

Liver Function	Manifestations of Altered Function
Production of bile salts	Malabsorption of fat and fat-soluble vitamins
Elimination of bilirubin	Elevation of serum bilirubin and jaundice
<i>Metabolism of steroid hormones</i> Sex hormones Glucocorticoids Aldosterone	Disturbances of gonadal function Signs of increased cortisol levels (Cushings) Signs of hyperaldosteronism (Na retention and hypoK)
Metabolism of drugs	Decreased drug metabolism Decreased plasma binding of drugs owing to a ↓ in albumin production
Carbohydrate metabolism	HypoG may develop d/t impaired glycogenolysis and gluconeogenesis
Stores glycogen and synthesizes glucose from AA, lactic acid and glycol	Abnormal glucose tolerance curve may occur d/t impaired uptake and release of glucose by the liver
Fat metabolism	impaired synthesis of lipoproteins, altered cholesterol levels
<i>Protein metabolism</i> formation of urea from ammonia synthesis of plasma proteins synthesis of clotting factors	Elevated blood ammonia levels Decreased levels of plasma proteins (albumin) → edema Bleeding tendencies
Storage of minerals & vitamins	Deficiency of fat-soluble and other vitamins that are stored in liver
Filtration of blood and removal of bacteria and particulate matter by Kupffer cells	Increased exposure of the body to colonic bacteria and other foreign matter

Why is the protein function so important?

The liver has the greatest rate of protein synthesis per gram per tissue. It produces proteins for its own cells to use and secretes proteins into circulation, the most important of which is ALBUMIN. Albumin contributes significantly to plasma colloidal osmotic pressure, and to the binding and transport of many substances (hormones, fatty acids, bilirubin, other anions).

Why is bile such a big deal?

The secretion of bile is essential for the digestion of dietary fats and the absorption of fats and fat-soluble vitamins from the intestine. Bile is made u of water, bile salts, bilirubin, cholesterol, fatty acids, lecithin and electrolytes. The bile salts are the ones that are responsible for digestion and the liver makes about 0.6g of them each day. Most of these salts that enter the intestine are reabsorbed into the portal circulation and go to the liver where they are recycled. They'll follow this circular route about 18 times before they are expelled into the feces.

Cholestasis is a decrease in bile flow and a reduction in the secretion of water, bilirubin and bile acids by the hepatocytes. As a result, the materials that are normally transferred to the bile (bilirubin included) accumulate in the blood. This can be caused by intrahepatic disease or an obstruction. A common feature to all types of obstruction and hepatocellular cholestasis is the accumulation of bile pigment in the liver. The most common presentation of this is pruritis, d/t an increase of bile acids in the blood.

Bilirubin

Bilirubin is what gives bile its color. It comes from old, broken-down red blood cells. In the process of breaking down these blood cells for recycling or excretion, the heme group is broken down to form biliverdin which is rapidly converted to UNCONJUGATED bilirubin. The unconjugated bilirubin goes to the liver where it moves into the hepatocytes. Inside the hepatocytes, the free bilirubin is converted to CONJUGATED bilirubin and secreted as a constituent of bile. In the intestine about half of the bilirubin is converted to urobilinogen. This urobilinogen is either absorbed back into portal circulation or excreted in feces. Only a small amount is absorbed into general circulation and excreted by the kidneys.

Jaundice

Jaundice results when there is a lot of bilirubin in the blood. Because bilirubin is attracted most to elastici tissue, it is usually first noted in the slcera of the eye.

There are four major causes of jaundice:

- 1) excessive destruction of RBCs
- 2) impaired uptake of bilirubin by the liver
- 3) decreased conjugation of bilirubin
- 4) obstruction of bile flow

Jaundice can be characterized as pre-hepatic, intra-hepatic and post-hepatic. Common causes are:

- Pre-hepatic: hemolytic blood transfusion rxn, hereditary disorders of the RBC, hemorrhage (I think), autoimmune hemolytic anemias
- Intra-hepatic: decreased bilirubin uptake by the liver, decreased conjugation inside the liver, hepatocellular liver damage (hepatitis, cirrhosis, caner of the liver), drug-induced cholestasis
- Post-hepatic (obstruction of bile flow): structural disorders of the bile duct, cholelithiasis, bile duct obstruction

Disorders of Hepatic and Biliary Function (briefly)

- Hepatitis A
 - Usually is benign, does not cause chronic hepatitis or induce a carrier state.
 - Brief incubation period, travels via oral-fecal route
 - Vaccine available
- Hepatitis B
 - Can produce acute, chronic, or fulminating hepatitis; can lead to cirrhosis; this person is a carrier.
 - Participates in the development of Hep D
 - 4-6 week incubation period; travels via blood or serum, sexual contact, oral contact
 - Vaccine available
- Hepatitis C
 - Most common cause of chronic hep, cirrhosis and hepaticellular cancer in the world
 - 2-26 week incubation, blood-borne route
 - No vaccine
- Hepatitis D
 - Infection depends on concurrent infection with Hep B
 - Route of transmission similar to Hep B route
 - Get Hep B vaccine
- Hepatitis E
 - Transmitted by oral-fecal route
 - Manifestations of acute hepatitis similar to Hep A
 - Does not cause chronic hepatitis or a carrier state
 - Its distinguishing feature is the high mortality rate (20%) among pregnant women
 - Endemic areas are India and other Southeast Asian countries, parts of Africa and Mexico

Acute Hepatitis	Chronic Hepatitis
Asymptomatic acute infection often seen with Hep C Three phases: prodromal, icteric, convalescent Prodromal = flu-like, anorexia out of proportion to illness Icteric = jaundice, pruritus, liver tenderness Convalescent = return of appetite, jaundice goes away, feel better	Symptoms are highly variable Many are asymptomatic at time of Dx Elevated ALT may be first sign Fatigue, malaise, loss of appetite, occasional jaundice

- Alcoholic Liver Disease
 - spectrum of diseases are fatty liver disease, alcoholic hepatitis, cirrhosis
 - most deaths from alcoholic cirrhosis are d/t liver failure, bleeding esophageal varices, or kidney failure
 - three stages of changes: fatty changes (fatty liver), alcoholic hepatitis and cirrhosis
- Cirrhosis
 - Cirrhosis is the end-stage of chronic liver disease
 - Much of the functional tissue has been lost and been replaced by fibrous tissue
 - This fibrous tissue forms constricting bands that disrupt flow in the vascular channels and biliary duct systems
 - This leads to:
 - portal hypertension and its many, many complications
 - obstruction of biliary channels
 - loss of liver cells
 - Manifestations range from asymptomatic hepatomegaly to hepatic failure; often no symptoms until disease is advanced
 - weight loss (can be masked by ascites)
 - weakness
 - anorexia
 - jaundice is mild at first and increases in severity
 - possible abd pain d/t liver enlargement
 - late manifestations are r/t portal hypertension and liver failure: splenomegaly, ascites, portosystemic shunts
 - other late complications are: bleeding, thrombocytopenia, gynecomastia, spider angiomas, palmar erythema, encephalopathy with asterix and neurologic signs

Complications of Cirrhosis

- Portal Hypertension
 - characterized by increased resistance to flow in the portal venous system and elevated portal venous pressure
 - normally, venous blood returning to the heart from the abdominal organs collects in the portal vein and travels through the liver before entering the vena cava.
 - Pre-hepatic causes of portal hypertension = portal vein thrombosis; compression on the vein (tumor)
 - Intra-hepatic causes = conditions that obstruct blood flow within the liver (fibrous tissue of cirrhosis)
 - Post-hepatic causes = any obstruction beyond the liver lobules (thrombosis, severe right-sided heart failure, veno-occlusive disease)
 - Complications of portal hypertension arise from:
 - increased pressure and dilation of veins behind the obstruction
 - collateral channels that open to connect portal circulation with the systemic circulation
 - these main problems are ascites, splenomegaly, and the formation of portosystemic shunts with bleeding from esophageal varices
- Ascites
 - Late-stage manifestation of cirrhosis and portal hypertension
 - A person could have 15 L in there! Very uncomfortable...dyspnea, insomnia, difficulty walking
 - Several factors contribute to fluid accumulation:
 - increase in capillary pressure d/t portal hypertension
 - obstruction of venous flow through the liver

The Mighty Liver (pg 4 of 5)

- salt and water retention by the kidney (Recall that the liver is not metabolizing aldosterone properly. This leads to an increase in salt and water retention by the kidneys)
- decreased colloidal osmotic pressure r/t low albumin. this limits reabsorption of the fluid from the peritoneal cavity.
- Treatment of ascites:
 - dietary restriction of sodium
 - give Lasix and Spironolactone
 - give oral potassium supplements
 - bedrest b/c the upright position is associated with activation of the renin-angiotensin-aldosterone system
 - paracentesis (may give albumin concurrently)
 - TIPS procedure
- Splenomegaly
 - The spleen enlarges b/c of shunting of blood into the splenic vein.
 - The spleen is now bigger than usual and now it takes longer for the blood to travel through it. As the blood travels through the spleen some of it is removed or filtered out. If the spleen is larger than it is supposed to be, there is an increased rate of removal of RBCs. An example would be that it takes you longer to walk through Arden Fair Mall than it does your local Albertsons....the mall is simply larger. As you walk through the grocery store you spend money on the things that are there. If you walk through the mall, you spend more more because there are more items there. So, when you shop at Albertsons you lose \$50, but if you shop at the mall you lose \$200. Make sense?
 - So, with splenomegaly you will have a decrease in all formed elements of the blood leading to anemia, thrombocytopenia and leukopenia.
- Portosystemic Shunts
 - Large collateral channels develop between the portal and systemic veins that supply the lower rectum and esophagus and the umbilical veins on the anterior of the abdomen. (If these are dilated you have caput medusae).
 - Portopulmonary shunts can also develop that bypass the pulmonary capillaries leading to decreased oxygenation.
 - The most important collateral channels are those connecting the portal and coronary veins that lead to reversal of flow and formation of thin-walled varices in the esophagus.
 - These esophageal varices are prone to rupture and can produce fatal hemorrhaging. The risk of this is compounded even more b/c you have reduced PLT and clotting factors.
 - 65% of pts with advanced cirrhosis have these; half of them will die b/c of hemorrhage.

Liver Failure

The most severe consequence of liver disease is liver failure. 80-90% of function must be lost before liver failure occurs. Manifestations reflect alterations in the various functions of the liver. Feto hepaticus (foul liver breath) results from the metabolic byproducts of the intestinal bacteria.

- Hematologic Disorders
 - anemia, thrombocytopenia, coagulation deficits, leukopenia
 - anemia can be caused by blood loss, excessive RBC destruction, impaired formation of RBCs
 - folic acid deficiency can lead to anemia also
 - bleeding disorders are d/t declines in clotting factors
 - malabsorption of fat-soluble Vit K leads to further clotting troubles
 - thrombocytopenia results from splenomegaly
- Endocrine Disorders
 - liver metabolizes steroid hormones and these levels are often elevated in liver failure
 - decrease in aldosterone metabolism may contribute to salt/water retention by kidneys
 - disturbances in gonads are common, as is loss of libido and impotence d/t increased androgens in women and increased estrogen in men
- Skin Disorders
 - vascular spiders, telangiectases, spider angiomas and spider nevi are seen most often on upper half of body. they consist of a central pulsating arteriole from which smaller vessels radiate
 - palmar erythema is redness of the palms d/t increased blood flow from higher cardiac output
 - jaundice is usually a late sign

The Mighty Liver (pg 5 of 5)

- Hepatorenal Syndrome
 - Renal failure sometimes seen during the terminal stages of liver failure with ascites.
 - Characterized by progressive azotemia, increased serum creatinine, and oliguria
 - Cause is believed to be a decrease in renal blood flow
 - Thought to contribute to hepatic encephalopathy and coma
- Hepatic Encephalopathy
 - Characterized by neural disturbances: lack of mental alertness, confusion, coma, convulsions
 - Very early sign is asterixis (flapping tremor)
 - Includes memory loss, personality changes, euphoria, irritability, anxiety
 - Speech may be impaired
 - Caused by accumulation of neurotoxins, mainly ammonia
 - Can be treated with neomycin (to kill gut bacteria) and lactulose (to bind it up and poop it out)