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Learning Series - #17

Making sense of Hepatitis

Hepatitis is a general term that refers to inflammation of the liver. Chronic inflammation of the liver increases the risk for development of fibrosis (scarring), cirrhosis (scarring and death of liver cells) and hepatocellular carcinoma (HCC). Hepatitis can result from a variety of causes listed below.

For the remainder of this infographic, we will focus on infectious hepatitis only:

1. **Infectious** – viral (hepatitis A, B, C, D or E; cytomegaloviruses, Epstein-Barr virus, etc), bacterial, fungal, and parasitic organism
2. **Noninfectious** – drugs, alcohol, heavy metal poisoning, environmental toxins, acute obstruction of the portal vascular system (blood vessels) that perfuse and drain the liver, autoimmune disorders (lupus, IBD), metabolic or hereditary (Wilson's disease, Hemochromatosis), ischemic and vascular (Cardiogenic/Distributive shock; Hypotension; Heatstroke; acute Budd-Chiari syndrome)
3. **Cryptogenic** (unknown cause)

Viral hepatitis is a systemic infection with predilection for the liver. All hepatitis viruses are RNA viruses, except for HBV which is a DNA virus. Each type of hepatitis produces clinically similar disease with slight variations in severity and chronicity based on a given virus' different molecular and antigenic properties.

Viral hepatitis can be classified by transmission route and duration of illness

- **by transmission:**
  a. enteric (fecal-oral) : A and E – self-limiting; latter is rare in Canada
  b. blood and body fluids – B, C and D – prolonged viremia and development of chronic liver disease
- **by duration**
  a. Acute: causes self-limiting inflammation which does not lead to fibrosis
  b. Chronic: persistent infection for at least 6 month and development of long-term. Chronic hepatitis is classified according to etiology and severity, the latter being based on liver biopsy.

HDV (delta hepatitis virus) – It occurs as a co-infection with hepatitis B, that is that it requires the helper function of HBV for replication and expression. Patients with coinfection of B and D have significant mortality at about 20%.

Our adaptive immunity develops after birth and the cells of the adaptive system, its antibodies, and molecular mediators work in conjunction with the innate immune system to amplify the strength of the response to an infectious organism.

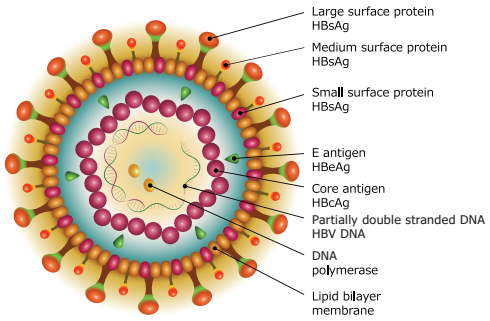
In immunology, an antigen (Ag) refers to a molecular structure that causes antibody (Ab) production.

- Antibodies are specialized proteins also called immunoglobulins. Each antibody is directed against a single antigen.
- Antigens are only portions of molecular structures, so organisms can have more than one antigenic site recognized by the immune system.

Hepatitis B becomes chronic in about 0.5-2.0% of adult infected individuals. This percentage increases to 25-90% if the infection is passed from mother to child or is acquired during childhood.

Chronic hepatitis can be asymptomatic (carrier – between 6%-10% of the people who've been infected with the virus will become carriers and can infect others without knowing it) or associated with chronic inflammation of the liver.

HBV infection provokes the production of 3 antibodies:
1) surface: HBsAb ; 2) e: HBeAb; 3) core: HBcAb
These antibodies correspond to a specific antigen on the hepatitis B virus as seen beside.



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Making sense of Hepatitis (cont'd)

The serologic hallmark of chronic hepatitis B is persistence of HBsAg and anti HBc (HBcAb), but absence of anti HBs (HBsAb). The following classification developed by the European Association for the Study of Liver is a useful scheme in recognizing those with chronic hepatitis B who have, or might, develop progressive liver injury.

Chronic hepatitis B **Chronic HBV infection**	**HBeAg positive**		**HBeAG negative**		
	Phase 1	Phase 2	Phase 3	Phase 4	Phase 5
	Chronic HBV infection	Chronic hepatitis B	Chronic HBV infection	Chronic hepatitis B	Resolved HBV infection
HBsAg	+++	++	+	++	-
HBeAg	+	+	-	-	-
HBV DNA	> 107 IU/mL (> 107 x 5.6 copies/mL	102-107 IU/mL (102-107 x 5.6 copies/mL)	< 2,000 IU/mL (< 104 x 5.6 copies/mL)	> 2,000 IU/mL (> 104 x 5.6 copies/mL)	< 10 IU/mL (< 56 copies/mL)
ALT	Normal	Elevated	Normal	Elevated	Normal
Liver disease	None/minimal	Moderate/severe	None	Moderate/severe	None
Old terminology	Immune tolerant	Immune reactive HBeAg positive	Inactive carrier	HBeAg negative chronic hepatitis	HBsAg negative/ anti-HBc positive

The hepatitis B viral load is a Polymerase Chain Reaction (PCR) test that measures the amount of hepatitis B virus DNA is in the blood of chronically infected patients. DNA viral load is correlated with disease progression, cirrhosis and HCC.

A viral load of > 10 000 copies/mL (2000 IU/mL) is a strong risk predictor of HCC, independent of HBeAg status, ALT level and liver cirrhosis.

Today, viral load is usually measured using international units per milliliter (IU/mL). Traditionally, it was measured in copies per milliliter (copies/mL); Some regions and labs, maintain the traditional nomenclature.

HBV Viral Load Conversion

- 1 copy = 0.2 IU ; 1 IU = 5 copies; 1 IU/mL = 5.6 copies/mL
- 2000 IU = 10000 copies ; 2,000 IU/mL = 104 copies/mL
- 20000 IU = 100000 copies; 20,000 IU/mL = 105copies/mL
- Inactive carriers (i.e. HBeAg-negativity, anti-HBe-positivity, normal ALT levels, and HBV DNA < 2000 IU/mL)
- HBV reactivation is defined as the elevation of the HBV DNA level to ≥ 2000 IU/mL
- For HBeAg (+) or (-) patient with chronic HBV with DNA > 104 copies/mL (> 2000 IU/mL) & ALT > ULN, treatment should be started with a first-line agent

Examples:

1. HBV DNA viral load @ 4.73E+1 IU/mL = 4.73 x 10 exponent 1 = 47 -> good risk - 'healthy carrier'
2. HBV DNA viral load @ 1.00E+8 IU/mL = 10 exponent 8 = 100,000,000 -> active hepatitis - PP

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Making sense of Hepatitis (cont'd)

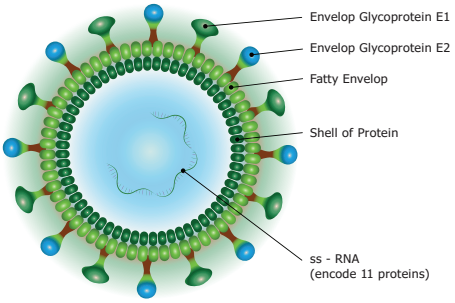
Goal for HBV therapy:

1. Suppress HBV DNA
2. Elimination of HBeAg
3. Elimination of HBsAg
4. Decrease risk of long-term complications

Many HBV genotypes, sub-genotypes, mutants, and recombinants emerge. Differences between genotypes in response to antiviral treatment have been determined. To date, 10 HBV genotypes, scattered across different geographical regions, have been identified. Pathogenic differences between HBV genotypes explain disease intensity, progression to cirrhosis and HCC.

In conclusion, genotype determination in Chronic Hepatitis B infection is important in estimating disease progression and planning optimal antiviral treatment.

Hepatitis C virus (HCV) is a major cause of liver disease worldwide, with 130-170 million people infected according to the World Health Organization. Approximately 10%-20% of chronically infected patients experience persistent inflammation and develop liver cirrhosis and eventually hepatocellular carcinoma.



Chronic hepatitis C is marked by the persistence of HCV RNA in the blood for at least 6 months after the onset of acute infection.

The risk of progression to chronic infection by HCV is influenced by various factors including:

- Age at the time of infection (more if infection occurs at age > 25 years)
- Gender (males > females)
- Ethnicity (higher in Africans than in Caucasians and Hispanic whites)
- Coinfection with human immunodeficiency virus (HIV), HBV
- Concomitant alcohol consumption
- Comorbid conditions like cancer, immunosuppression, insulin resistance, nonalcoholic steatohepatitis, obesity, etc

Extrahepatic manifestations include but not limited to:

- Glucose and lipid metabolic disorders
- Atherogenic disease
- Mixed cryoglobulinemia
- Lymphoproliferative disorders
- Renal disease
- Insulin resistance and type 2 diabetes
- Autoimmune diseases (sicca syndrome, rheumatoid arthritis-like polyarthritis)
- Metabolic bone disease and osteopenia

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Hepatitis C tests include:

- HCV antibody test — detects antibodies in the blood, produced in response to an HCV infection
- HCV RNA test — detects and measures viral hepatitis C RNA in the blood – viral load
- HCV genotype test — determines the specific subtype of the virus; this information is useful in guiding treatment.

As with HBV, the definitive test is a molecular test for hepatitis C RNA (HCV-RNA). If present, the patient is considered infected. Molecular tests vary widely in their sensitivity, therefore when reviewing an APS, the sensitivity of the test that was reported for HCV needs to be determined.

HCV Antibody	HCV RNA	Interpretation
-		No infection or it is too soon after exposure and HCV antibody has not yet developed; If suspicion remains high, an HCV RNA test is done.
-	+	Early, acute HCV infection
+ or weakly positive	-	Past infection or no infection (false-positive screen, most are weakly positive)
+	+	Current, active infection

Treatment goals:

- Achieve sustained eradication of HCV (persistent absence of detectable HCV RNA in serum for 6 months or more after completing antiviral treatment)
- Prevention of progression to cirrhosis, HCC, and decompensated liver disease requiring liver transplantation.

Cure does not mean the risk has ceased to exist – it means that viremia and viral replication have been reduced. There is residual risk based on the amount of fibrosis and or cirrhosis that was present before treatment an sustained viral response. In addition, mortality risk remains high for untreated chronic hepatitis.

Hepatitis is normally detected by an increase in liver enzyme levels, but advanced fibrosis/cirrhosis can lead to normal and even low enzyme levels because few functioning liver cells remain.

Individuals with low AST, ALT levels (usually in conjunction with low albumin and high globulin levels) have high excess mortality and should be evaluated carefully.

Underwriting considerations

- Clinical status including the pattern of liver enzymes
- Qualification and quantification of alcohol intake
- Other investigations: these include a full viral serology screen, routine lab tests (CBC, LFTs, albumin, INR) and liver imaging (ultrasound, CT or MRI)
- Results of liver biopsy including evidence of inflammatory activity, piecemeal necrosis, cirrhosis or fibrosis
- Replication tests- HBeAg, HBV DNA, anti-HBe
- Co-infection tests: anti-HCV, anti-HIV
- Treatment strategy and response
- Family history of hepatitis viral infection as well as HCC

Prognosis can best be assessed by the results of biopsy, blood work, serology and imaging tests in conjunction with the clinical picture and comorbid risk factors.