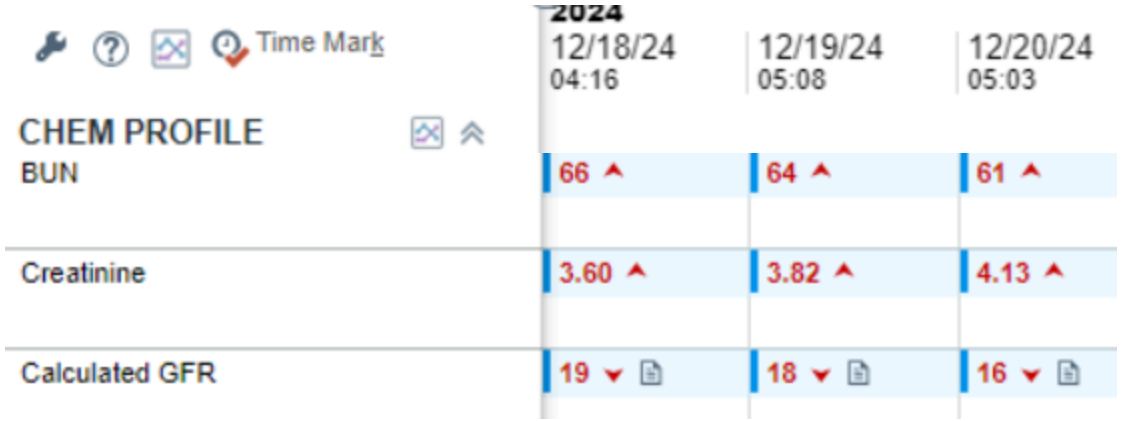
- Mimics natural somatostatin. Nonspecific antagonist of various splanchnic vasodilators that underlies pathogenesis of HRS-AKI

Terlipressin:

- Synthetic vasopressin analogue with 2x selectivity for vasopressin V1 → producing extended duration of systemic vasoconstriction, reduces portal pressure and blood flow into portal vessels, increases effective arterial blood volume and MAP, increases blood flow to the kidneys

Example Case: Treatment HRS-AKI

- HRS-AKI confirmed when renal function did not improve after 2 days of volume expansion with albumin 25% 1 g/kg IV daily
  - Lack of response to volume challenge is criterion for diagnosis of HRS-AKI because it eliminates prerenal AKI from the differential diagnosis
  - Vasoconstrictors (midodrine + octreotide) initiated



Ascites	Paracentesis, combination diuretic: spironolactone 100 mg PLUS furosemide 40 mg
Spontaneous bacterial peritonitis	Ceftriaxone 1 g IV q24 hr x 5 days PLUS albumin 25% if criteria (SCr > 1, BUN > 30, or Bili > 5) 1.5 g/kg IV DAY 1 and 1 g/kg DAY 3 to prevent AKI
Variceal hemorrhage	Octreotide 50 mcg IV x 1 followed by 50 mcg/hr x 2 – 5 days, protonix 80 mg IV followed by 40 mg IV BID until endoscopy, transfuse RBCs to target Hgb 7 g/dL, secondary prevention with NSBB (propranolol, nadolol, or carvedilol)
Hepatic encephalopathy	If confusion start lactulose 30 g TID to 2 loose BMs/day, adjunctive rifaximin 400 mg TID (or 550 mg BID)
Acute alcoholic hepatitis	If MDF ≥ 32 or MELD > 20 initiate prednisolone 40 mg daily for 28 days, re-assess bilirubin on day 4 – 7 days, if Lille model ≥ 0.45 stop steroids
Hepatorenal syndrome (HRS)	Albumin 25% 1 g/kg IV (max 100 g/day) x 2 days, if no improvement in renal function start octreotide 100 – 200 mcg SC TID PLUS midodrine 5 – 10 mg TID (if ICU use norepinephrine low dose infusion 0.5 mg/hr)

References

- Simonetto DA, et al. ACG Clinical Guideline: Disorders of the Hepatic Mesenteric Circulation. Am J Gastroenterol. 2020 Jan;115(1):18-40.
- Jagdish RK, et al. Pathophysiology and management of liver cirrhosis: from portal hypertension to acute on chronic liver failure. Front. Med. 2023 Jan;10. https://doi.org/10.3389/fmed.2023.1060073
- Tapper EB, Parikh ND. Diagnosis and Management of Cirrhosis and Its Complications: A Review. JAMA. 2023 May 9;329(18):1589-1602.
- Heidelbaugh JJ, et al. Cirrhosis and chronic liver failure: part I. Diagnosis and evaluation. Am Fam Physician. 2006 Sep 1;74(5):756-62.
- Biggins SW, et al. Diagnosis, Evaluation, and Management of Ascites, Spontaneous Bacterial Peritonitis and Hepatorenal Syndrome: 2021 Practice Guidelines by the American Association for the Study of Liver Diseases. Hepatology. 2021 Aug;74(2):1014-1048
- Khan S, Linganna M. Diagnosis and management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome. Cleve Clin J Med. 2023 Apr 3;90(4):209-213.
- Smith A, Baumgartner K, Bositis C. Cirrhosis: Diagnosis and Management. Am Fam Physician. 2019 Dec 15;100(12):759-770.
- Bolognesi M, Pascoli MD, Verado A, et al. Splanchnic vasodilation and hyperdynamic circulatory syndrome in cirrhosis. World J Gastroenterol. 2014 Mar 14;20(10):2555-2563.
- Rattan P, Shah VH. Review article: current and emerging therapies for acute alcohol-associated hepatitis. Aliment Pharmacol Ther. 2022 Jul;56(1):28-40.
- Arab JP, Diaz LA, Baeza N, et al. Identification of optimal therapeutic window for steroid use in severe alcohol-associated hepatitis: A worldwide study. J Hepatol. 2021 Nov;75(5):1026-1033.

References

- Patidar KR, Belcher JM, Regner KR, et al. Incidence and outcomes of acute kidney injury including hepatorenal syndrome in hospitalized patients with cirrhosis in the US. J Hepatol. 2023 Dec;79(6):1408-1417.
- Merli M, Nicolini G, Angeloni S, et al. Incidence and natural history of small esophageal varices in cirrhotic patients. J Hepatol. 2003 Mar;38(3):266-72.
- Kaplan DE, Ripoll C, Thiele M, et al. AASLD Practice Guidance on risk stratification and management of portal hypertension and varices in cirrhosis. Hepatology. 2024 May 1;79(5):1180-1211.
- Villanueva C, Albillos A, Genesca J. β blockers to prevent decompensation of cirrhosis in patients with clinically significant portal hypertension (PREDESCI): a randomized, double-blind, placebo-controlled, multicentre trial. Lancet. 2019 Apr 20;393(10181):1597-1608.
- Chavez-Tapia NC, Barrientos-Guitierrez T, Tellez-Avila F, et al. Meta-analysis: antibiotic prophylaxis for cirrhotic patients with upper gastrointestinal bleeding: an updated Cochrane review. Aliment Pharmacol Ther. 2011 Sep;34(5):509-18.
- Louvet A, Thursz MR, Kim DJ, et al. Corticosteroids Reduce Risk of Death Within 28 Days for Patients with Severe Alcoholic Hepatitis, Compared with Pentoxifylline or Placebo – a Meta-analysis of Individual Data From Controlled Trials. Gastroenterology. 2018 Aug;155(2):458-468.
- Amjad W, Alukal J, Doycheva I, et al. A Combination of N-Acetylcysteine and Prednisone Has No Benefit Over Prednisolone Alone in Severe Alcoholic Hepatitis: A Retrospective Analysis. Dig Dis Sci. 2020 Ded;65(12):3726-3733.
- Nguyen-Khac E, Thevenot T, Piquet MA, et al. Glucocorticoids plus N-acetylcysteine in severe alcoholic hepatitis. N Engl J Med. 2011 Nov 10;365(19):1782-9.

References

- Osna NA, Donohue TM, Kharbanda KK. Alcoholic Liver Disease: Pathogenesis and Current Management. Alcohol Res. 2017;38(2):147-161.
- Michalska-Ciecko I, Szczepanek M, Slowik A. Pathogenesis of Hepatic Encephalopathy. Gastroenterol Res Pract. 2012 Dec 17;2012:642108.
- Anand AC, Acharya SK. The Story of Ammonia in Liver Disease: An Unraveling Continuum. J Clin Exp Hepatol. 2024 Jul-Aug;14(4):101361.
- AASLD. Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases. J Hepatol. 2014 Sep;61(3):642-59.
- Jophlin LL, Singal AK, Bataller R, et al. ACG Clinical Guideline: Alcohol-Associated Liver Disease. Am J Gastroenterol. 2024 Jan 1;119(1):30-54.
- Hisseubu Nm Shor J, Szabo G. Alcoholic Hepatitis: A Review. Alcohol 2019 Jul 1;54(4):408-416.
- Jophlin LL, Singal AK, Bataller R, et al. ACG Clinical Guideline: Alcohol-Associated Liver Disease. Am J Gastroenterol. 2024 Jan 1;119(1):30-54.
- Arab JP, Diaz LA, Braeza N, et al. Identification of optimal therapeutic window for steroids use in severe alcohol-associated hepatitis: a worldwide study. J Hepatol. 2021 Jun 21;75(5):1026-1033.
- Crabb DW, Im GY, Szabo G, et al. Diagnosis and Treatment of Alcohol-Associated Liver Diseases: 2019 Practice Guidance From the American Association for the Study of Liver Diseases. Hepatology. 2020 Jan;71(1):306-333.