HEPATITIS

A BRIEF SCIENCE REFRESHER

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CONTINUING EDUCATION

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LEARNING OBJECTIVES

Upon completion of this course, learners should be able to:

- Describe the normal anatomy of the liver
- Describe the functions of the liver
- Describe the serum tests used to measure liver function (normal and abnormal)
- List other causes of hepatitis that are not viral, auto-immune, or alcohol related (drug-induced, metabolic, etc.)
- Describe the etiology, epidemiology, pathophysiology of alcoholic & autoimmune hepatitis
- Describe the etiology, epidemiology, pathophysiology of viral hepatitis (A, B, C, D, & E)

CONFLICTS OF INTEREST

I have no conflicts of interest to report and attest that I have no financial relationship with any commercial interests relevant to this presentation and received no monetary support for providing this continuing education opportunity.

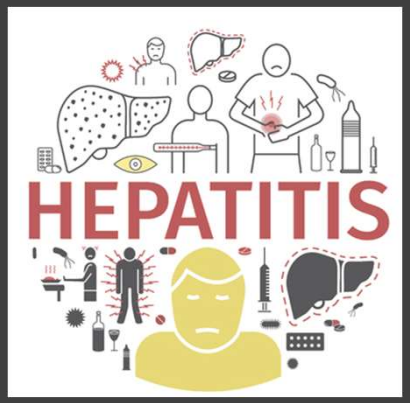

Figure 1: (Prockopenko, 2022)

ANATOMY OF THE LIVER

Location: The RUQ of the abdominal cavity (beneath diaphragm and atop the stomach and right kidney)

Weight: Approximately 1.3–1.8 kg (2.86-3.96 lb)

Height: 4–8 cm at the mid-sternal line, 6–12 cm at the right mid-clavicular line

Color: Reddish-brown

Anatomy: 4 lobes (right, left, caudate, and quadrate),
4 sectors (right anterior, right posterior, left medial and left lateral)
8 segments (Claude Couinaud classification)
Thousands of lobules made up of hepatocytes

Functional Construction: Segment I – the caudate lobe – is the posterosuperior part of the left medial sector.

Segment II is the posterosuperior segment of the left lateral sector.

Segment III is the anteroinferior part of the left lateral sector.

Segment IV includes the entire left medial lobe anteriorly, and the quadrate lobe viscerally. It is further subdivided into segments IVa and IVb. Segment IVa lies superiorly, while IVb lies inferiorly and corresponds with the location of the quadrate lobe.

Segment V forms the inferior part of the right medial sector.

Segment VI is the inferior part of the right lateral sector.

Sector VII is the superior aspect of the right lateral sector.

Sector VIII is the superior aspect of the right medial sector (Crumbie & Mytilinaios, 2021)

*Fun Fact: The liver contains about 450 mL or approximately one pint (13%) of the body's total blood volume at any time (Bickley et al., 2020)

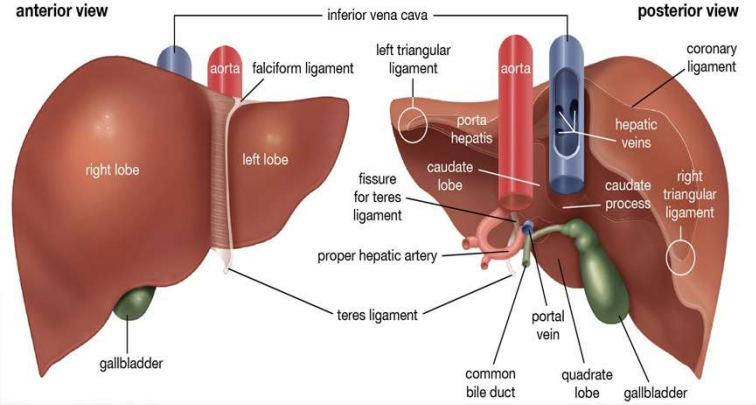

Figure 2: (Britannica, 2020)

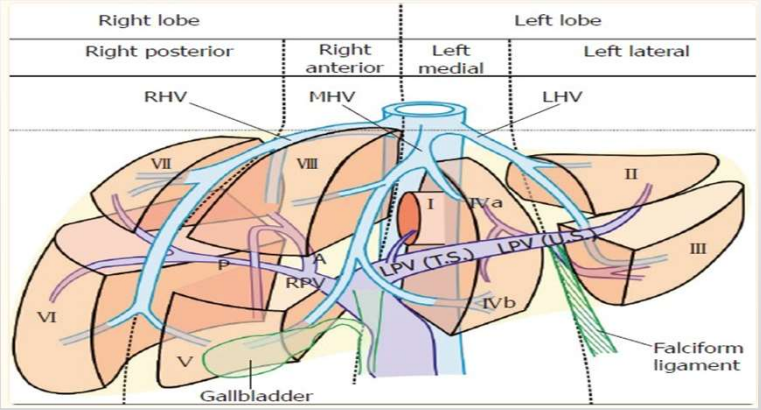

Figure 3: (Sharma et al., 2018)

ANATOMY OF THE LIVER

Assessment: Border is palpable in adults with inspiration

Coupled with percussion, size and consistency estimation of the liver is possible by clinicians

Vascular Flow: Hepatic Artery: Oxygenated blood flows in from the hepatic artery

Portal Vein: receives nutrient-rich blood and with digestive products from the intestines

Central veins: Permeate the lobules to allow cellular circulation and empties into hepatic vein

Hepatic sinusoids: Branch off central veins and receive blood from both hepatic artery and the portal vein

Cellular Structure: Epithelial Cells: allow nutrient transfer from the blood

Kupffer Cells: largest collection of tissue macrophages that seek and destroy bacteria entering the liver from the intestinal circulation

Canaliculi: collect bile produced by the hepatic cells and form a conduit to the bile ducts, located in the fibrous tissue between lobules

Space of Disse: areas that connect to the lymphatic vessels where excess fluid can be removed from the liver

(Bickley et al., 2020; Vernon et al., 2021)

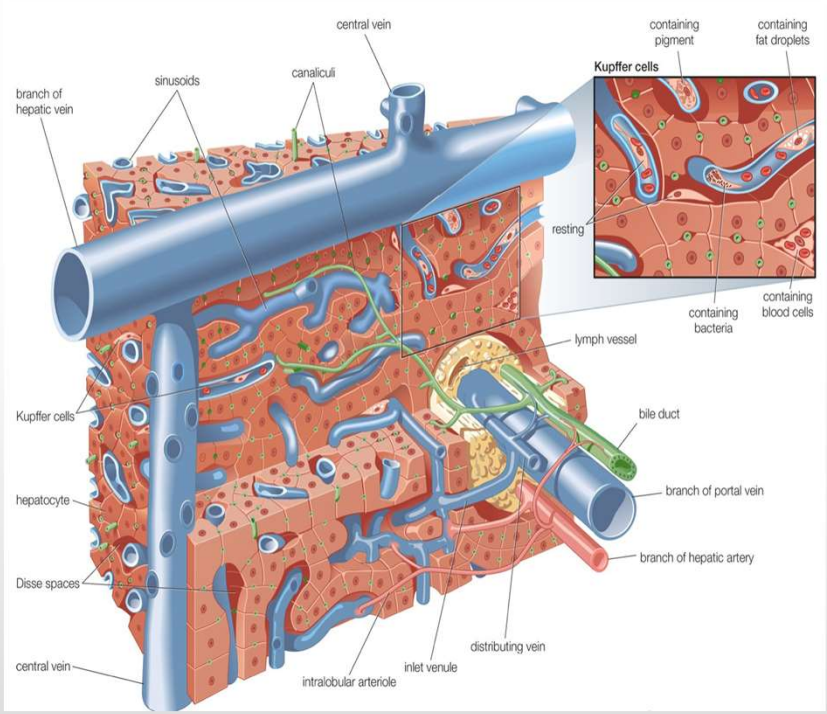

Figure 4: (Britannica, 2022)

FUNCTIONS OF THE LIVER

There liver takes part in HUNDREDS of functions in the human body including:

- Being both an active and passive reservoir for blood for hyper- and hypovolemic conditions
- Bile production to move waste products and emulsify fats in the small intestines
- Synthesis of cholesterol, lipoproteins, phospholipids and many proteins for blood plasma
- Carbohydrate metabolism and gluconeogenesis with glycogen storage
  (fructose & galactose→glucose; lactate, glycerol, amino acids→glucose)
- Production of hormones (ex. FGF21, IGF-1) and pro-hormones (angiotensinogen)
- Iron storage, regulation of iron via production of 25-amino acid peptide, hepcidin
- Production of blood clotting factors in hemostasis and fibrinolysis
  (all clotting factors, α1-antitrypsin, Proteins C & S, plasminogen, etc.)
- Regulation of serum amino acids levels
- Ammonia conversion to urea for renal excretion
- Filtering of the blood for medications, illicit drugs, alcohol, and other substances (ex. caffeine)
- Synthesis of immune factors and bacteria removal (interleukin-10 and transforming growth factor β (TGF-β),
- Bilirubin metabolism and canalicular excretion Storage of lipid-soluble vitamins A, D, E, K as well as $B_{12.}$

(Hall & Hall, 2020; John Hopkins Medicine, 2022)

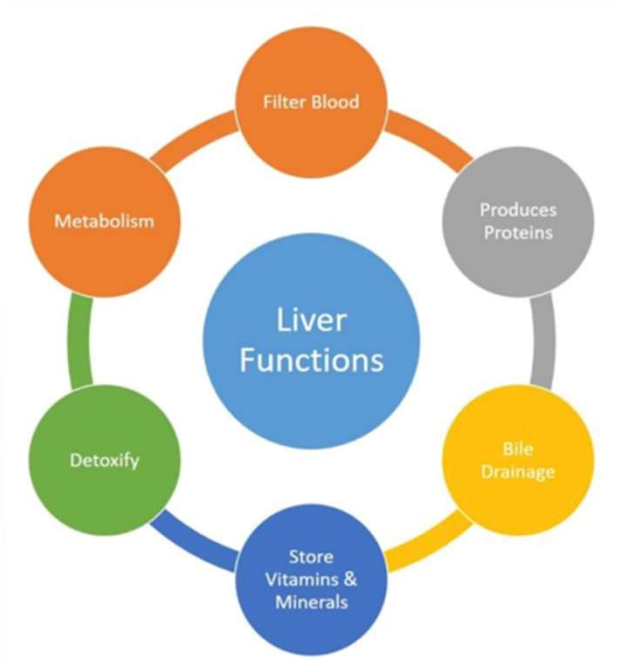

Figure 5: (BookmeriLab, 2022)

DIAGNOSTIC TESTS

Name	Abbreviation	Normal Range	Abnormal indications
Alanine transaminase	ALT	7 to 55 international units per liter (IU/L)	When the liver is damaged, ALT is released into the bloodstream and levels increase.
Aspartate transaminase	AST	8 to 48 IU/L	An increase in AST levels may indicate liver damage, disease or muscle damage.
Alkaline phosphatase	ALP	40 to 129 IU/L	Higher-than-normal levels of ALP may indicate liver damage or disease, such as a blocked bile duct, or certain bone diseases.
Albumin		3.5 to 5.0 grams per deciliter (g/dL)	Lower-than-normal levels of albumin and total protein may indicate liver damage or disease.
Total protein		6.3 to 7.9 g/dL	Lower-than-normal levels of albumin and total protein may indicate liver damage or disease
Total Bilirubin		0.1 to 1.2 milligrams per deciliter (mg/dL) (1.71 to 20.5 µmol/L)	Elevated levels of bilirubin (jaundice) might indicate liver damage or disease or certain types of anemia.
Direct (or Conjugated) Bilirubin		less than 0.3 mg/dL (less than 5.1 µmol/L)	Elevated levels of bilirubin (jaundice) might indicate liver damage or disease or certain types of anemia.
Gamma-glutamyltransferase	GGT	8 to 61 IU/L	Higher-than-normal levels may indicate liver or bile duct damage
L-lactate dehydrogenase	LD	122 to 222 IU/L	Elevated levels may indicate liver damage but can be elevated in many other disorders
Prothrombin time	PT	9.4 to 12.5 seconds	Increased PT may indicate liver damage but can also be elevated if you're taking certain blood-thinning drugs, such as warfarin.

(MFMER, 2022)

WHAT IS HEPATITIS?

Hepatitis means inflammation of the liver and there are MANY causes!

Infectious Causes

Viral	Bacterial	Fungi
Hepatitis A-E	Enterococcus	Candida
CMV	E. coli	Aspergillus
EBV	coagulase-negative Staphylococci	Cryptococcus neoformans
HSV	Staphylococcus aureus	Histoplasma capsulatum
VZV	Klebsiella pneumonia	Mucor
Coxsackievirus	Syphilis	Trichosporon
Adenovirus	Q fever	
Dengue virus	Yersinia	
Covid-19		
Yellow fever		
Parvovirus B19		
Rubella		
HHV6		

Non-infectious Causes

Toxins	Vascular	Pregnancy
Alcohol	Shock/hypotension	Acute Fatty liver of pregnancy
Idiosyncratic drug reactions	Hyperthermia	Pre-eclampsia
Acetaminophen	Acute Budd-Chiari Syndrome	HELLP syndrome
Amanita phalloides	Sinusoidal Obstruction Syndrome	
Carbon tetrachloride		
Sea anemone sting		
Congenital	**Autoimmune**	**Malignancy**
Hemochromatosis	Primary biliary cholangitis	Hepatocellular carcinoma
Alpha-1 Antitrypsin Deficiency	Primary sclerosing cholangitis	Metastatic disease
Wilson Disease	Autoimmune hepatitis	
Tyrosinemia		
Galactosemia		
Mitochondrial disorders		

Drug-induced Liver Injury (DILI)

Most Common Drugs Associated with DILI	
Acetaminophen	Rifampin
Amoxicillin-clavulanate	Cefazolin
Nitrofurantoin	Sulfonylureas
Isoniazid	Azithromycin
Minocycline	Fluoroquinolones
Trimethoprim-sulfamethoxazole	Diclofenac

(Waller, 2022)

ALCOHOLIC HEPATITIS (AH)

Etiology:

- Caused by excessive alcohol (ETOH) intake and a history of chronic heavy alcohol consumption until at least 3 to 4 weeks before the onset of jaundice, fever, tachycardia, tachypnea, hepatomegaly, leukocytosis with neutrophilia, and an AST:ALT ratio elevation with absolute AST/ALT typically <500 U/L (Shah et al., 2022)

-Acute, severe inflammatory form of alcohol-related liver disease (ALD), characterized by swollen, dying hepatocytes (i.e., ballooning degeneration), neutrophilic infiltration, development of Mallory-Denk bodies within hepatocytes, and activation of Kupffer cells (Osna et al., 2017)

- AH can occur at any stage of ALD, must distinguish from alcoholic steatohepatitis (histologically)

-National Institute on Alcohol Abuse and Alcoholism (NIAAA), Alcoholic Hepatitis Consortia defines alcoholic hepatitis:

- Onset of jaundice within 60 days of heavy alcohol consumption (more than 50 g/day) for a minimum of 6 months
- Total bilirubin more than 3 mg/dL
- ↑ AST of 50 U/L to 400 U/L
- AST:ALT ratio >1.5
- No other identifiable cause of acute hepatitis (Knight, 2021; Shah et al., 2022)

Figure 6: (Knight, 2021)

ALCOHOLIC HEPATITIS (AH)

Epidemiology:

- Exact prevalence unknown due to asymptomatic nature and underdiagnosis though it is suspected to high with an increased mortality risk
- Prevalence of alcohol use disorder (AUD) ~8% of the U.S population (16 million people) as of 2011 (Basra & Anand, 2011; Mehta & Reddivari, 2021)
- In 2011, 10-35% with AUD diagnosis have changes consistent with AH (up to ~5 million in US) (Basra & Anand, 2011; Mehta & Reddivari, 2021)
- From 2001-2011, 211 hospitals reported 0.08% to 0.09% admissions related to alcoholic hepatitis (Shah et al., 2022)
- 2001–2002 to 2015–2016 (NHANES), weighted ALD prevalence was stable (8.8% to 8.1%) but ALD with stage ≥3 fibrosis increased from 2.2% to 6.6% (Dang et al., 2020)
- 2007 to 2014, # of hospitalizations per 1,000 patients with alcoholic cirrhosis (AC) ↑ 32.8% (Dang et al., 2020)
- 2007 to 2014, proportion of hospitalizations among patients with AC with ≥3 cirrhosis complications ↑ 11.6% to 25.8% (Dang et al., 2020)
- 2007 to 2017, adults with ALD listed for liver transplant ↑63.4%, proportion with concurrent hepatocellular carcinoma ↑ 178% (Dang et al., 2020)
- Last 10–15 years, high-risk drinking prevalence ↑ 30% and AUD 50% (Simonetto et al., 2020)
- In 2016, alcohol related cirrhosis became the leading indication for liver transplantation, chronic HCV cirrhosis #2 (Simonetto et al., 2020)
- 2/3 of U.S adults consume alcohol, 7.2% have AUD (Shah et al., 2022)
- Excessive alcohol intake = 3rd leading U.S. preventable cause of death in. (Shah et al., 2022)

ALCOHOLIC HEPATITIS (AH)

Pathophysiology:

- ETOH undergoes an oxidative metabolic pathway in the hepatocytes, leading to a reduced ratio of the nicotinamide adenine dinucleotide (NAD) to NADH resulting in the inhibition of fatty acid and triglyceride oxidation results from lipogenesis.
- Gut-derived bacterial endotoxins in the form of hydrophobic lipid A from lipopolysaccharides (LPS) being translocated into the hepatocytes can also cause alcohol-induced liver injury. The way that occurs is in Kupffer cells, when LPS binds to CD 14 and toll-like receptor 4 to release a barrage of reactive oxygen species (ROS) activating the release of cytokines such as tumor necrosis factor-alpha (TNF alpha), interleukin-8, monocyte chemotactic protein 1 (MCP-1), and platelet-derived growth factor (PDGF), resulting in the accumulation of neutrophils, macrophages, and systemic clinical features of alcohol injury.
- Gut-barrier permeability and dysfunction have been shown to increase susceptibility to alcoholic liver disease and AH.

(Shah et al., 2022)

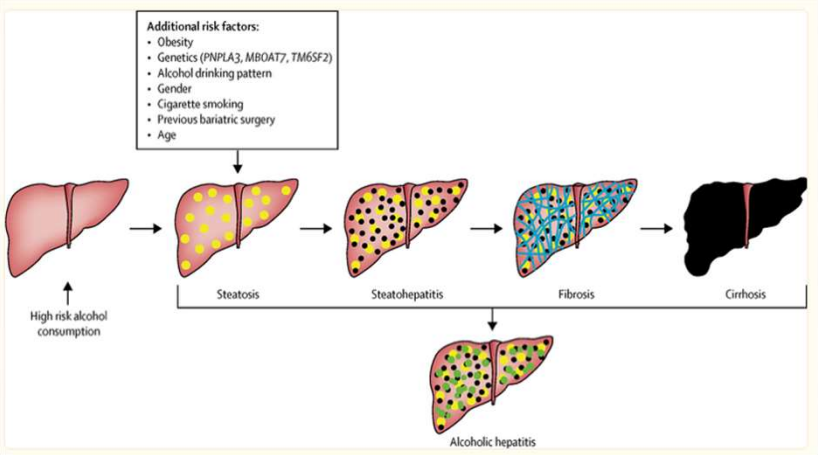

Figure 7: (Simonetto et al., 2020)

AUTOIMMUNE HEPATITIS

Etiology: - 2 types, idiopathic, 60% have chronic hepatitis with no serologic evidence of a viral infection
- Associated with anti-smooth muscle autoantibodies.

Epidemiology: -Paucity of epidemiologic research overall (likely unreported and underrecognized)
- More common in females than males (3.6:1)
- Actual U.S incidence and prevalence unknown, 100,000 to 200,000 cases annually.
- European incidence is 0.9-2/100,000 people per year, Prevalence of 11-25/100,000 people per year.

Type 1: - 80% of autoimmune cases, proportional 75% in young or middle-aged females.
- Distinguished by anti-smooth muscle antibodies (ASMA) w/ or w/o without anti-nuclear antibodies (ANA)

Type 2: - Presents usually as fulminant hepatic failure, most often in children and young adults
- Distinguished by positive anti-liver/anti-kidney microsome (anti-LMK) type 1 antibodies or anti-liver cytosol (anti-LC) type 1 antibodies

(Linzay et al., 2021)

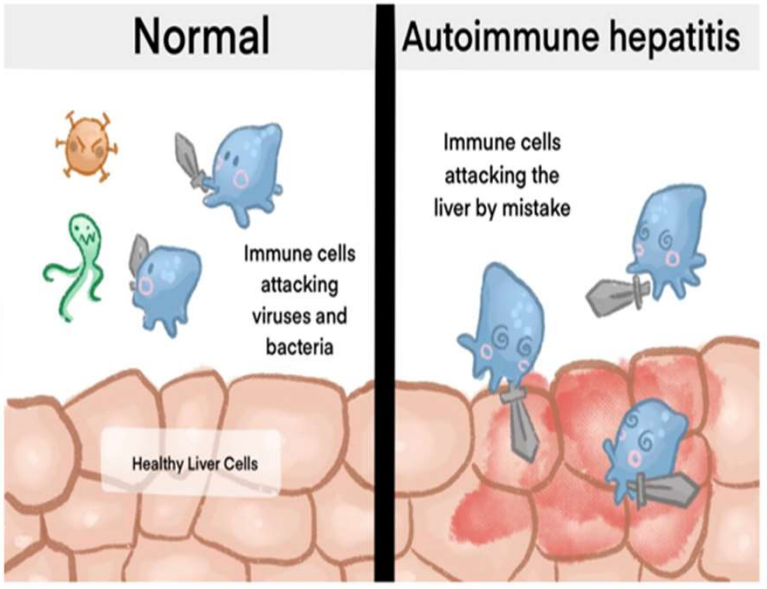

Figure 8: (Volk & Reau, 2021)

AUTOIMMUNE HEPATITIS

Pathophysiology:

- Suspected pathogenesis is secondary failing immune tolerance leading to a T-cell mediated inflammation caused by various environmental triggers in those genetically susceptible.
- Trigger include infections, medications, and toxins.
- Certain human leukocyte antigen (HLA) haplotypes are more susceptible
- Susceptible alleles are different in different ethnic groups.
- Nitrofurantoin, minocycline, & tumor necrosis factor-alpha drugs are culprits of drug-induced cases
- 50% 5-year survival rate for untreated cases, 10% 10-year survival rate for untreated cases
- 60-80% will enter remission after treatment, 50% of these will relapse requiring more therapy
- Some may require life-long immunosuppressive therapy
- 10% treatment failure with prednisone.
- Approximately 1/3 of patients have a recurrence despite liver transplantation,

(Linzay et al., 2021)

HEPATITIS A (HAV)

Etiology:

- One of most common causes of infectious acute hepatitis globally
- Endemic rates are high in developing countries with low socioeconomic conditions and poor sanitation and hygiene practices.
- Exposure in these developing countries usually occurs in childhood.
- Infection rates are low in developed countries such as the United States, Canada, and Western Europe.
- High-risk groups outside endemic countries are injection-drug users, MSM, travelers to endemic areas, close quarter facilities like nursing homes & day-care centers.
- Most cases of transmission are from person to person and limited to close contacts. Blood transfusion is a very rare cause of hepatitis A (Iorio & John, 2022; Shin & Jeong, 2018).

Epidemiology:

- Estimated 1.4 - 1.5 million cases worldwide annually
- Pre-vaccine, annual U.S. cases peaked at 59,606 (1971), post-vaccine cases ↓ 92% (1995-2010) due in part to herd immunity
- Sharp decrease in incidence (92%) from 12 cases/100,000 persons (1995) to 1 case/100,000 (2007)
- U.S & European cases have ↑ since 2016 due to person-to-person and food-related outbreaks
- Virus genotyping has improved tracking of outbreak origin and trajectory.
- Incidence correlates with SES factors like income, housing density, sanitation and water quality practices
- U.S increased 1,325% from 2015-2019 with 18,846 cases, 37,700 infections estimated, and an incidence of 5.7 cases/100,000 people in 2019

(Centers for Disease Control and Prevention, 2022; Langan & Goodbred, 2021; WHO, 2022)

HEPATITIS A

Pathophysiology:

- Classified in genus Hepatovirus of the Picornaviridae family
- RNA virus (+-sense, single-stranded) that replicates mostly in hepatocytes but also small intestine
- If ingested orally, virus is absorbed in GI tract are carried to the basolateral membrane of the hepatocyte via portal circulation.
- Hepatic injury mediated by immune mechanisms with virus-specific T-cell mediated release of cytotoxic interferon-gamma and hepatocellular apoptosis and inflammation associated with the innate immune response
- Excreted in bile and released via stool after hepatic replication with highest stool concentration during 2 weeks before the onset of jaundice,
- Most infectious during stool shedding and viremia but less so 1 week after jaundice appears

(Iorio & John, 2022).

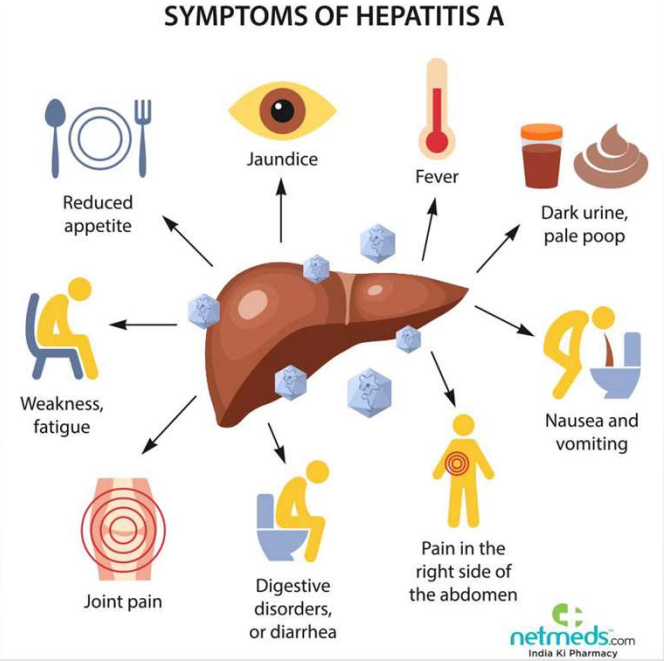

Figure 9: (Krishna, 2020)

HEPATITIS B (HBV)

Etiology: - The only DNA virus of the hepatotropic viruses (A, B, C, D, E)

- May transmit horizontally through sexual contact or mucosal surface contact with unprotected sex and injection drug use most commonly responsible for cases in regions of low-intermediate prevalence
- May transmit vertically with maternal-to-newborn perinatal transmission most common in regions of high-prevalence

Epidemiology: - The U.S had 3,192 acute cases reported in 2019 with 20,700 infections estimated, and an incidence of 1.0 cases/100,000 people

- 10 genotypes have been identified (A-J)
- Hepatitis B vaccination has resulted in low child and adolescent cases
- Rates of HBV are lower in U.S than Africa, India, and central Asia due to vaccine availability, access to care, and preventative measures
- During 2012–2019, cases fluctuated from 2,895 in 2012 to 3,192 in 2019 (low of 2,791 in 2014, high of 3,409 in 2017)
- WHO 2019 estimates 296 million people worldwide with hepatitis B and 1.5 million people newly infected with chronic hepatitis B
- In 2019, 1,662 hepatitis B-associated deaths were reported in the US (age-adjusted death rate of 0.42 cases/100,000 population)
- Age-adjusted death rates remained consistent from 2015–2019 (0.46 cases/100,000 population in 2015)

(CDC, 2022a; CDC, 2022c; Terrault et al., 2018; Tripathi & Mousa, 2022)

HEPATITIS B

Pathophysiology: - Transmitted via percutaneous inoculation or through mucosal exposure with infectious bodily fluids

- Fecal to oral transmission is rare but not impossible
- Incubation period is between 30 - 180 days
- A small % progress to chronic hepatitis B, defined as HBsAg presence >6 months
- Proximity to infected individuals increase risk of acquiring hepatitis B
- Mostly immune mediated potentially causing cytotoxic liver damage injury to the liver
- HBsAg and nucleocapsid proteins on cell membranes promote T cells-induced cellular lysis of HBV-infected cells but this is largely ineffective
- S/P liver transplant, those with hepatitis B that are on immunosuppressants can develop fibrosing cholestatic hepatitis from high HBsAg exposure

(Iannacone & Guidotti, 2022; Nguyen et al., 2020; Tripathi & Mousa, 2022)

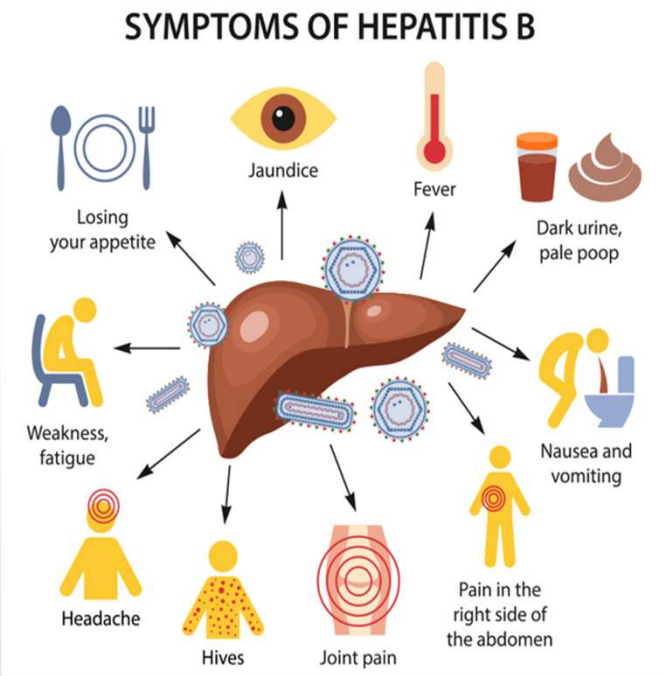

Figure 10: (Health Promotion and Disease Prevention Directorate, 2021a)

HEPATITIS C (HCV)

Etiology:

- May transmit horizontally through infected blood products (pre-1992 in U.S.) or bodily fluids containing blood (parenteral exposure) especially injectable drug use
- May transmit vertically with maternal-to-newborn perinatal transmission (main cause of HCV in children)
- May also transmit through other parenteral routes like via tattooing, occupational needlestick injuries, invasive medical procedures, and sexual contact

Epidemiology:

- U.S had 34,136 acute cases reported in 2019 with 57,500 infections estimated, and an incidence of 1.3 cases/100,000 people
- In 2019, 14,242 hepatitis C-associated deaths were reported in the US (age-adjusted death rate of 3.3 cases/100,000 population)
- Those ages 55–74 years old accounted for 76% of those deaths in 2019
- Age-adjusted death rates have declined each year from 2015–2019 (19,566 deaths and 4.91 cases/100,000 population in 2015)
- Approximately 2.4 million people in the U.S were living with hepatitis C during 2013–2016
- Estimated global prevalence is approximately 1.8% in the general population (>3% of world population) though the African continent has a prevalence of 7.1%

(CDC, 2021d; Manns et al., 2017; Puchades Renau & Berenguer, 2018; Salari et al., 2022)

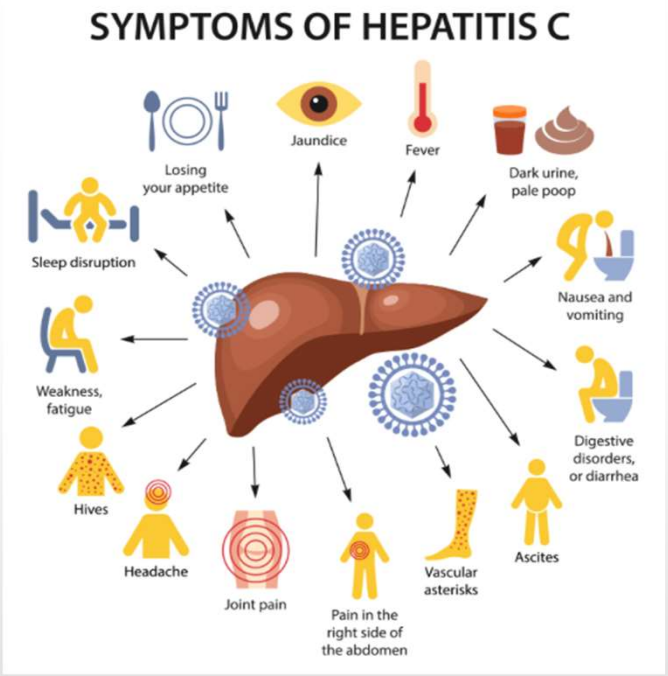

Figure 11: (Health Promotion and Disease Prevention Directorate, 2021b)

HEPATITIS C

Pathophysiology:

- +-stranded, RNA virus enters hepatocyte via endocytosis mediated by at least 4 co-receptor molecules
- After being internalized by cytoplasm it is uncoated and translated into 10 mature peptides
- The peptides get cleaved by both host proteases and virally encoded proteases known as NS3-4a serine proteases
- Mature peptides go to the endoplasmic reticulum, forming a replication complex that contains an important enzyme, the NS5B RNA dependent RNA polymerase
- That polymerase then catalyzes the + RNA strand into its negative strand intermediate serving as the template for the synthesis of new + strands
- These are then packaged with core and envelop glycoprotein into mature virions, which then exit the cell via exocytosis
- Unlike HBV, HCV is unable to integrate into the genome of a host
- There are 7 genotypes with genotype 1 being dominant globally (associated with more severe liver disease and a much greater risk of developing liver CA)
- Genotype 1 accounts ~60% of cases in the U.S
- Genotypes 2a, 2c, & 3b account for about ~10% of cases in the U.S but respond well to medications
- HCV is detectable within days and Viremia peaks in the first 8 to 12 weeks before plateauing or dropping to undetectable levels (viral clearance)
- 50% to 85% develop persistent infection due to failure to halt replication of HCV by weak CD4+ and CD8+ T-cell responses
- When a chronic infection is established, HCV does not appear to be cytopathic; local inflammatory response triggers fibrogenesis
- Comorbidities and external factors are association with the development of with accelerated fibrosis progression and cirrhosis (ex. HIV, HBV, ETOH use, obesity,
- ↑ hepatic fibrosis correlates with ↑ risk of hepatocellular carcinoma

(Basit et al., 2022)

HEPATITIS D (HDV)

Etiology:

- Can be acute or chronic inflammatory process
- HDV replication occurs independently in hepatocytes but requires hepatitis B surface antigen for propagation
- Primarily transmitted through activities injectable drug use or needle-stick injury and via infected blood products (multiple transfusions)
- Less likely transmission occurs via mucosal contact with infected bodily fluids/blood including sexual contact and open contact with wounds
- Vertical transmission is rare but not impossible
- Successful vaccination against HBV prevents HDV coinfection
- Infection with both HDV and hepatitis B surface antigen (HBsAg) a superinfection occurs in ~5% of patients resulting in fulminant liver failure

Epidemiology:

- The WHO estimates that HDV affects nearly 5% of people globally with chronic HBV infection
- Co-infection with HDV contributed to about 18% of cirrhosis and 20% of hepatocellular carcinomas in those with a chronic HBV infection
- For those who are HBsAg-positive, estimated HDV prevalence is 4.5% globally
- HDV prevalence in HBsAg-positive hepatology clinic attendees is 16.4% worldwide
- About 1 in 22 people with hepatitis B also have hepatitis D (12 million people worldwide)

(Masood & John, 2021; Stockdale et al., 2020; WHO, 2020b)

HEPATITIS D

Pathophysiology: - HDV enters hepatocytes by binding to the carbohydrate side chains of heparin sulphate proteoglycan present on the surface

- N-terminal amino acids of the pre-S1 domain of L-HBsAg are thus obligatory to HDV entry into hepatocytes.
- Mutations/deletions in highly conserved pre-S1 sequence and acetylation or myristoylation of pre-S1 N-terminal amino acids have been found to inhibit HDV entry into hepatocytes.
- It is suspected that pre-S1 domain of L-HBsAg interacts with sodium-taurocholate co-transporting polypeptide, an integral transmembrane glycoprotein involved in enterohepatic circulation, to facilitate HDV infection.
- After HDV enters the cell, the uncoating of viral particle occurs and HDAg translocates the viral genome into the nucleus where RNA polymerases I and II are employed to replicate the genome.
- Polymerase I involves the transcription of antigenome from viral genome in the nucleolus, while polymerase II catalyzes genome replication from antigenome and transcription of mRNA in the nucleoplasm.

(Abbas & Afzal, 2013)

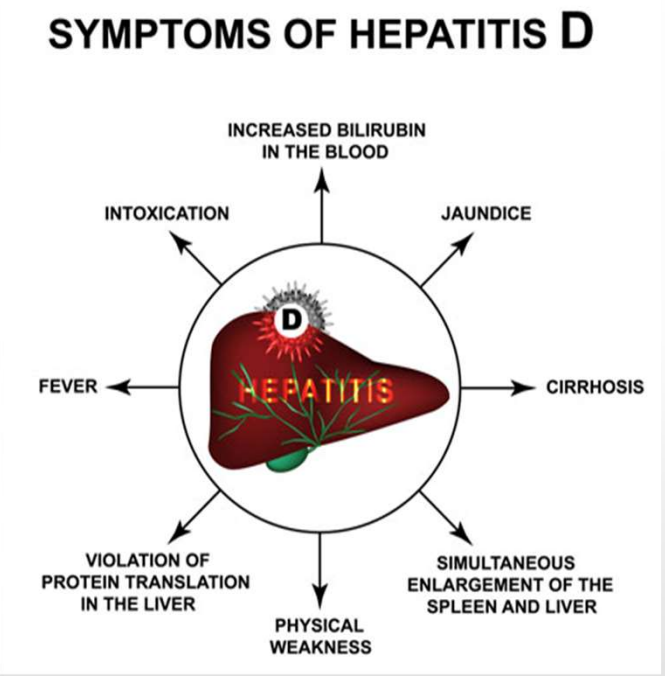

Figure 12: (Magnus Medi, n.d.)

HEPATITIS E (HEV)

Etiology:

-An icosahedral, nonenveloped, single-stranded RNA virus approximately 27 to 34 nm in diameter

- 8 identified genotypes of HEV (1-8) but only 1-4 can infect humans
- Genotype 1 and 2 are human viruses transmitted through the fecal-oral route from contaminated water, found mainly in developing countries in Africa, Asia, Central America and the Middle East

-Genotype 3 and 4 are mainly found in animals (pigs, wild boars and deer) without causing disease but can be transmitted to humans by eating undercooked meat, found in developed countries such as the United States, Australia, Japan and China

-Genotypes 1 and 2 are usually seen in young adults (15-40) as part of outbreaks, causing acute infection that is self-limited and does not progress to chronic infection. However, acute infections in pregnant patients or patients with chronic liver disease can be severe with progression to fulminant liver failure

-Genotype 3 and 4 usually cause sporadic cases and are mainly see in older adults (older than 40). They can cause acute infections with a possibility of progression to chronic infections mainly in immunocompromised patients such as solid organ transplant patients on immunosuppressants and those with AIDS

- HEV is shed in stool of infected persons entering via the intestines and is transmitted predominantly by contaminated water particularly after heavy rainfall and flooding
- Infection is usually self-limiting, resolves within 2–6 weeks, on occasion fulminant hepatitis (acute liver failure) develops and is potentially fatal
- Though person-to-person transmission is rare, it can be transmitted via blood transfusion or vertically mother to infant resulting in significant perinatal mortality and fetal loss

Epidemiology:

- Estimated 20 million HEV infections annually worldwide and as estimated 3.3 million symptomatic cases
- WHO estimates that HEV caused approximately 44,000 deaths in 2015 or 3.3% of the mortality secondary to viral hepatitis
- Overall case-fatality rate is about 1% though for women who are pregnant pregnant , HEV can cause third trimester mortality reaching 10%–30%
- 2015 survey in 30 European countries found # of cases with HEV infection ↑ from 514/year in 2005 to 5,617/year in 2015
- Only 0.002% of plasma donations in the United States were found HEV RNA positive

(Aslan & Balaban, 2020; Sherman, 2021; WHO, 2020c;)

HEPATITIS E

Pathophysiology:

- Poorly understood for HEV
- Incubation period ranges from 28 to 40 days .
- After ingestion, the virus is absorbed through the GI mucosa into the portal circulation
- HEV replication not observed in non-hepatic tissues
- HEV can produce morphologic changes resembling cholestatic and classic acute hepatitis, though not diagnostic
- HEV is excreted in feces
- Virus exposes its RNA within the host cell's cytoplasm then translated into a negative RNA strand containing open reading frames (ORFs 1, 2 & 3) involved in HEV replication

-Not cytopathic but the innate immune response toward infection can cause hepatic damage

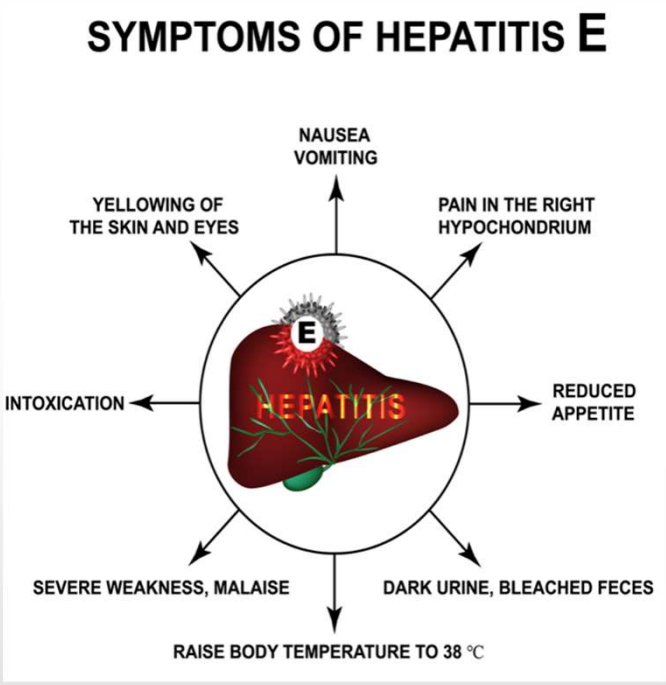

Figure 13: (Stoker, 2021)

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