Hepatic Physiology

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Physiology Education Series

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Outline

- Anatomy and blood supply of the liver
- Physiologic immaturity of hepatic function
- Mechanisms of hepatic regeneration
- Hepatic serum protein synthesis
- Hepatic carbohydrate metabolism
- Hepatic fatty acid metabolism
- Biochemical parameters of hepatic integrity
- Pathways of hepatic drug metabolism
- Bilirubin uptake, metabolism, excretion
- Portal hypertension
- Board review questions

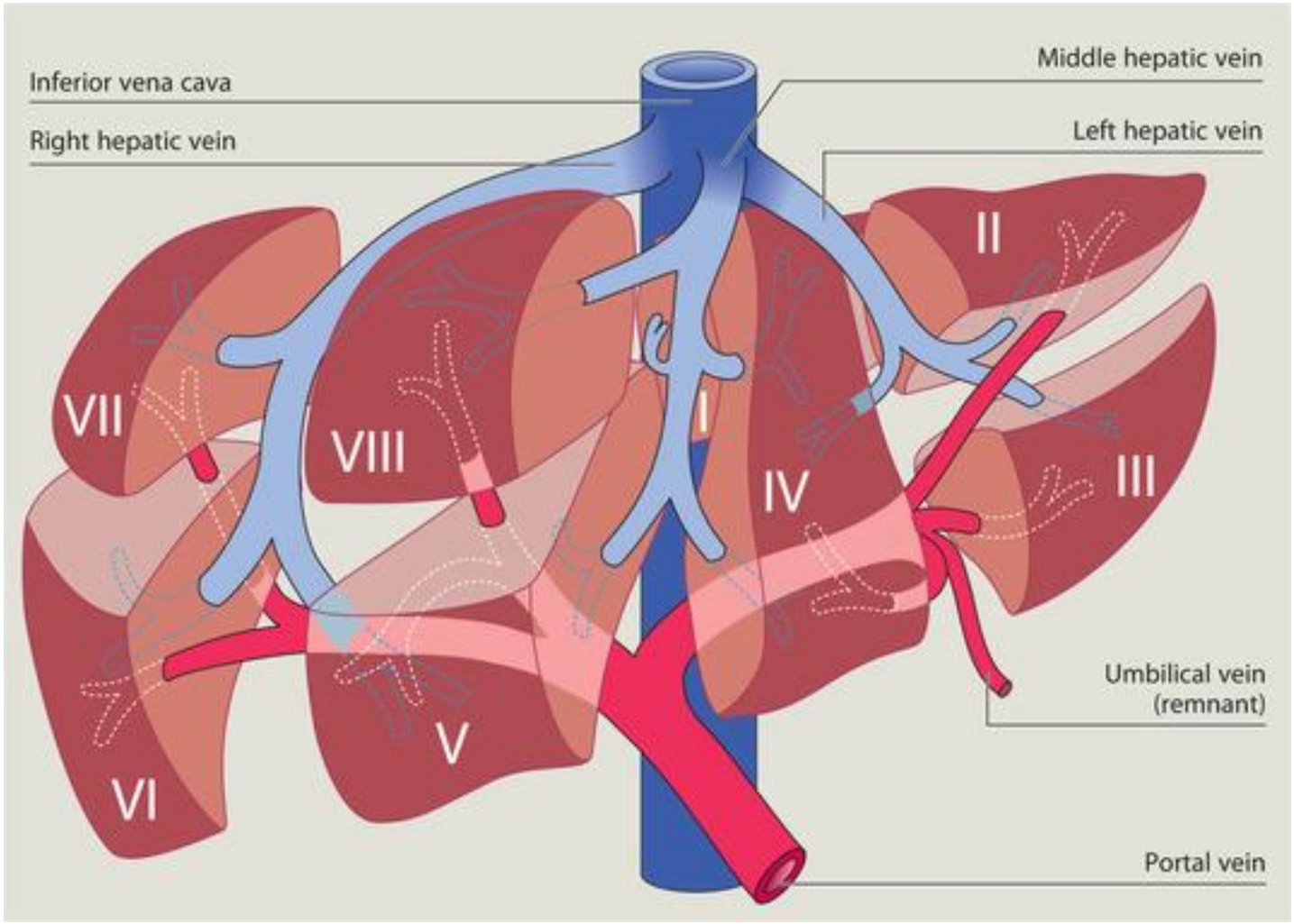
Segmental anatomy of the liver

- Couinaud (“French” system)
  - based on tranverse plane through bifurcation of mail portal vein
  - Functional lobes divided into total of 8 subsegments
    - Caudate 1
    - Lateral 2,3
    - Medial 4a, 4b
    - Right 5,6,7,8
  - Caudate lobe is separate, receiving blood flow from R and L -sided vasculature

Blood supply liver

- Hepatic artery (25%) – oxygenated
- Hepatic portal vein (75%) – deoxygenated blood, nutrient- rich
- Oxygen comes equally form both sources
- Terminal branches of hepatic portal vein and hepatic artery empty together and mix entering the liver
- Blood flows through liver sinusoids, empties into central vein of each lobule
- Central veins coalesce into hepatic veins
- Blood exits liver via hepatic vein and returns to the heart via IVC, deoxygenated and detoxified

Blood supply and segments of the liver



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Extramedullary hematopoiesis

- Until 32 weeks of gestation in fetal development, hematopoiesis occurs primarily by the liver (and also the spleen)

Physiologic Immaturity of hepatic function

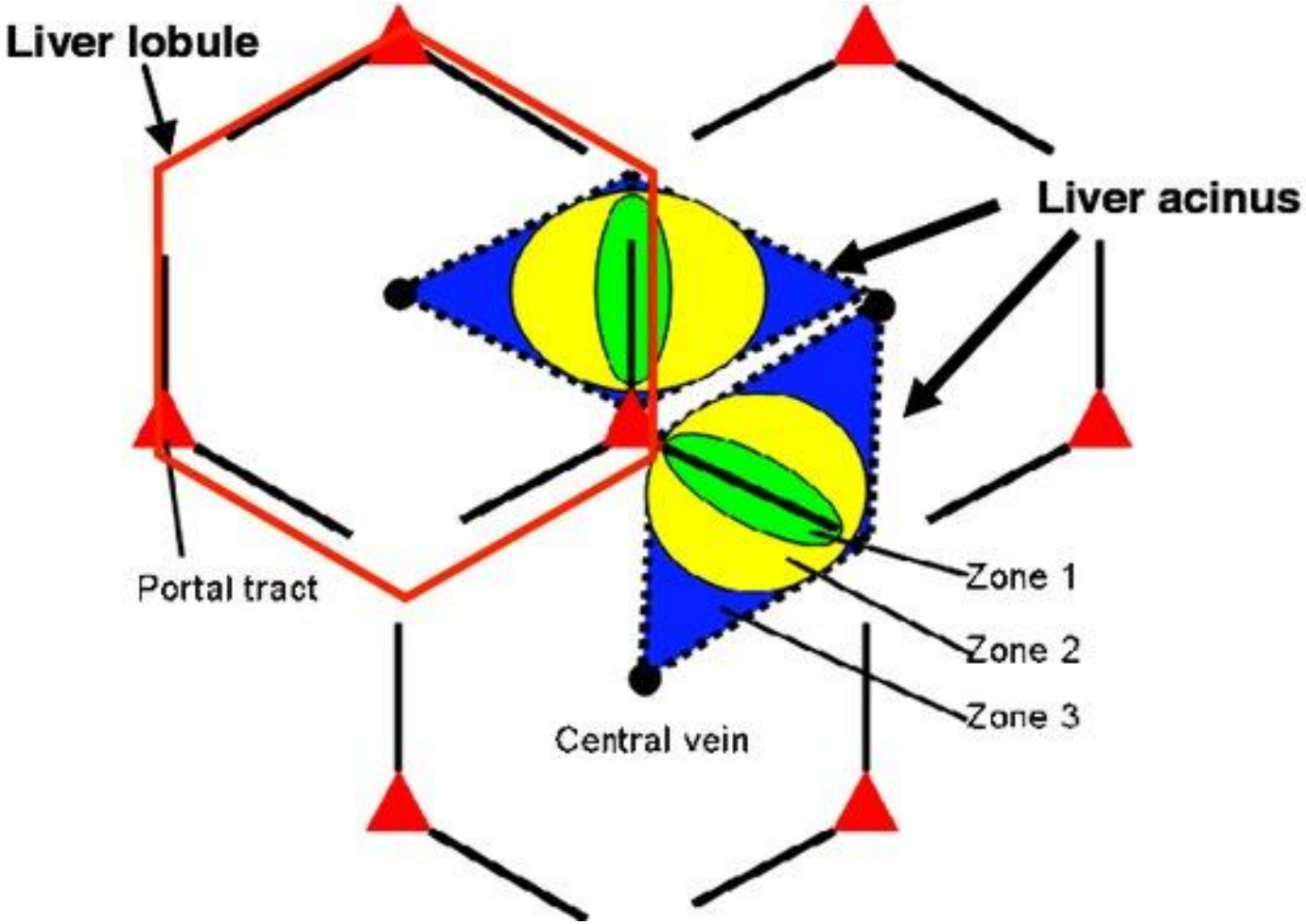
- Full maturity of biliary secretion takes up to 2 years after birth to be achieved
- Involves normal expression of signalling pathways including JAG1 genes, amino acid transport, insulin growth factors
- Hepatocytes are specialized at birth with 2 surfaces:
  - Sinusoidal surface absorbs mixture of oxygenated blood and nutrients from portal vein
  - Other surface delivers bile and products of conjugation, metabolism to bile canaliculi

Physiologic Immaturity of hepatic function

- With interruption of umbilical supply at birth, rapid induction of transamination, glutamyl transferase, coagulation factor synthesis, bile production and transport
- Preterm infants have immaturity and delay in achieving normal detoxifying and synthetic function, risk of hypoxia and sepsis – all placing them at risk for hepatic decompensation

Lobule and its zones

- 3 distinct zones of the hepatic acinus:
  - Zone 1: periportal hepatocytes
    - Hepatocyte regeneration
    - Bile duct proliferation
    - gluconeogenesis
  - Zone 2: mixed function between zones 1 and 3
  - Zone 3: borders central vein
    - Detoxification
    - Glyocolysis
    - Hydrolysis



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Hepatic Regeneration

- In fully developed liver, only 1/10-20,000 hepatocytes are dividing
- As little as 25% of liver can regenerate a full liver
- If stimulated, the liver can regenerate rapidly:
  - Viruses
  - Cirrhosis
  - Ischemia
  - Trauma
  - Partial hepatectomy

Hepatic Regeneration

- Requires new hepatocyte recruitment and ECM restoration
- IL-6, epidermal growth factor (EGF), TGF-a, TGF-B hepatocyte growth factor (HGF): initiation and regulation of regeneration
- EGF works with insulin and glucagon to promote hepatocyte DNA synthesis

Liver Protein synthesis

- Plasma proteins
  - Alpha-fetoprotein (AFP), fibronectin, C-reactive protein, opsonin, acute phase proteins, globulins
- Hemostasis, fibrinolysis
  - All coagulation cascade (except factor VIII – endothelium), alpha1 antitrypsin, antithrombin III, protein C and S, plasminogen, complement components
- Hormones, prohormones
  - IGF-1, thrombopoietin, angiotensinogen
- Carrier proteins
  - Albumin, ceruloplasmin, transcortin, haptoglobin, hemopexin, IGF binding protein, retinol binding protein, sex hormone binding globulin, thyroxine-binding globulin, tranferrin, vitamin D binding globulin
- Apolipoproteins
  - All except apo B48 (intestine)

Taurine

- Conditionally essential amino acid in early life
- Essential amino acid for preterm/newborn infants and assured by breast milk
- Diet is usual source, but in presence of vitamin B6, synthesized from methionine and cysteine
- Patients on chronic TPN are at risk of taurine deficiency and need supplementation
- Also at risk are those with hepatic, cardiac and renal failure
- Taurine involved in bile acid conjugation and cholestasis prevention

Hepatic carbohydrate metabolism

- Gluconeogenesis
  - Synthesis of glucose from amino acids, lactate, glycerol
- Glycogenolysis
  - Breakdown of glycogen into glucose
- Glycogenesis
  - Formation of glycogen from glucose

Fatty acids and lipid transport

- Triglycerides absorbed as free fatty acids (FA), packaged in chylomicrons/liposomes released through lymphatic system into the blood and binding to hepatocytes
- Liver processes chylomicron remnants and liposomes into VLDL and LDL
- FA synthesized by the liver get converted to triglycerides and are transported into the blood as VLDL
- In peripheral tissue, lioprotein lipase converts VLDL to LDL and free FA by removing triglycerides
- The remaining VLDL then becomes LDL, absorbed by LDL receptors
- LDL is then converted into free fatty acids, cholesterol
- Liver controls serum cholesterol concentration by removal of LDL
- HDL carries cholesterol from the body back to the liver to be broken down and excreted

Hepatocyte biochemical parameters

- Hepatocellular injury –
  - membranes of hepatocytes become permeable when damaged
  - alanine aminotransferase (ALT) and aspartate aminotransferase (AST) escape into bloodstream
- Cholestasis –
  - obstructed/damaged intra- and extra- hepatic bile ducts
  - induction of alkaline phosphatase and gamma-glutamyl transferase (GGT)

Hepatic drug metabolism

- Mostly in the smooth endosplasmic reticulum of the liver
- Factors that increase and decrease drug biotransformation affect enzymes in the Cytochrome P450 monooxygenase system
- Phase 1 (utilized by acetaminophen and steroids)
  - Oxidation: cytochrome P450 and flavin-containing monooxygenase, alcohol and aldehyde dehydrogenase, monoamine oxidase, peroxidase
  - Reduction: NADPH P450 reductase, reduced (ferrous) cytochrome P450
  - Hydrolysis: esterase, amidase, epoxide hydrolase
- Phase 2 (detoxifying)
  - Conjugation reactions
  - Methylation, sulphation, acetylation, glucuronidation, glutathione and glycine conjugation

Clinical vignette: acetaminophen toxicity

- Acetaminophen metabolism: normal dose
  - Phase II metabolism: sulfate and glucuronide metabolism
  - Cytochrome P450: only 5% of acetaminophen converted to NAPQI
  - NAPQI detoxified via glutathione conjugation to cysteine and mercapturic acid conjugates

Clinical vignette: acetaminophen toxicity

- In acetaminophen toxicity:
  - Phase II metabolism becomes saturated
  - Shunted to P450 pathway
  - Glutathione becomes depleted and NAPQI remains in toxic form
  - Damages hepatocyte cell membrane and leads to acute hepatic necrosis
  - Made worse with chronic alcohol use, concomitant use of anti-epileptics, large amounts of caffeine
  - *N*-acetylcysteine replenishes body stores of glutathione and is treatment for acetaminophen toxicity

Bilirubin metabolism

- Formed by breakdown of heme (80% from hemoglobin, 20% from other hemoproteins)
- Heme –via heme oxygenase—biliverdin---via biliverdin reductase---bilirubin IX alpha
- Heme oxygenase is rate-limiting step in bilirubin production
- Heme oxygenase is found in Kupffer cells of the liver and reticuloendothelial cells of the spleen

Bilirubin metabolism

- Albumin binds to bilirubin, reversible except in states of bilirubin obstruction/conjugated bilirubinemia
- Albumin-bilirubin complex dissociates in liver sinusoids where bilirubin is taken up by hepatocytes
- This is via facilitates diffusion, bidirectional
- Defects in transporters in these steps cause hyperbilirubinemia (eg Gilbert’s)
- Unconjugated hyperbilirubinemia also results from cirrhosis when bilirubin produced from the spleen bypasses the liver via portosystemic collaterals

Bilirubin conjugation

- Bilirubin poorly water soluble because of internal hydrogen bonding which makes it toxic and prevents its elimination
- Glucuronic acid conjugation of bilirubin makes it water-soluble and excretable into bile
- Phototherapy in neonatal jaundice produces configurational and structural bilirubin photoisomers, excreted into bile without further metabolism

Bilirubin conjugation

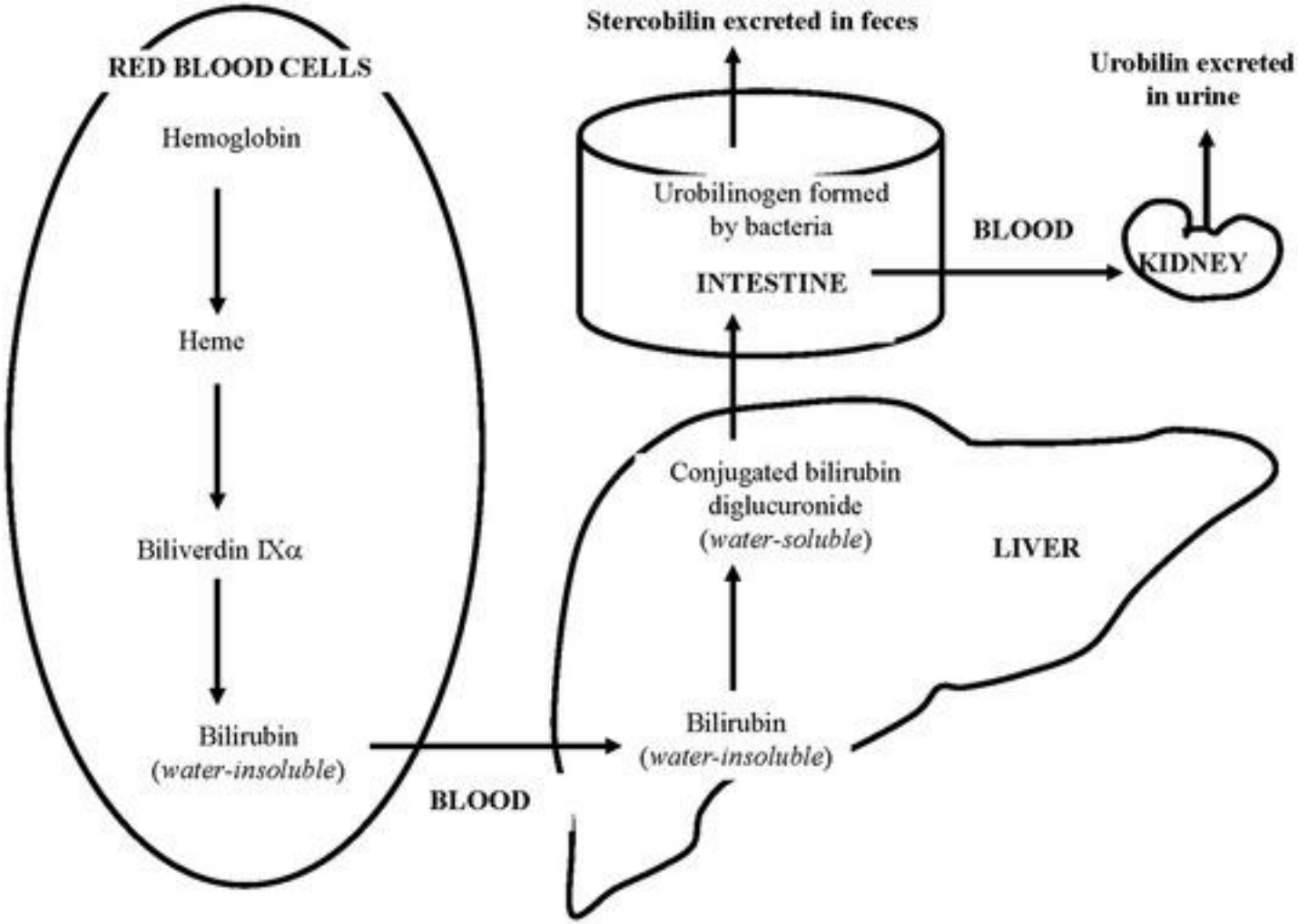
- Mediated by a family of enzymes called uridine-diphosphoglucuronate glucuronosyltransferase (UGT)
- UGT1A1 is the main enzyme of conjugation
- UGT1A1 deficiency – Gilbert's and Crigler-Najjar syndromes
- Inhibition of UGT1A1 can occur via a factor in breast milk (breast milk jaundice)
- Inhibitory factor from maternal plasma can be transferred to fetus transplacentally (Lucey Driscoll syndrome)
  - Inhibits UGT1A1 activity in newborn
  - Results in unconjugated hyperbilirubinemia

Bilirubin excretion

- Conjugated bilirubin is excreted in bile across the bile canalicular membrane via active transport
- 4 types of transporters (eg MRP2, ABCC2)
- Excretion impaired by viral hepatitis, cholestasis of pregnancy, Dubin-Johnson and Rotor syndrome

Bilirubin degradation

- 98% of the bile pigment in bile is conjugated and is water-soluble and will not be absorbed across lipid membrane of small intestinal epithelium
- Unconjugated fraction is partially reabsorbed through enterohepatic circulation
- Bilirubin is reduced by bacterial enzymes in the colon to urobilinoids (urobilinogen and stercobilinogen)
- Intestinal microflora influence serum bilirubin levels and antibiotic use can increase serum bilirubin levels



From Trowers and Tischler *Gastrointestinal Physiology* 2014 in SpringerImages database (non-commercial use permitted)

Bilirubin metabolism in newborns

- Generally infants not jaundiced at birth because placenta can clear bilirubin well from the fetal circulation, but can develop jaundice because
  - Bilirubin production in term neonates is 2-3 times higher than adults because they have more red blood cells and the the red blood cells have a shorter life span than in adults
  - Bilirubin clearance is decreased in neonates because of UGT1A1 deficiency and does not achieve adult levels until 14 weeks of age
  - Neonates have an increase in the enterohepatic circulation of bilirubin

Clinical vignette: breastmilk jaundice

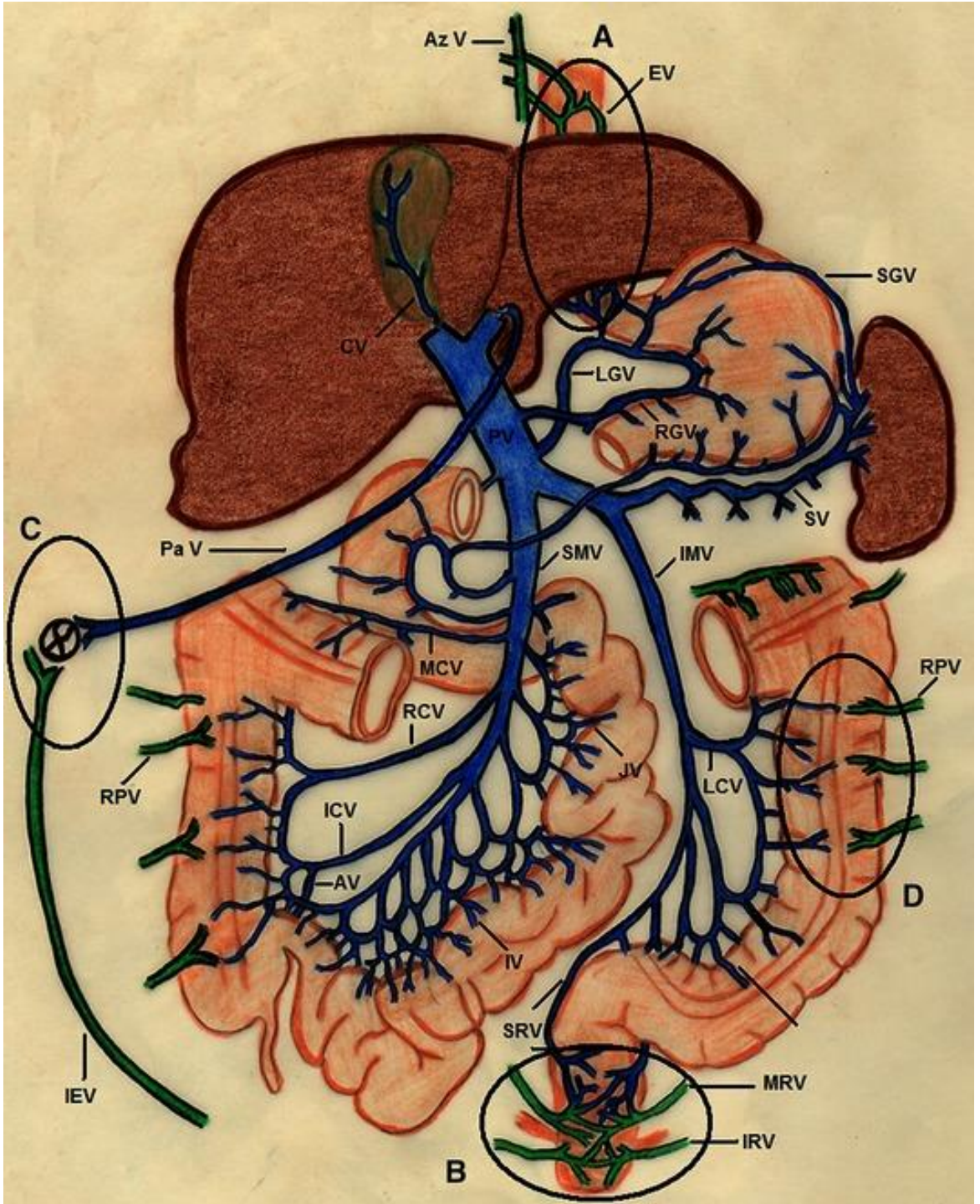
- Starts at 10-21 days of age (after physiologic jaundice period)
- Effects 0.5-2.4% of newborns
- Can last 3-12 weeks
- Theory: factor in breast milk is inhibiting breakdown of bilirubin
- As long as infant is feeding and growing and bilirubin is being monitored, no reason to stop breastfeeding

Portal hypertension

- Portal system definition: begins and ends with capillaries
- Liver portal system: capillaries of intestinal and splenic mesentery ending in the hepatic sinusoids
- Portal hypertension: elevation of portal blood pressure >5 mm Hg
- Because of high prevalence of pediatric biliary disease compared to adult liver disease, portal hypertension occurs earlier in the course of liver disease versus hepatic insufficiency

Portal hypertension

Physiologic porto-systemic anastomoses. Portal circulation in blue, systemic circulation in green



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Portal hypertension

- Combination of increased portal resistance and/or increased portal blood flow
  - Splenomegaly/hypersplenism – congestion
  - Esophageal and rectal varices – decompression through portosystemic collaterals
  - Decompression leads to hepatic encephalopathy and hepatopulmonary syndrome
  - Portal hypertension leads to ascites and complications: peritonitis and hepatorenal syndrome

Portal hypertension

- Hepatic encephalopathy
  - Reversible impairment in neuropsychiatric function
  - Pathogenesis unclear
    - Increase in ammonia concentration
    - Inhibitory neurotransmitter through GABA receptors in the CNS
    - Changes in central neurotransmitters and amino acids

Portal Hypertension

- Hepatopulmonary syndrome
  - Triad: liver disease, impaired oxygenation, intrapulmonary vascular dilatations
- Hepatorenal syndrome
  - Usually from portal hypertension from cirrhosis, but also in fulminant hepatic failure
  - Diagnosis of exclusion of acute renal failure
  - Associated with poor prognosis
  - Increasingly severe hepatic injury results in reduction in renal perfusion

Summary

- The liver is organized by its vascular supply into segments, and has a unique blood supply that includes arterial and ‘venous’ blood (portal system) draining the intestine, pancreas, and spleen.
- The microscopic functional unit is the liver lobule, composed of hepatocytes, vessels, and bile ducts, organized in a fashion that promotes the functions of the liver.

Summary-2

- The liver produces the majority of serum proteins, ranging in function from albumin to sex hormone binding proteins to numerous clotting factors.
- Liver glucose storage, breakdown, and generation maintain serum glucose in a physiologic range
- Serum lipoprotein make up and content is heavily influenced by liver synthesis and uptake of lipoproteins.
- Drug metabolism occurs in hepatocytes via phase I and/or phase II enzyme systems– a goal of which is to produce chemical structures which are excretable in the bile.

Summary-3

- Bilirubin metabolism is a robust example of a waste product biotransformed into a substance that can then be excreted in the bile. Particular enzymes are responsible for bioconversion and transport.
- Portal hypertension is a pathophysiologic state established by the existence or development of resistance to portal blood flow toward the liver.

Board review question

- A 16 year old female presents to the ER with RUQ abdominal pain, nausea and malaise. She has a history of depression and seizure disorder. AST and ALT are greater than 10,000 IU/L. She admits to taking acetaminophen for a headache the night before. What of the following is true:
- A. checking a serum acetaminophen level before 4 hours of ingestion is generally helpful
- B. Concomitant use of anti-epileptic medications is protective for her liver
- C. If the patient has presented less than 8 hours of ingestion, NAC reduces risk of hepatotoxicity and improves survival
- D. all of the above

Board review question

- A 3 day old full term breast-fed infant is noted to have jaundice. He is otherwise behaving normally and has normal-colored urine and stools. There was no ABO or Rh incompatibility. The most likely reason for the jaundice is:
- A. biliary atresia
- B. a factor in the maternal breast milk that is inhibiting UGT1A1
- C. inadequate milk intake and dehydration
- D. none of the above

Please send any questions or comments to:

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or

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