

HEPATIC ENCEPHALOPATHY & TIPS

PRESENTED BY IVONNE GRABOW, PA-C

SPEAKER INTRODUCTION: IVONNE GRABOW, PA-C



Outline



Brief Liver Basic Review

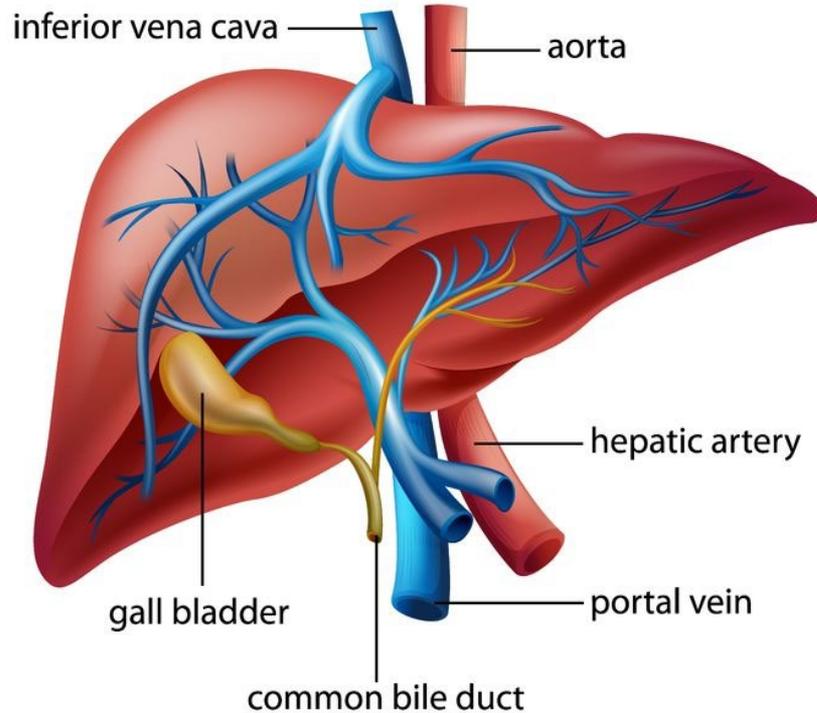


Hepatic Encephalopathy



TIPS

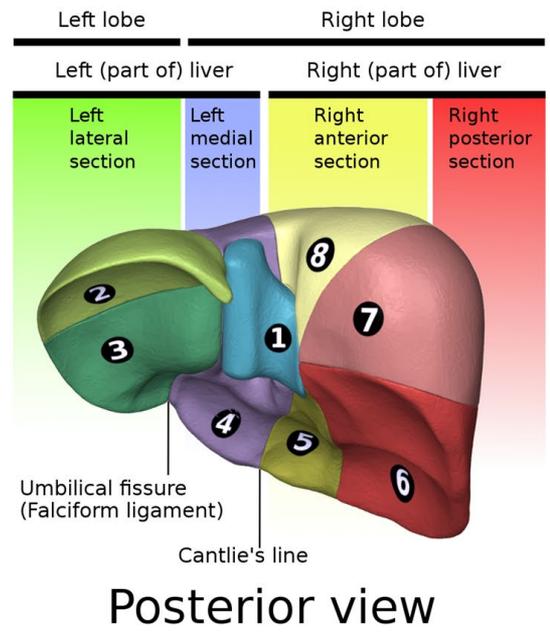
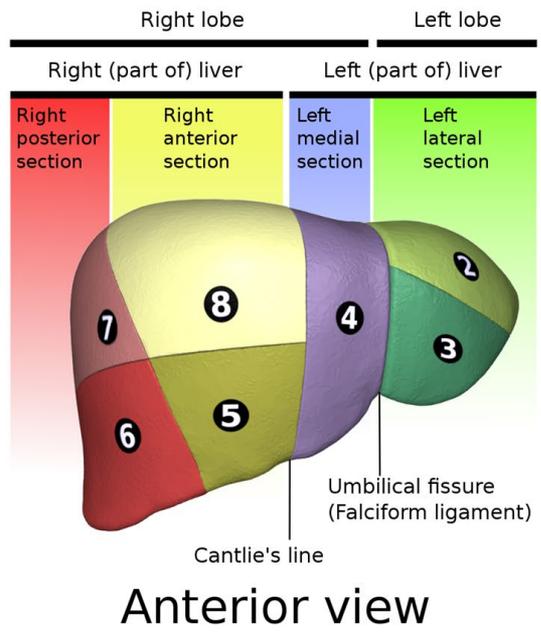
Human Liver Anatomy



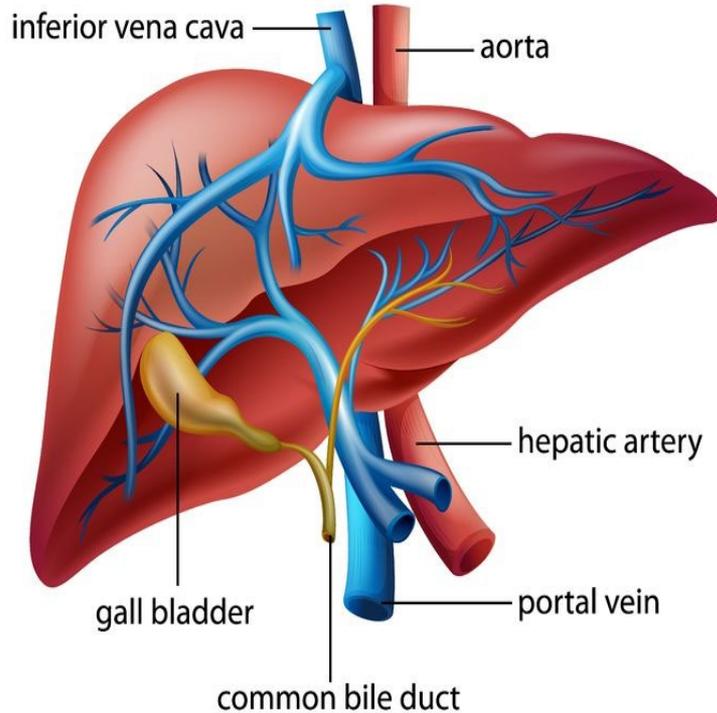
- Located in the RUQ
- 2nd largest organ
- Capable of Regenerating
- Functions- more than 500 identified

Anatomy

- 8 liver segments



Human Liver Anatomy



Functions

- Production of bile
- Production of proteins
- Production of cholesterol
- Regulation of glucose
- Regulation of blood levels of amino acids
- Stores Iron and vitamins
- Conversions of ammonia to urea
- Regulates blood clotting factors

Blood Glucose Regulation

When things go wrong:

- Pt has a hard time keeping their sugars up. Usually end of life

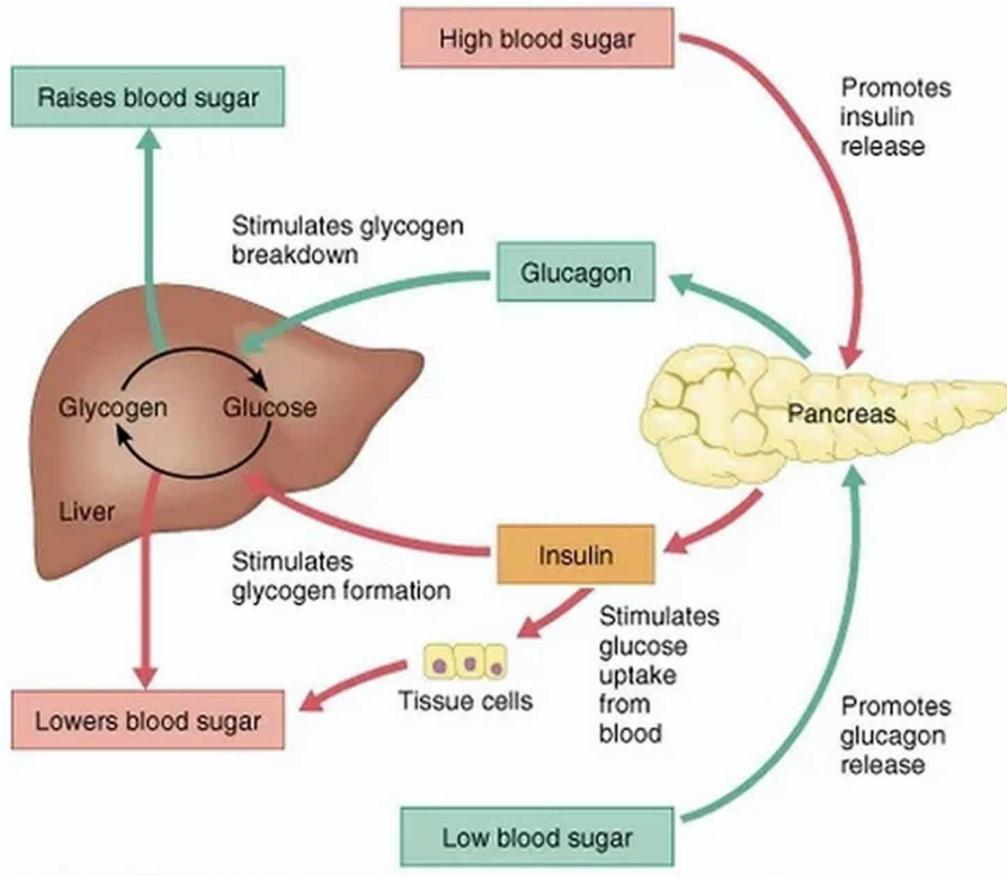
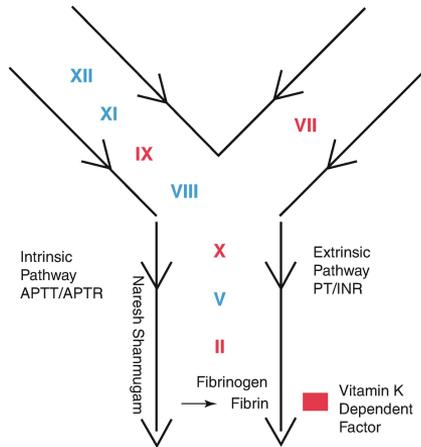


Table 1
The liver's role in coagulation: coagulation factors synthesized by the liver

| Procoagulants | Anticoagulants | Profibrinolysis | Antifibrinolysis |
|---|---|--|---|
| <ul style="list-style-type: none"> • Fibrinogen • Prothrombin • Factor V • Factor VII • Factor VIII • Factor IX • Factor X • Factor XI • Factor XII • Factor XIII • Thrombopoietin | <ul style="list-style-type: none"> • Protein C • Protein S • Tissue factor pathway inhibitor • Antithrombin | <ul style="list-style-type: none"> • Factor XIIa • Plasminogen | <ul style="list-style-type: none"> • Plasminogen activator inhibitor-1 • Alpha-antiplasmin • Tissue activatable fibrinolysis inhibitor |

Blood Clotting

- Liver responsible for producing most coagulation factors
- Requires Vit K for synthesis
 - Vit K is a fat soluble vitamin
 - How do you get it? Bile salt essential for intestinal absorption of this
 - And where is bile made? Liver



When things go wrong:

- Pt bleeds!

Proteins

Function

- Liver produces most of the proteins found in blood
- Especially Albumin!
 - Regulates blood volume & distribution of fluids
- Ferritin
 - A protein used to store iron

When Things go Wrong

- Low Albumin levels contribute to LE edema and ascites

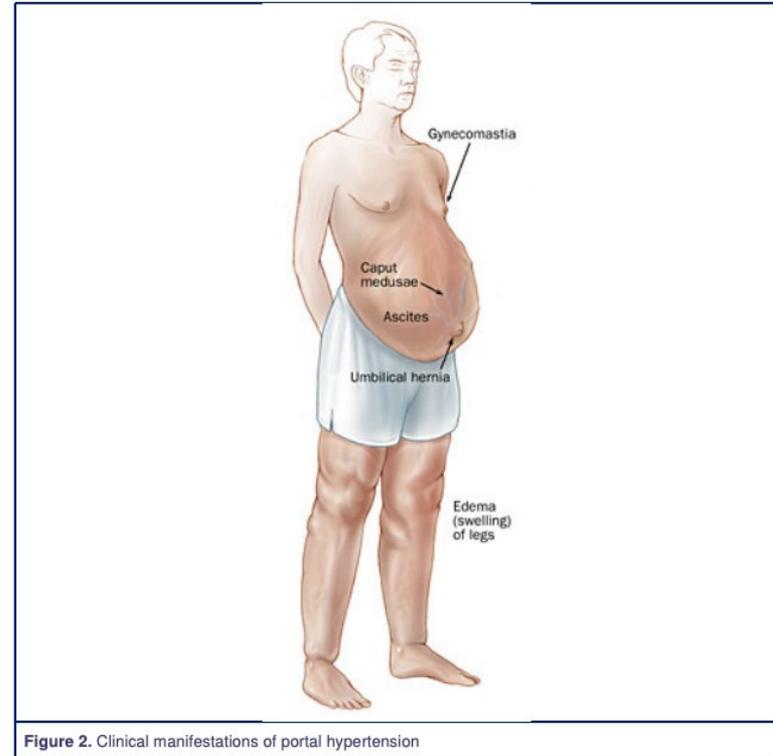


Figure 2. Clinical manifestations of portal hypertension

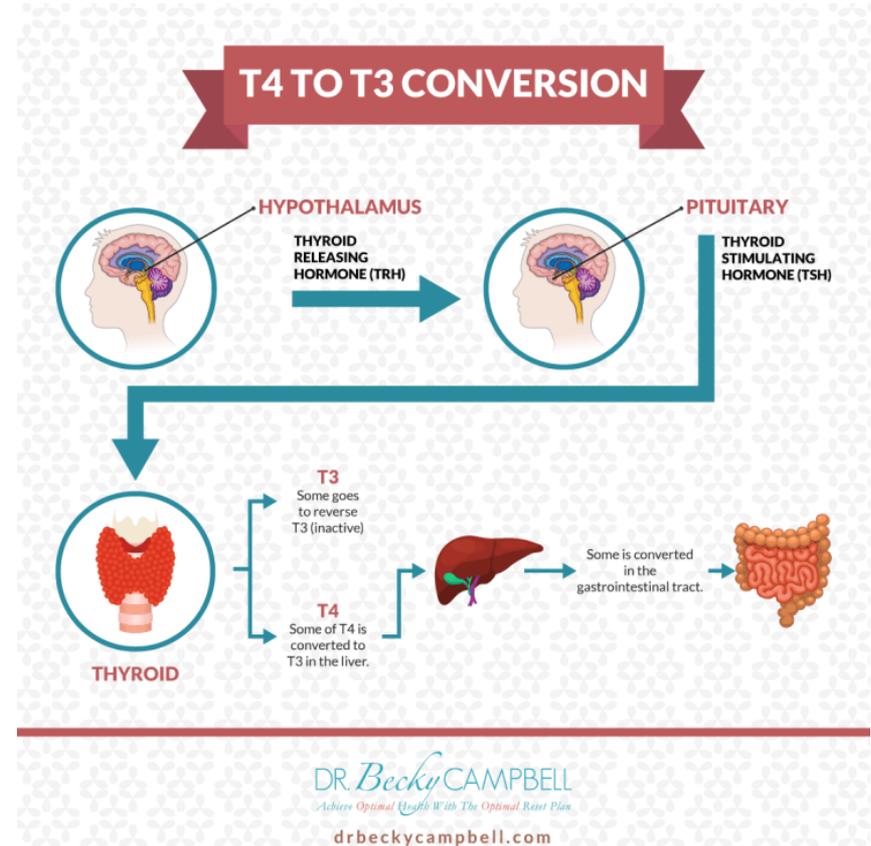
Hormonal Functions

Function

- 60% of Thyroid Hormone T4 is converted to T3 the active form in the liver.
- Secretes IGF-1 (Insulin Growth Factor 1) which promotes cell growth
- Produces Angiotensinogen – regulates sodium and potassium levels, BP control

When Things go Wrong

- Fatigue
- Feeling cold
- Hypotension

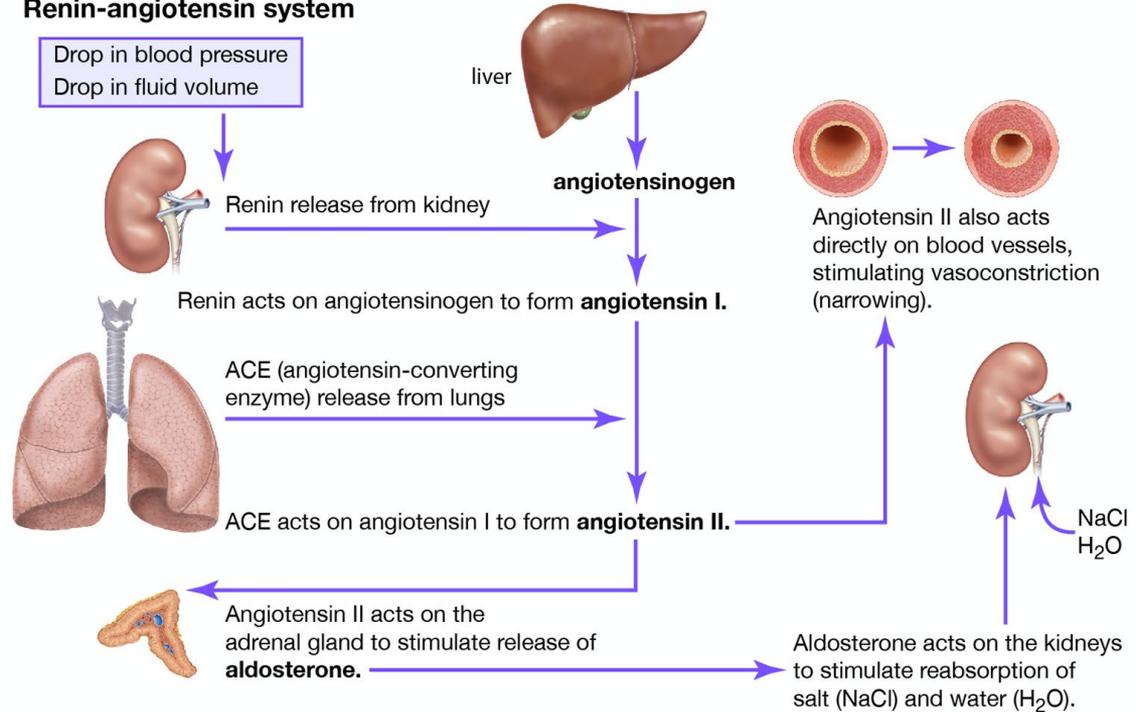


Hormonal Functions

Liver makes
Angiotensinogen

Contributes to
controlling BP via the
Renin-Angiotensin
system

Renin-angiotensin system



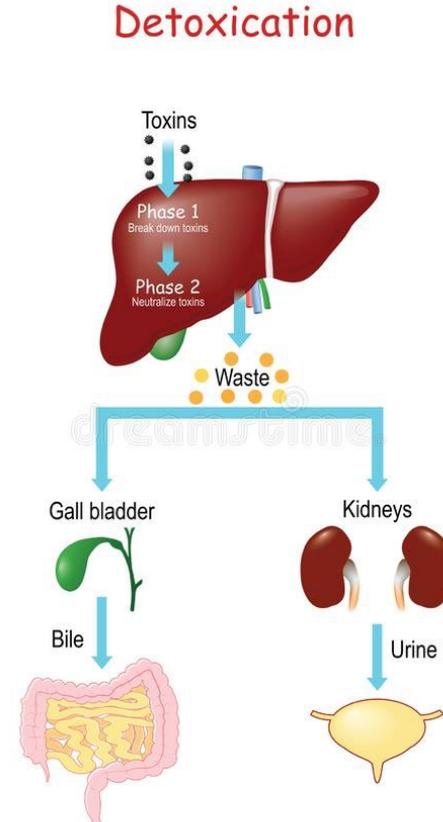
Detoxification

Function

- Degrade old red blood cells into breakdown products
- Breaks down toxic poisons, drugs, alcohol

When Things go Wrong

- Bilirubin builds up- They turn Yellow!
- Build up of toxins – Encephalopathy



Hepatic Encephalopathy

Hepatic encephalopathy (HE) Portosystemic encephalopathy (PSE)

Definition: A REVERSIBLE syndrome of impaired brain function occurring in patients with advanced liver failure

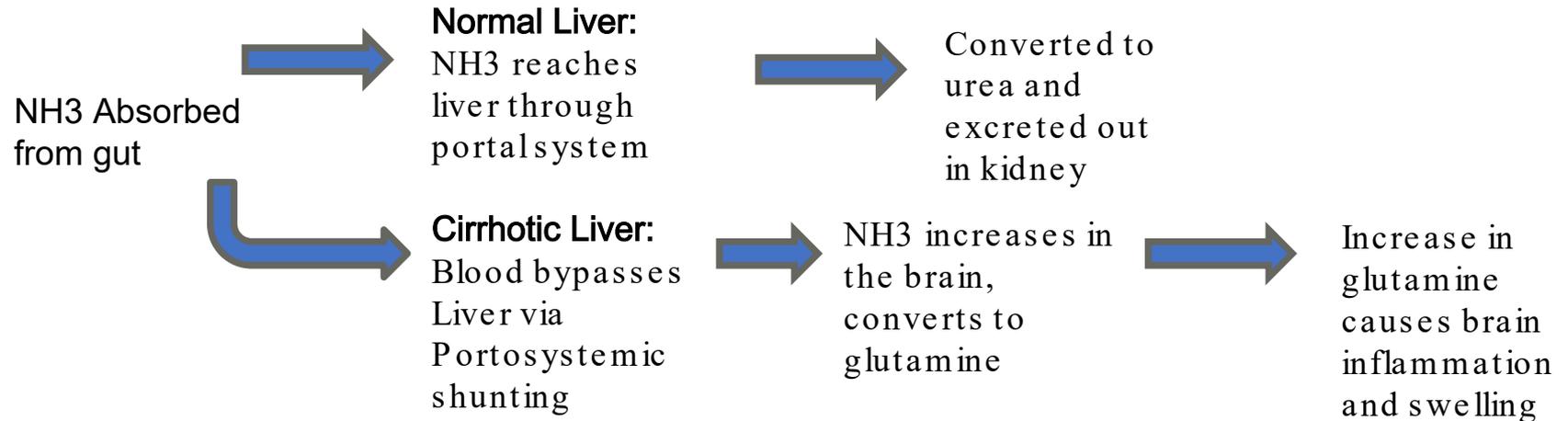
Frequent cause of hospitalizations for pts with cirrhosis

Economic burden: In 2012 cost per patient was \$25,634- \$58,625*

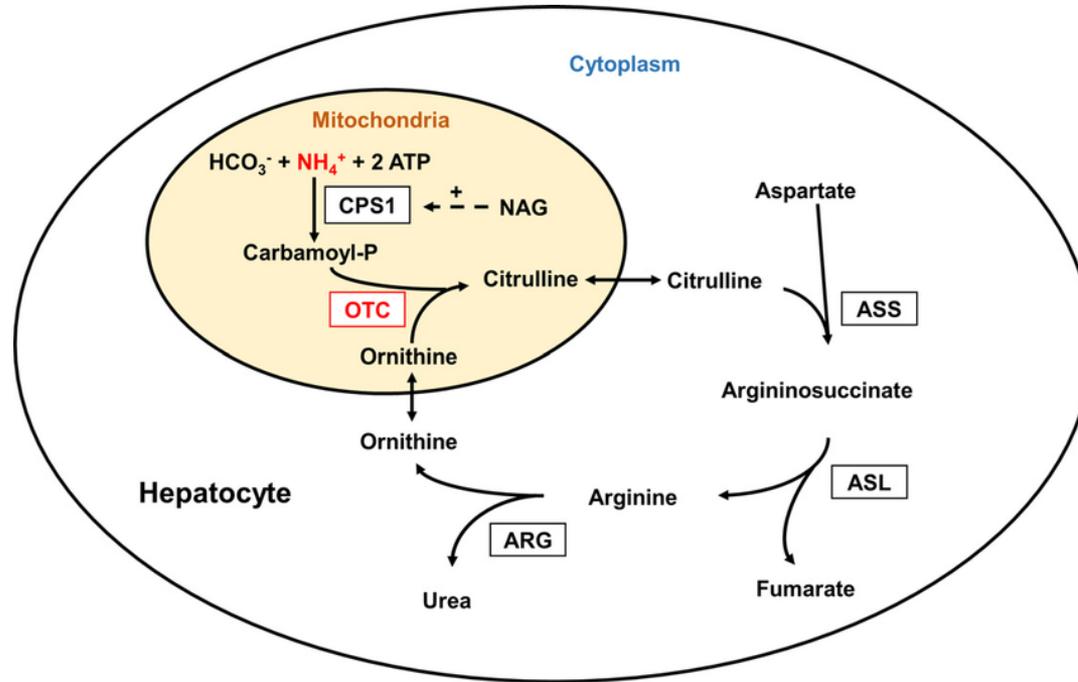
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5999147/#:~:text=Economic%20Impact%20of%20Hepatic%20Encephalopathy&text=Further%2C%20in%202014%2C%20for%20patient%24US620%20million%20%5B23%5D>

Pathogenesis

- Exact mechanism unknown; however one theory association with ammonia



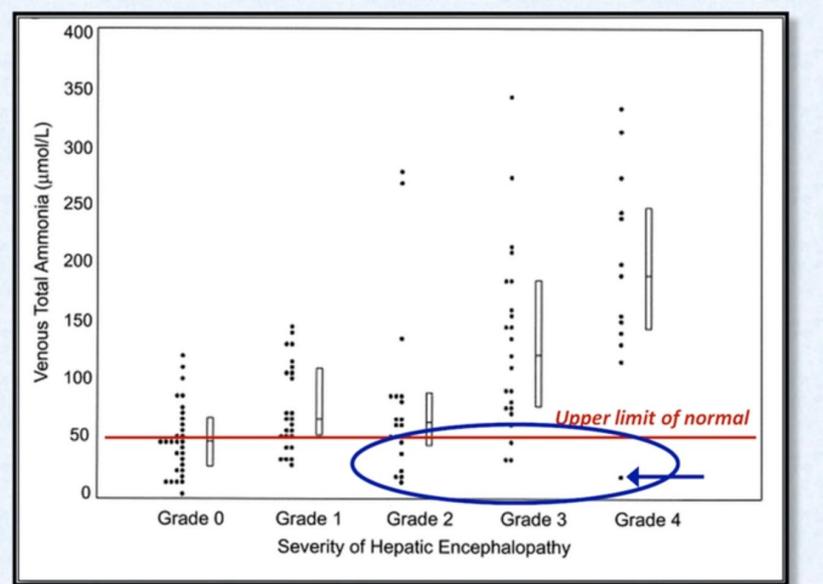
Urea cycle in the Liver



Big Picture:
Ammonia gets processed in the Liver into Urea

Ammonia Levels Do Not Equate Severity

- Do not go by Ammonia Levels!
Go by clinical status
- Ordering Levels not recommended in PSE hospitalizations



Ong JP, Aggarwal A, Krieger D, et al. Correlation between ammonia levels and the severity of hepatic encephalopathy. *Am J Med.* 2003;114(3):188-193.

It's not just Ammonia?

- Other theories
 - Altered Gut Microbiome?
 - Change in Neurotransmitters?
 - Increased permeability of blood brain barrier?
 - Increased inflammatory cytokines?? Think Sepsis

Symptoms- Interaction Time!

- How would you describe PSE symptoms to the patient's family?
- What to look for?
- How is it different from other altered mental status etiologies?
 - Stroke
 - Recreational Drugs
 - Dementia
 - Delirium

Physical Exam

- Asterixis
- Alert and Oriented Questions
 - What is your name?
 - What is the current year?
 - What city are you in?
 - Current President? Previous President?
- Length of Response to Questions, Repeating?



<https://www.medcampus.io/challenges/asterixis-5cc846de7bca5200013b59ad>

Stages of PSE Detailed

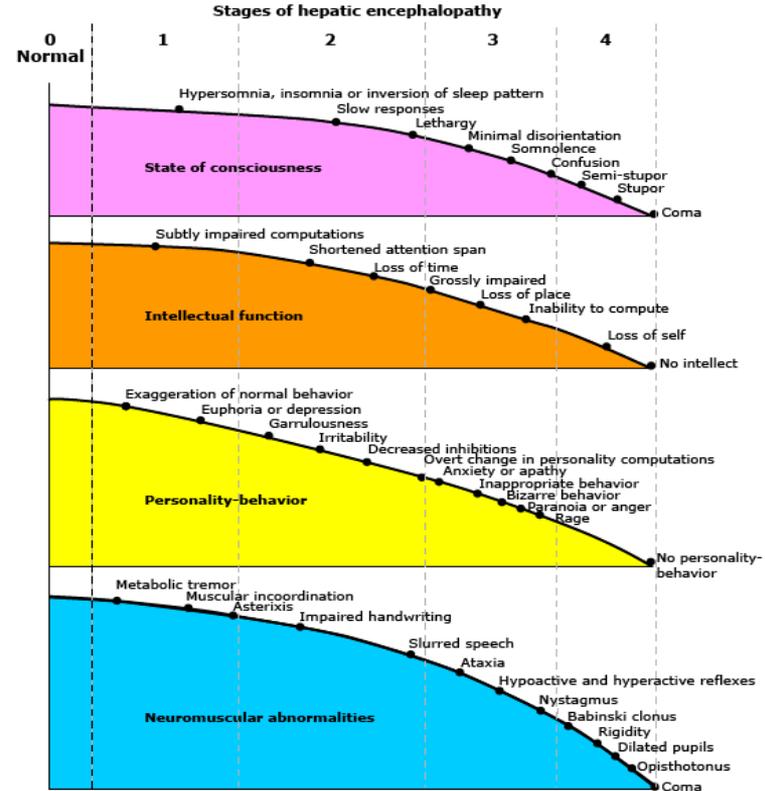


Diagram depicting the grade of hepatic encephalopathy and the clinical features associated with advancing stages.

Data from: Conn HO, Lieberthal MM. *The hepatic coma syndromes and lactulose*. Lippincott Williams & Wilkins, Baltimore 1979.

Stages of PSE

Concise

Grading system for hepatic encephalopathy

| Grade | Mental status | Asterixis | EEG |
|-------|------------------------|-----------|----------------|
| I | Euphoria/depression | Yes/no | Usually normal |
| | Mild confusion | | |
| | Slurred speech | | |
| | Disordered sleep | | |
| II | Lethargy | Yes | Abnormal |
| | Moderate confusion | | |
| III | Marked confusion | Yes | Abnormal |
| | Incoherent | | |
| | Sleeping but arousable | | |
| IV | Coma | No | Abnormal |

Precipitating Factors

Unique ones things to think about

- HCC
- PVT

Precipitants of hepatic encephalopathy in patients with cirrhosis

| Drugs |
|---|
| Benzodiazepines |
| Nonbenzodiazepine hypnotics (eg, zolpidem) |
| Narcotics |
| Alcohol |
| Increased ammonia production, absorption or entry into the brain |
| Excess dietary intake of protein |
| Gastrointestinal bleeding |
| Infection |
| Electrolyte disturbances such as hypokalemia |
| Constipation |
| Metabolic alkalosis |
| Dehydration |
| Vomiting |
| Diarrhea |
| Hemorrhage |
| Diuretics |
| Large volume paracentesis |
| Portosystemic shunting |
| Radiographic or surgically placed shunts |
| Spontaneous shunts |
| Vascular occlusion |
| Hepatic vein thrombosis |
| Portal vein thrombosis |
| Primary hepatocellular carcinoma |

Precipitating Factors- Remember these!

- Infection
- Electrolyte Imbalance
- Dehydration
- GI Bleed
- Hypoxemia
- Insufficient Bowel Movements
- Narcotic use
- Medication Noncompliance

What to Order

- GI Bleed
 - CBC, occult blood, stool
- Electrolyte Imbalance
 - CMP
- Rule out Infection
 - CXR
 - UA with reflex culture
 - Blood Culture x2
 - +/- diagnostic para to r/o SBP
 - +/- procal/lactic acid



Treatment

- Treat the underlying cause
 - Infections- antibiotics
 - GI bleed algorithm
 - Constipation- decrease narcotics, increase lactulose
 - Dehydration - give fluids, +/- albumin, stop diuretics
- **Lactulose**
- Rifaximin
- Zinc

Lactulose

Lactulose
converted by
gut bacteria

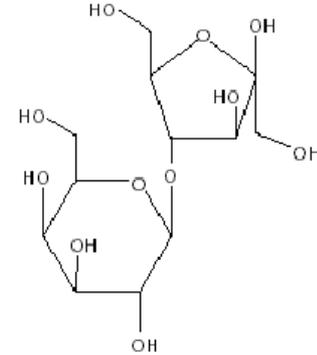


Lactic Acid/
Acetic Acid

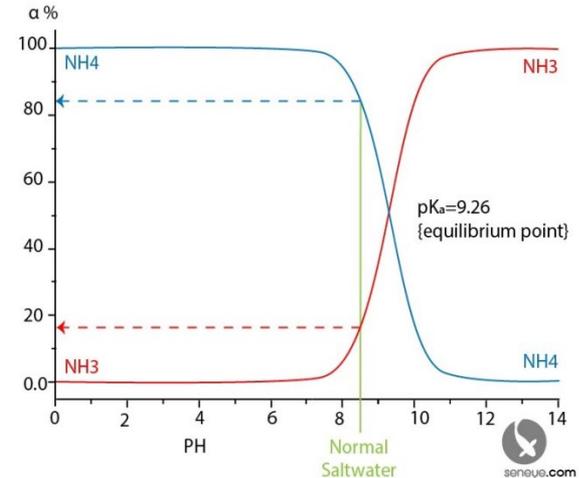


Decrease in pH
Converts
 NH_3 (ammonia)
to NH_4^+
(ammonium)
Trapping it in
the colon to
excrete out

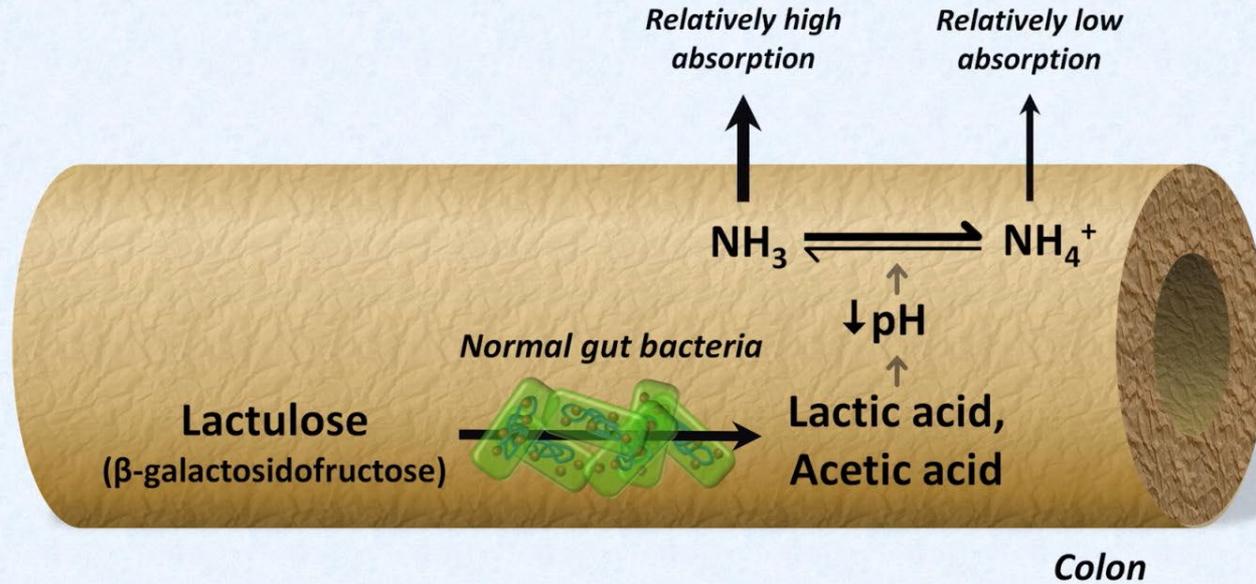
- Can increase excretion of nitrogen products 4x compared to other products



<https://www.rxlist.com/lactulose-solution-drug.htm>



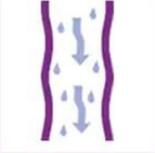
Lactulose: Mechanism of Action



Other possible contributing effects:

- Decreased GI transit time due to lactulose's cathartic actions leads to decreased time for ammonia absorption.
- Increased uptake of ammonia by gut flora.
- Displacement of urease-producing bacteria (which breakdown urea into ammonia) by non-urease producing species.

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| Over-the-counter laxatives: | Osmotic e.g., MiraLAX® | Psyllium Fiber e.g., Metamucil® | Stimulant e.g., Dulcolax® |
|-----------------------------|--|--|--|
| <p>How They Work</p> |  <p>Works with water to soften and ease stool through the colon</p> |  <p>Makes stool larger to push through the colon</p> |  <p>Stimulant laxatives work by forcefully stimulating the nerves in your colon</p> |
| <p>Side Effects</p> |  <p>Does not cause bloating, cramping, discomfort or urgency</p> |  <p>May cause bloating and gas buildup</p> |  <p>Some may cause stomach discomfort and cramps</p> |
| <p>Form</p> |  <p>A powder that you stir into a beverage and drink</p> |  <p>A capsule or powder that you stir into a beverage and drink</p> |  <p>A tablet that you take with a glass of water</p> |

*Images for illustrative purposes

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Dulcolax® is a trademark of Sanofi.

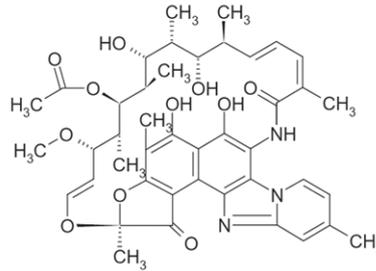
- <https://www.miralax.com/sites/g/files/vrxlpx36946/files/2020-12/miralax-is-different-chart.jpg>

KRISTALOSE®



- Powdered version of Lactulose
- Patient preference: reports of better tolerated taste
- More Expensive
- Goal is to promote compliance

Rifaximin



<https://www.rxlist.co>

- Antibiotics - usually used to treat traveler's diarrhea or Irritable Bowel Syndrome
- Poorly Absorbed in the GI system- See a trend?
- Reduction in translocation of bacteria
- Studies showed great benefit in the maintenance of PSE
 - decreased mortality, decreased hospitalization stays
 - risk of breakthrough HE by 58% in a randomized double blind study *
- FDA Approved in 2010 to use for PSE

■ Bass NM, Mullen KD, Sanyal A, Poordad F, Neff G, Leevy CB, et al. Rifaximin treatment in hepatic encephalopathy. *N Engl J Med.* 2010;362(12):1071–1081.

Zinc



- Cirrhotic patients commonly have a zinc deficiency.
- Play a role in neurotransmissions
- May enhance hepatic conversion of amino acids into urea
- Needs more research
- Zinc 220mg BID

NGT or to not NGT?

- Consider NGT if
 - High Risk for Aspiration, unsafe to give PO
 - First few Enemas not effective
 - More commonly seen in ICU/NICU

Readmissions

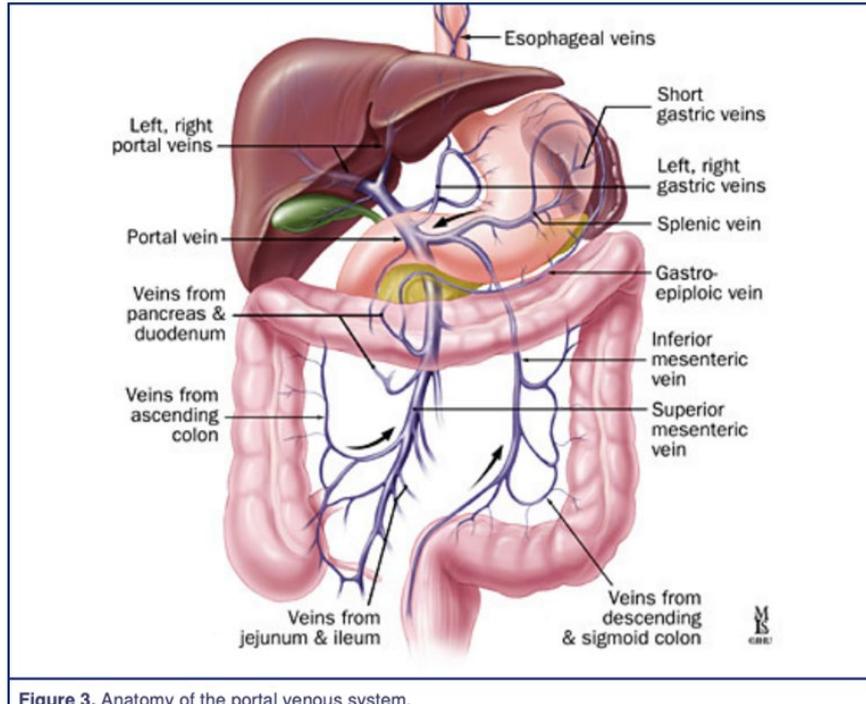
- Education on what Titrate Lactulose Means
 - Again and again and again
- Don't assume it's the same precipitator
 - Go through the steps
- What caused it this time? How can it be prevented or reduced?

Sources

- UpToDate
- MedScape
 - <https://emedicine.medscape.com/article/186101-overview>
 - <https://www.ncbi.nlm.nih.gov/pubmed/12637132>
- PubMed <https://www.ncbi.nlm.nih.gov/pubmed/30863953>

**TRANSJUGULAR
INTRAHEPATIC
PORTOSYSTEMIC SHUNT (TIPS)**

Anatomy review



Portal System

- Veins from the digestive tract carry blood to the Liver via the portal vein

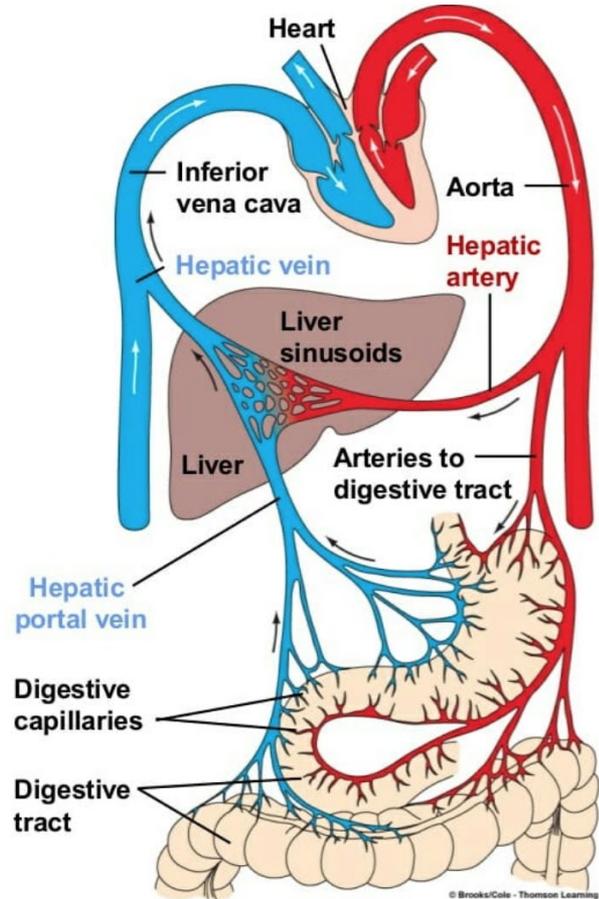
Figure 3. Anatomy of the portal venous system.

Anatomy review

Left Ventricle > Supply Digestive Tract
& Liver >

Portal System > Hepatic Portal Vein >

Liver > Hepatic Vein > Inferior Vena
Cava > Right Atrium



Portal Hypertension

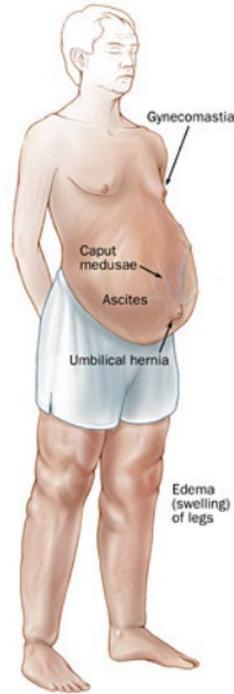
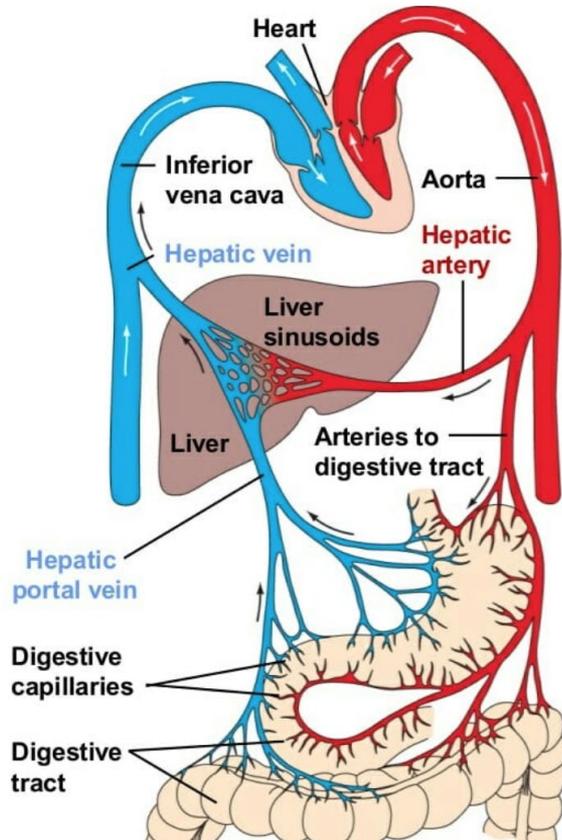


Figure 2. Clinical manifestations of portal hypertension

- Elevated Pressures in the Portal Venous System.
- Normal portal vein pressure
 - 5-10mmHg
- Typically noted by Clinical Manifestations
 - Variceal Bleeding >12mmHg
 - Ascites
 - Caput Medusae
 - Edema of legs



What Causes portal Hypertension?

- Prehepatic – Portal Vein Thrombosis, Increase portal flow (Massive splenomegaly)
- Hepatic- Cirrhosis, hepatic veno-occlusive disease (GVHD), primary biliary cholangitis
- Post Hepatic- Hepatic Vein thrombosis (Budd-chiari syndrome), obstruction of the IVC, Restrictive Cardiomyopathy

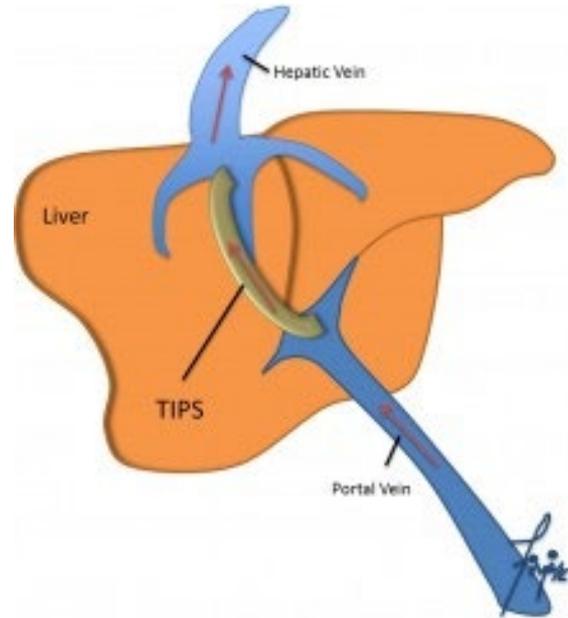
Cirrhosis



- Most common cause of Portal Hypertension

Portal Hypertension Management

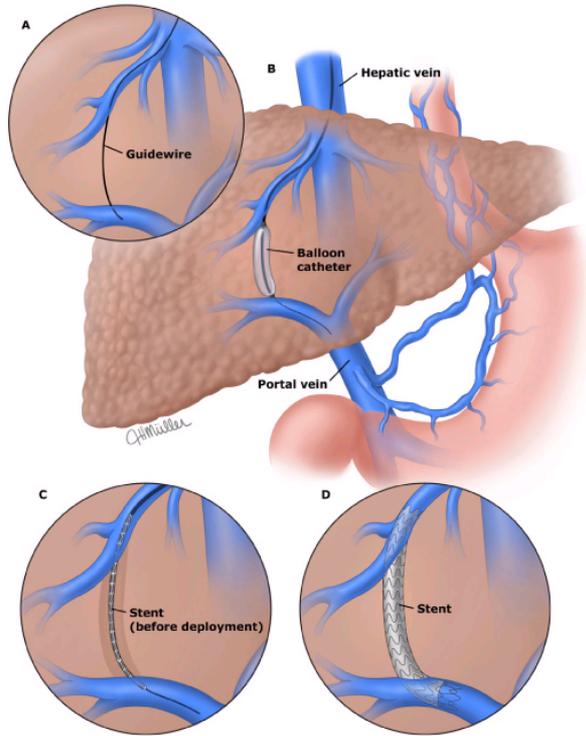
- Ascites
 - Paracentesis
- Varices
 - Endoscopic therapies- Banding, Sclerotherapy, Balloon Tamponade
 - Medication- Beta-blockers
- Surgical Shunts
 - Ex. Side to side portocaval shunt
- TIPS
- Liver Transplantation



<https://gastroliver.medicine.ufl.edu/hepatology/for-patients/tips-shunt/>

TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC sHUNT (TIPS)

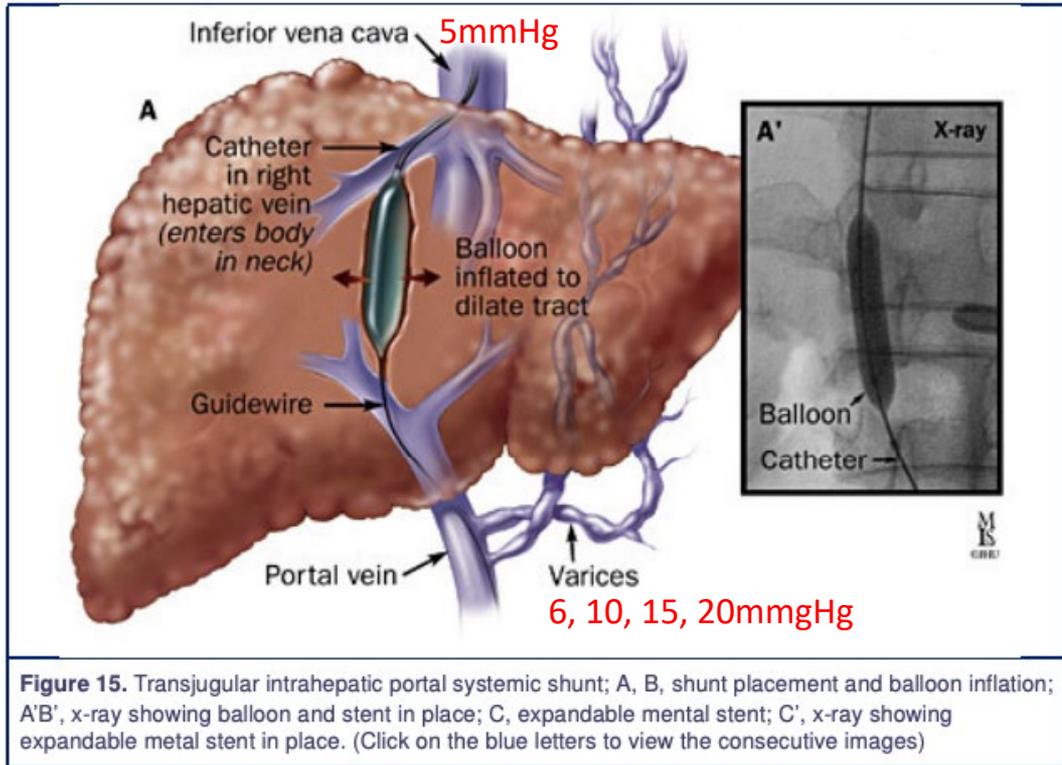
- Trans – Through
- Jugular- Right internal jugular vein
- Intra- In
- Hepatic- Liver
- Portosystemic- Portal System
- Shunt- Diverting



TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT (TIPS)

- Reduces Portal Hypertension by creating another path to relieve resistance
- Places connection between Hepatic Vein and Portal Vein

A transjugular intrahepatic portosystemic shunt (TIPS) is created by passing a needle catheter via the transjugular route into the hepatic vein and wedging it there. The needle is then extruded and advanced through the liver parenchyma to the intrahepatic portion of the portal vein and a stent is placed between the portal and hepatic veins. A TIPS functions like side-to-side surgical portacaval shunt, but does not require general anesthesia or major surgery for placement. (A) Passage of a guidewire between the hepatic vein and the portal vein. (B) Inflation of a balloon catheter within the liver to dilate the tract between the hepatic vein and the portal vein. (C) Deployment of the stent. (D) Stent in its final position.



- Portal Vein Pressure typically 5-10mmHG, anything higher is Portal Hypertension
- HVPG (Hepatic Venous Pressure Gradient) represents the gradient between the portal vein and the IVC
 - >10, start noticing symptoms
 - >12, variceal rupture
 - After TIPS is 6-10 range.

Indications- When to use TIPS

- Refractory Ascites
 - Pt getting large volume paracentesis frequently
- Active Bleeding
 - When first line therapy is unable to achieve homeostasis
 - According to UTD- if they can make it to TIPS then chance of immediate hemostasis is 90 to 100%,
- Failure to Prevent Recurrent Bleeding
 - First lines include- nonselective beta blocker, endoscopic variceal ligation

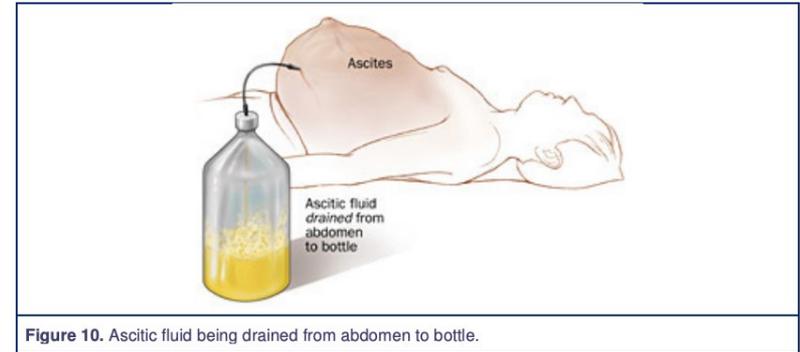
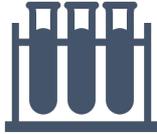


Figure 10. Ascitic fluid being drained from abdomen to bottle.

Pre-Procedure



Labs- CBC, INR, CMP
(Emphasis on Tbili and Cr)



Echocardiogram



Imaging (CT/MRI) to check
patency of portal and hepatic
veins

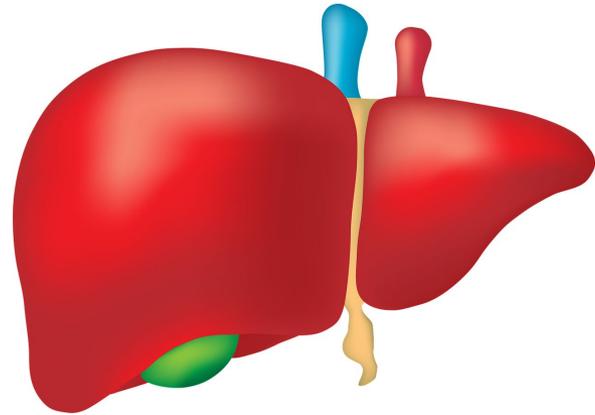
Post-procedure Care

Watch for:

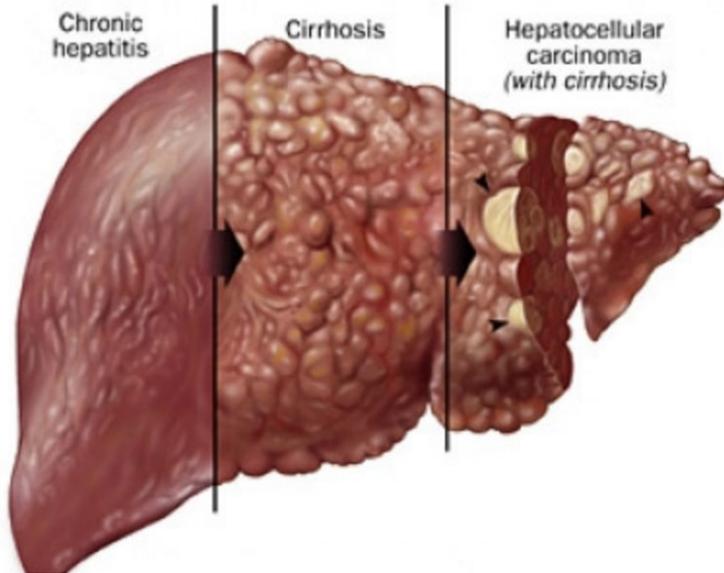
- Signs or symptoms of bleeding
- **Hepatic Encephalopathy**
- Cardiac Dysfunction- arrhythmias
 - remember: wire passed through the heart
- Pulmonary Hypertension
 - dyspnea- due to increase direct blood flow to the heart

Next Day labs

- Team will get a CBC, CMP, INR to check for Liver Failure, bleed, or renal failure
- Expect a rise in AST and ALT due to ischemia. (500-1000 range)



Complications: Liver Failure



<https://humanbodyanddiseases.weebly.com/cirrhosis.html>

- Patients with MELD >18 or Child-Pugh Class C
 - Risk for acute decompensation!
 - There are cases in which patients need to undergo transplant evaluation prior to TIPS
- Definition of failure according to UTD
 - ≥ 3 fold increase in total bilirubin
 - ≥ 2 fold increase in INR
- Occurs in 20% of cases

Complications- Encephalopathy

- Encephalopathy- up to 44% of patients¹
- Why does this happen?
 - Shunting blood from portal to systemic circulation- blood does not get filtered
- Risk Factors for Post TIPS Encephalopathy
 - Hyponatremia
 - Sarcopenia
 - Older age
 - **Prior history of HE**



Complications- Encephalopathy

- **Management**

- Same as in other settings- evaluate for precipitating factors and treat
- Lactulose and Rifaximin
- Revising the Shunt by making it narrower to reduce the amount of blood being diverted





TIPS Dysfunction

- Definition: Loss of decompression of the portal venous system due to occlusion or Stenosis
- Patient will present with recurrent ascites or variceal bleeding
- **Check Doppler!**
- Will need Revision or Anticoagulation

TIPS Summary

- TIPS stands for Transjugular Intrahepatic Portosystemic Shunt
- Relieves portal hypertension by creating a low resistance path from the portal vein to the hepatic vein via a shunt
- Indication for TIPS: recurrent ascites, recurrent bleeding, active bleeding but is typically not first line treatment
- Contraindications include heart failure and severe liver dysfunction
- Complications after procedure include liver failure and hepatic encephalopathy
- If ascites or recurrent bleeding reoccurs it is typically due to occlusion or stenosis

Resources

1. Brown, R. S. (2013). *Common liver diseases and transplantation: An algorithmic approach to work-up and management*. Thorofare, NJ: Slack.
2. UptoDate
3. Hopkins Medicine. Portal Hypertension. Retrieved October 10, 2020, from https://www.hopkinsmedicine.org/gastroenterology_hepatology/_pdfs/liver/portal_hypertension.pdf

Questions?



Left to Right: Ivonne, Lauren, Anne, Whitney