VIRAL AND AUTOIMMUNE HEPATITIS

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WHAT IS HEPATITIS ?

- Inflammation of the liver
- Almost always, inflammation implies elevation in liver enzymes
- AST and ALT are the key liver enzymes
- Other Liver Function Tests (LFTs) which can be abnormal in hepatitis include:
  - Bilirubin, albumin, alkaline phosphatase, gamma glutamyl transpeptidase

CAUSES OF ACUTE HEPATITIS

- Viral hepatitis
- Other infectious etiologies e.g. CMV, EBV, TB
- Alcoholic hepatitis
- Drug hepatitis
- Ischemic hepatitis
- Choledocholithiasis

Human Hepatitis Viruses

Virus	Genome	Genome size (kb)	Envelope	Family / genus
HAV	RNA positive sense, single stranded, linear	7.5	-	Picornaviridae hepatovirus
HBV	DNA partially double stranded, circular	3.2	+	Hepadnaviridae
HCV	RNA positive sense, single stranded, linear	9.6	+	Flaviviridae hepacivirus
HDV	RNA positive sense, single stranded, linear	1.7	+	Unclassified (viroid), delta virus
HEV	RNA positive sense, single stranded, linear	7.5	-	Unclassified, togavirus and alpha virus-like

OTHER INFECTIOUS ETIOLOGIES OF ACUTE HEPATITIS

- CMV - cytomegalovirus; immunocompromised host
- EPSTEIN-BARR – mononuclesosis; lymphadenopathy; splenomegaly
- TB and M. avium intracellurare (MAI)

SYMPTOMS OF ACUTE VIRAL HEPATITIS

- Fatigue, nausea, anorexia
- Jaundice
- Low-grade fever, abdominal pain
- Arthralgia, myalgia, headache

SIGNS OF ACUTE VIRAL HEPATITS

- Fever – low grade
- Jaundice
- Hepatomegaly with RUQ tenderness
- Splenomegaly - infrequent

LIVER BLOOD TEST ABNORMALITIES IN ACUTE VIRAL HEPATITIS

- AST AND ALT - 1000-5000 IU
- Bilirubin – generally elevated – both conjugated and unconjugated
- Alkaline Phosphatase – minimally elevated
- Bilirubin and urobilinogen increased in urine

OUTCOMES OF VIRAL HEPATITIS

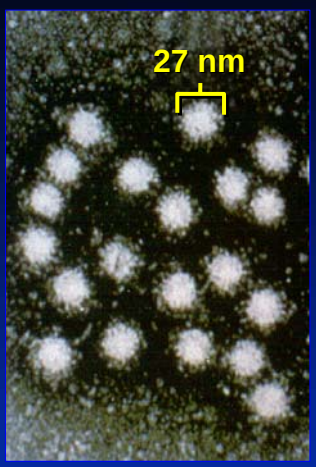
ACUTE ILLNESS

CHRONIC HEPATITIS

CURE

FULMINANT HEPATITIS

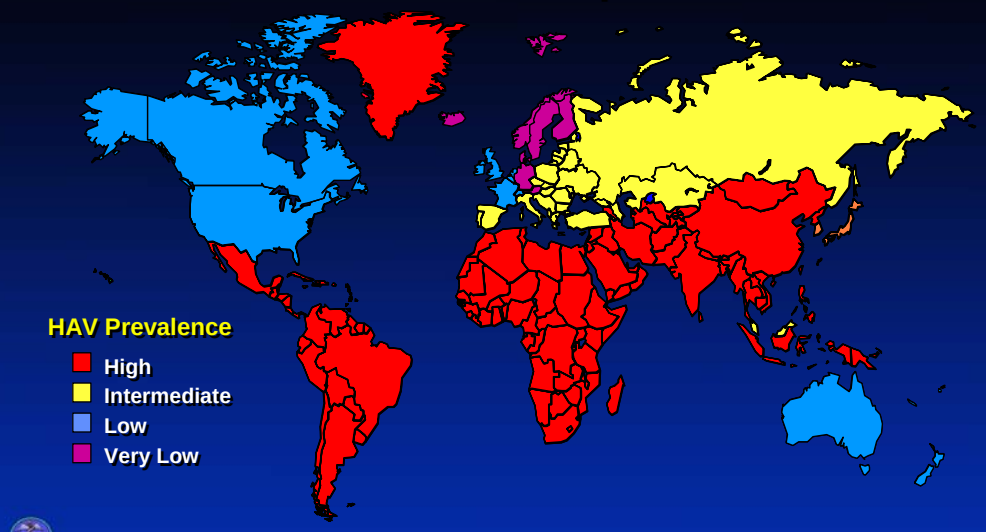
Hepatitis A Virus



- Nucleic Acid: 7.5 kb ssRNA
- Classification: *Picornaviridae, Hepatovirus*
- One serotype and multiple genotypes
- Nonenveloped, acid and heat stable
- In vitro model: monkey and human cell cultures
- In vivo replication: in cytoplasm of hepatocyte; human and other higher primates

HAV - Epidemiology

Global Prevalence of Hepatitis A Infection

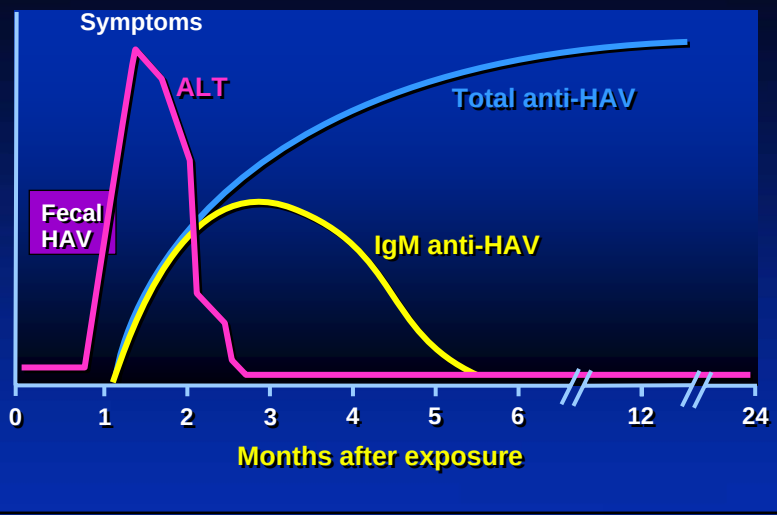


HEPATITIS A

- Oral fecal route of transmission
- Excreted in stool about 2 weeks prior to clinical illness
- 1 month incubation period
- Children often asymptomatic
- Never causes chronic hepatitis

HAV

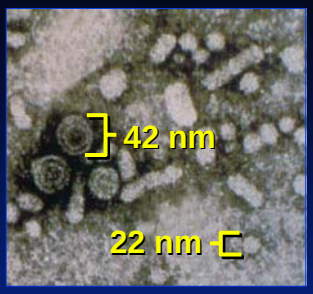
Typical Serologic Course of Acute Hepatitis A Virus Infection

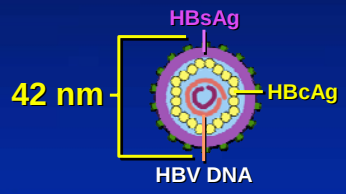


HEPATITIS A PREVENTION AND TREATMENT

- No treatment of infection available
- Passive immunity with gamma globulin can ameliorate disease in early stages of the infection
- Gamma globulin can prevent disease pre-exposure
- Vaccine available to induce active immunity

Hepatitis B Virus





- Nucleic Acid: 3.2 kb DNA
- Classification: *Hepadnaviridae*
- Multiple serotypes and genotypes A-F
- Enveloped
- In vitro model: primary hepatocyte culture and transfection of cloned HBV DNA
- In vivo replication: in cytoplasm, cccDNA in nucleus; hepatocyte and other tissues, human and other primates

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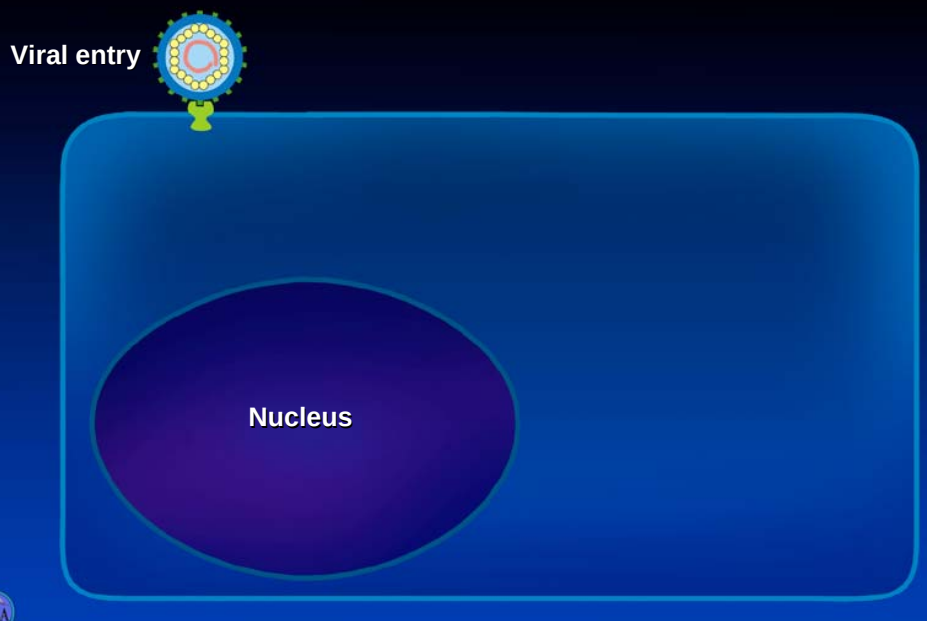
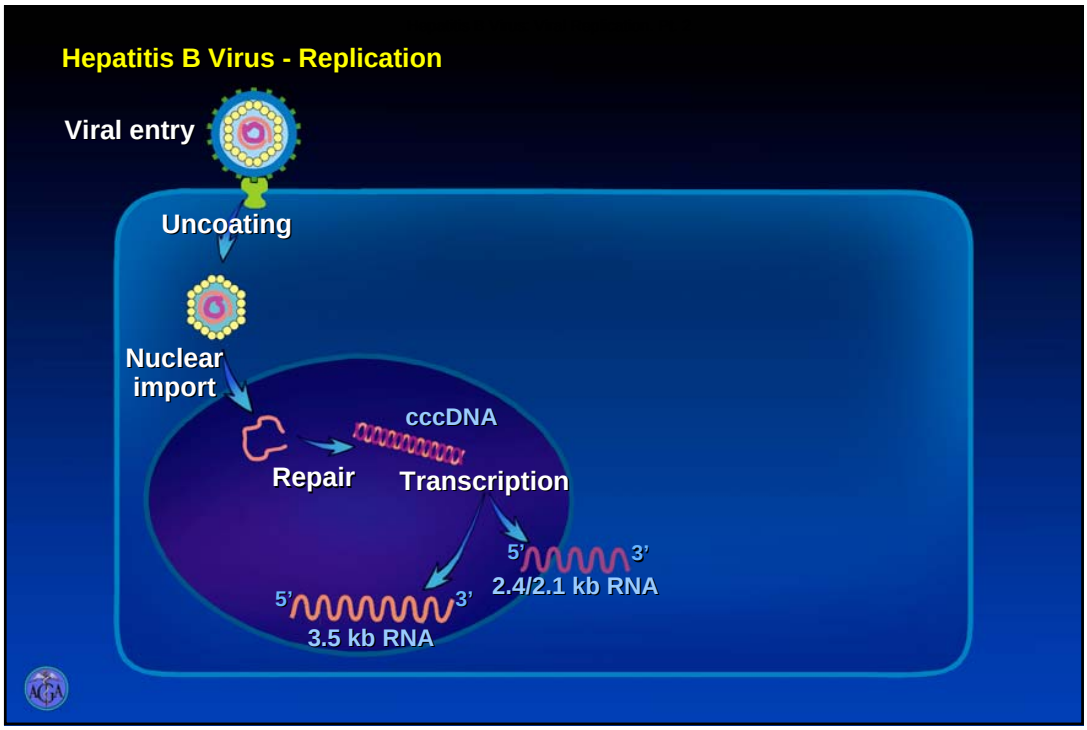
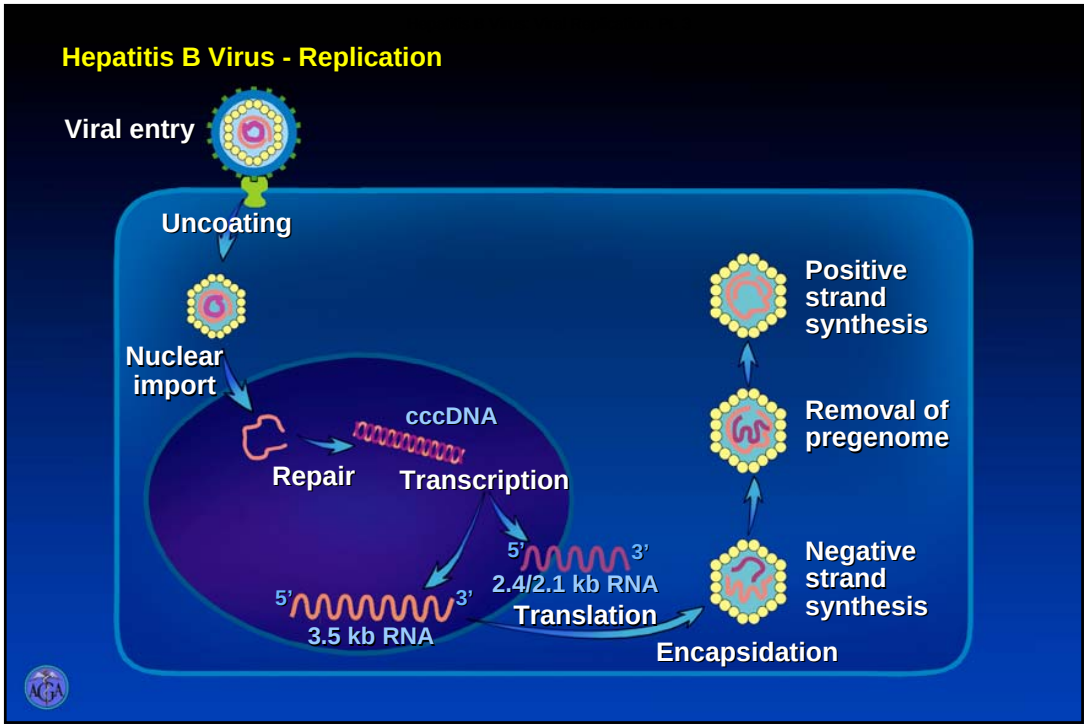
Hepatitis B Virus - Replication




Hepatitis B Virus - Replication
Viral entry
Uncoating
Nuclear import
cccDNA
Repair
Transcription
5'
3'
2.4/2.1 kb RNA
5'
3'
3.5 kb RNA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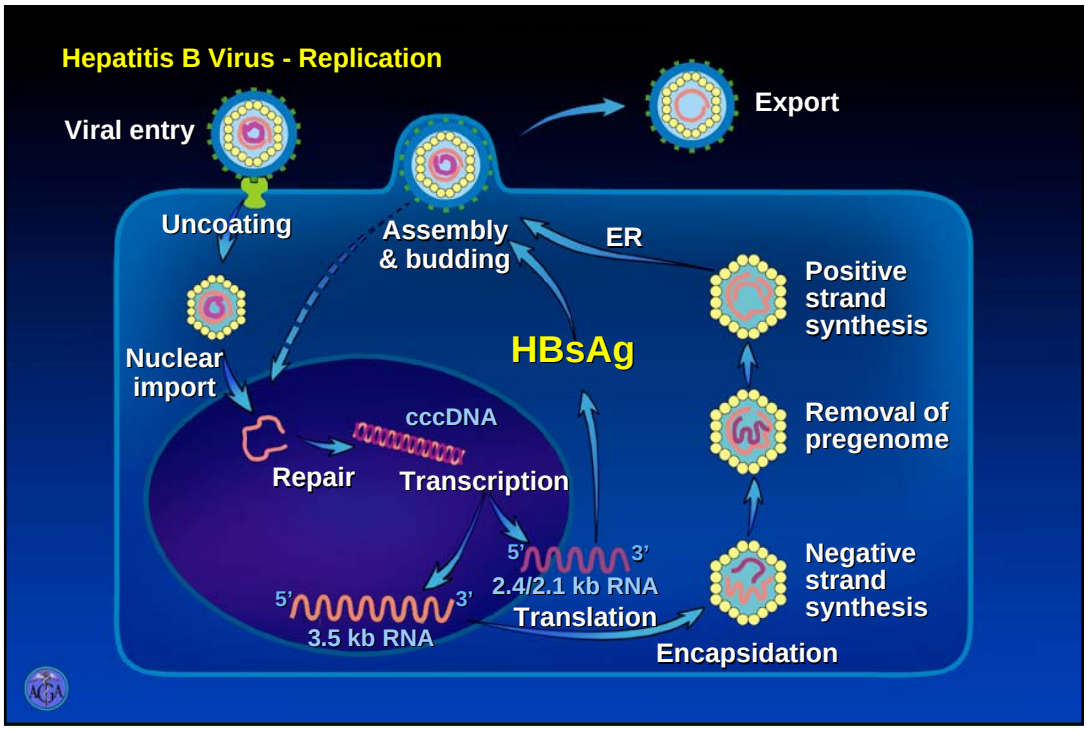
Translation
Encapsidation
Positive strand synthesis
Removal of pregenome
Negative strand synthesis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Viral entry
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Uncoating
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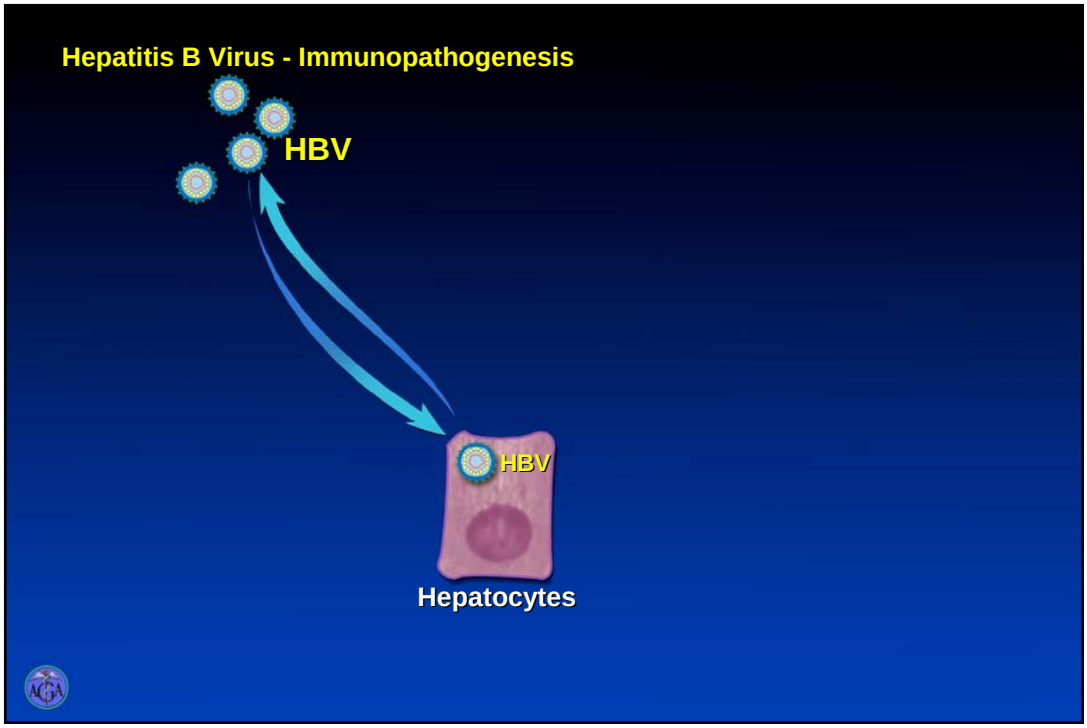
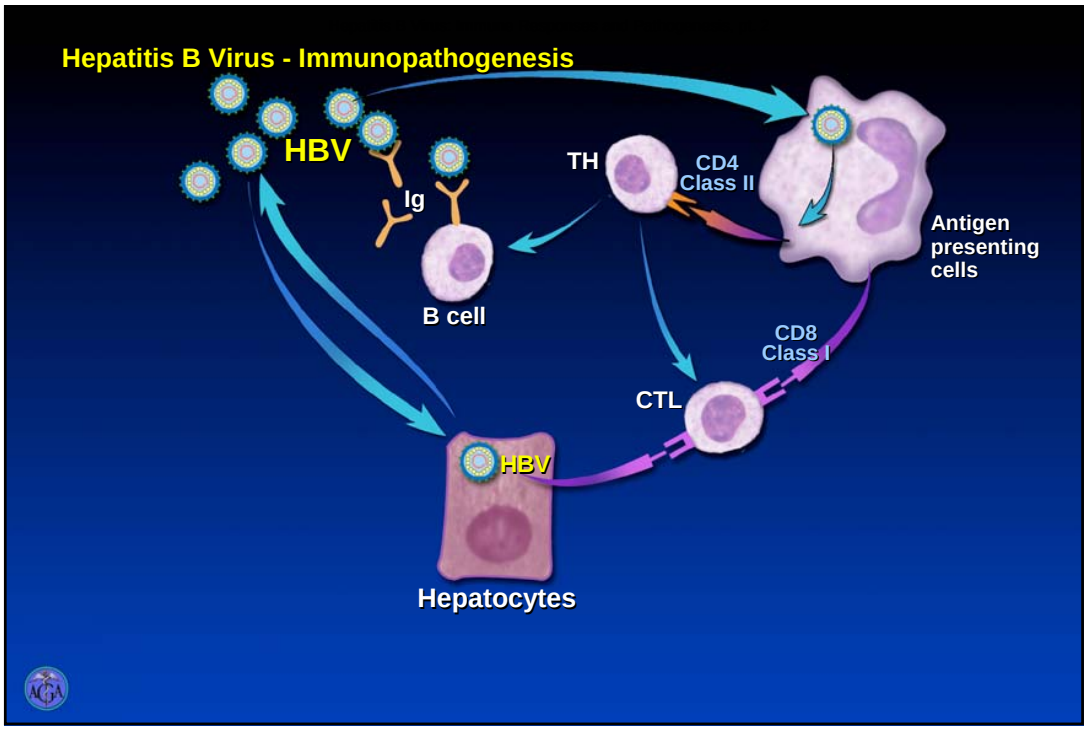

Hepatitis B Virus - Immunopathogenesis
HBV
HBV
Hepatocytes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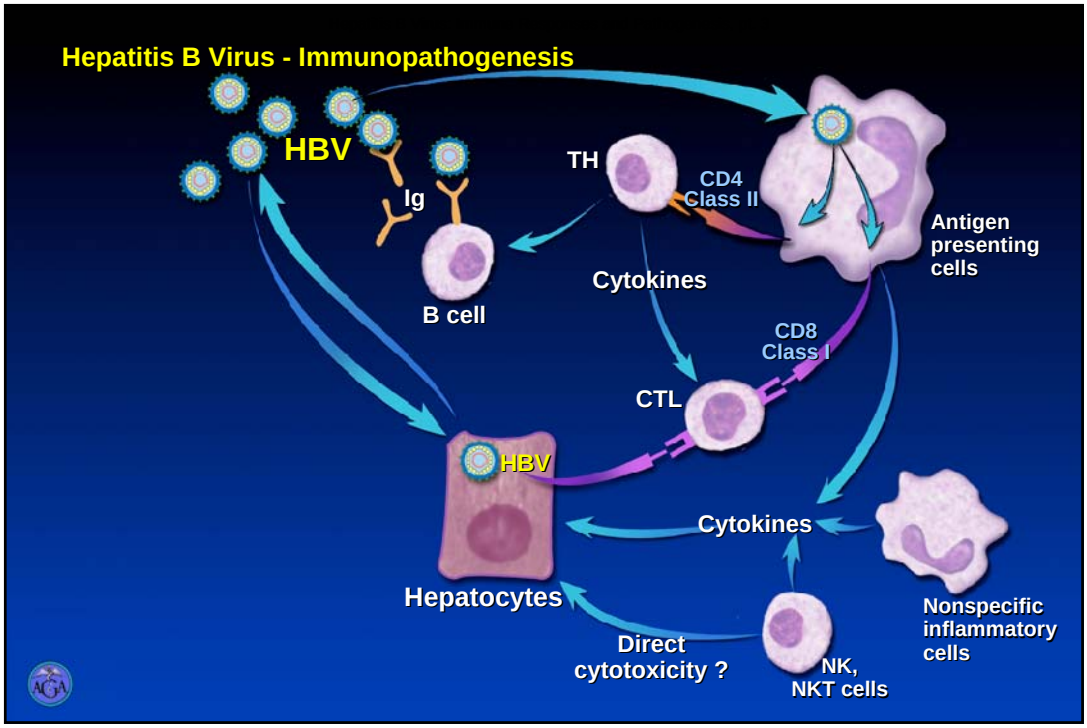
B cell
TH
CD4
Class II
Antigen
presenting
cells
CD8
Class I
CTL
HBV
Hepatocytes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CD4
Class II
Antigen
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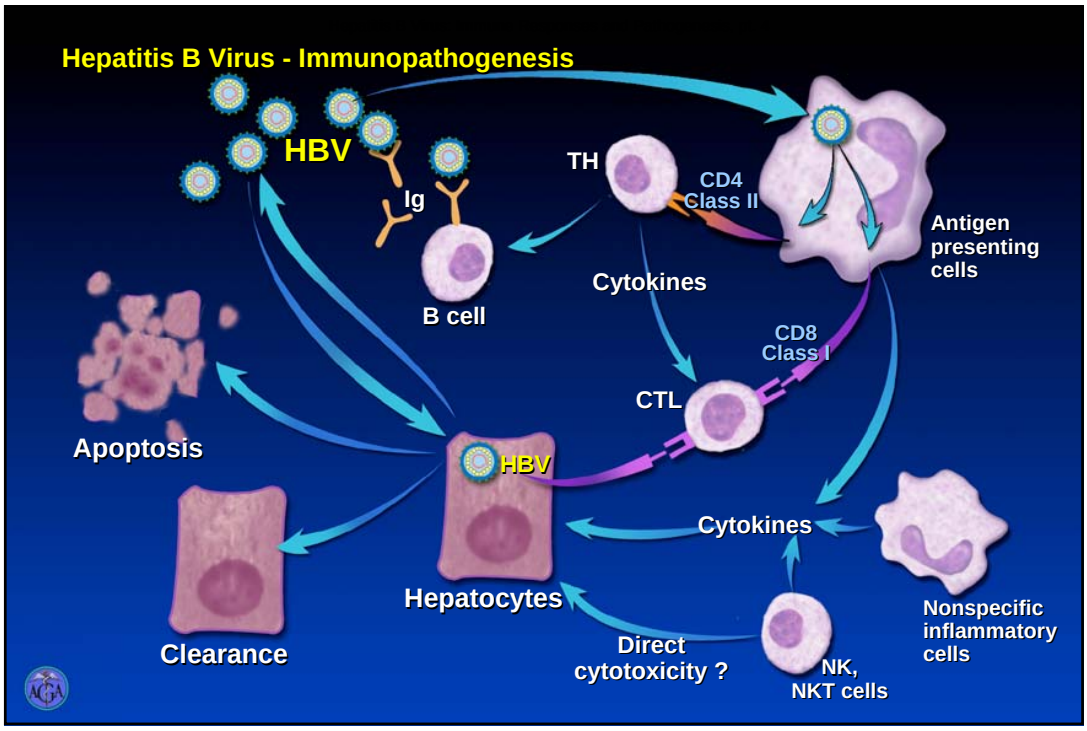
Cytokines
CD8
Class I
CTL
HBV
Cytokines
Hepatocytes
Nonspecific
inflammatory
cells
Direct
cytotoxicity ?
NK,
NKT cells



HEPATITIS B CLINICAL

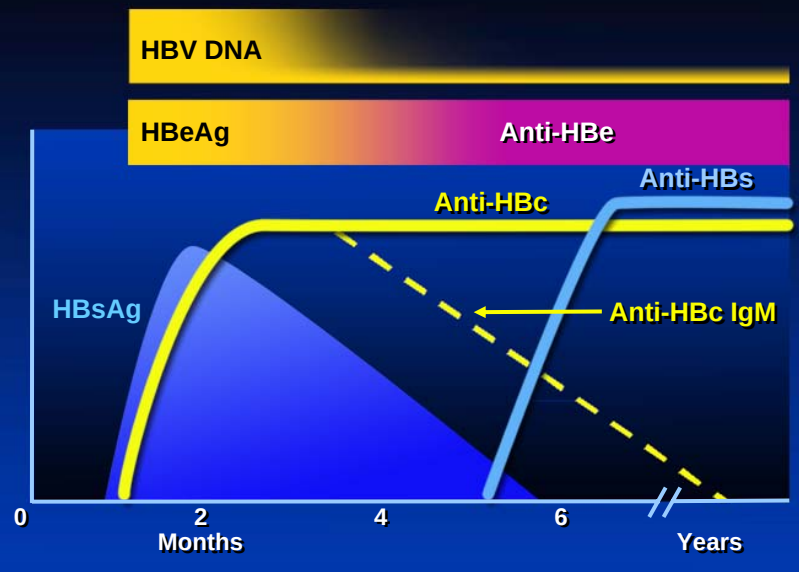
- Transmission – parenteral, secretions, sexual mother to child (vertical)
- 6-8 week incubation
- 20% pf patients have serum sickness prodrome
- 4% of patients develop chronic hepatitis
- Treatment and vaccine available

HBV - Diagnosis

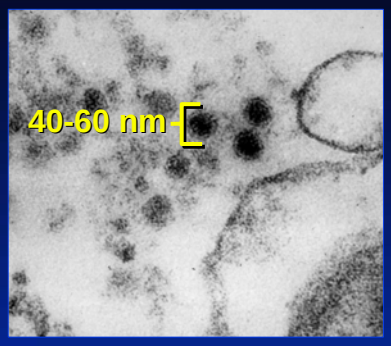
Serological Markers	Clinical Significance
HBsAg	Acute/Chronic infection
Anti-HBc IgM	Acute infection
HBeAg	High infectivity
Anti-HBe	Low infectivity
Anti-HBs	Immunity
Anti-HBc IgG and HBsAg	Chronic infection
Anti-HBc IgG and anti-HBs	Resolved infection

HBV - Diagnosis

Acute HBV Infection



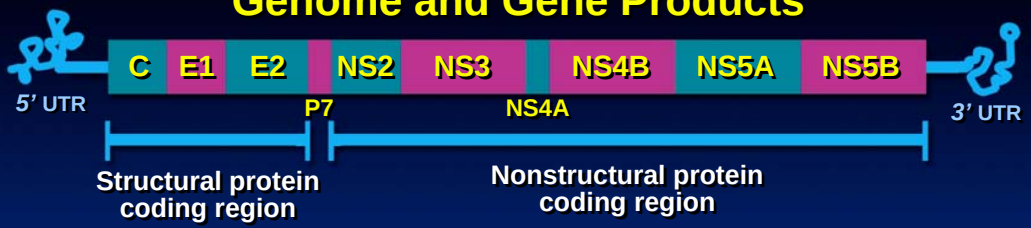
Hepatitis C Virus

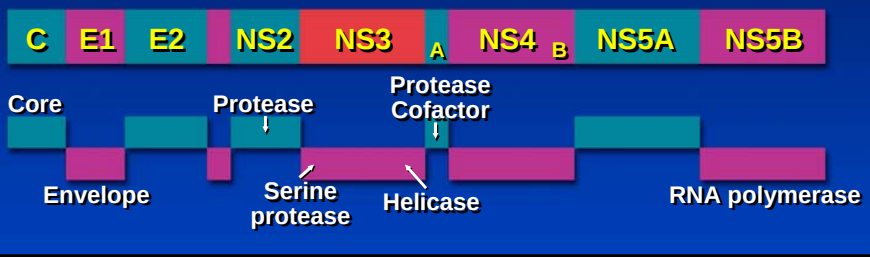


- Nucleic Acid: 9.6 kb ssRNA
- Classification: *Flaviviridae, Hepacivirus*
- Genotypes: 1 to 6
- Enveloped
- In vitro model: primary hepatocyte and T cell cultures; replicon system
- In vivo replication: in cytoplasm, hepatocyte and lymphocyte; human and other primates

Hepatitis C Virus

Genome and Gene Products

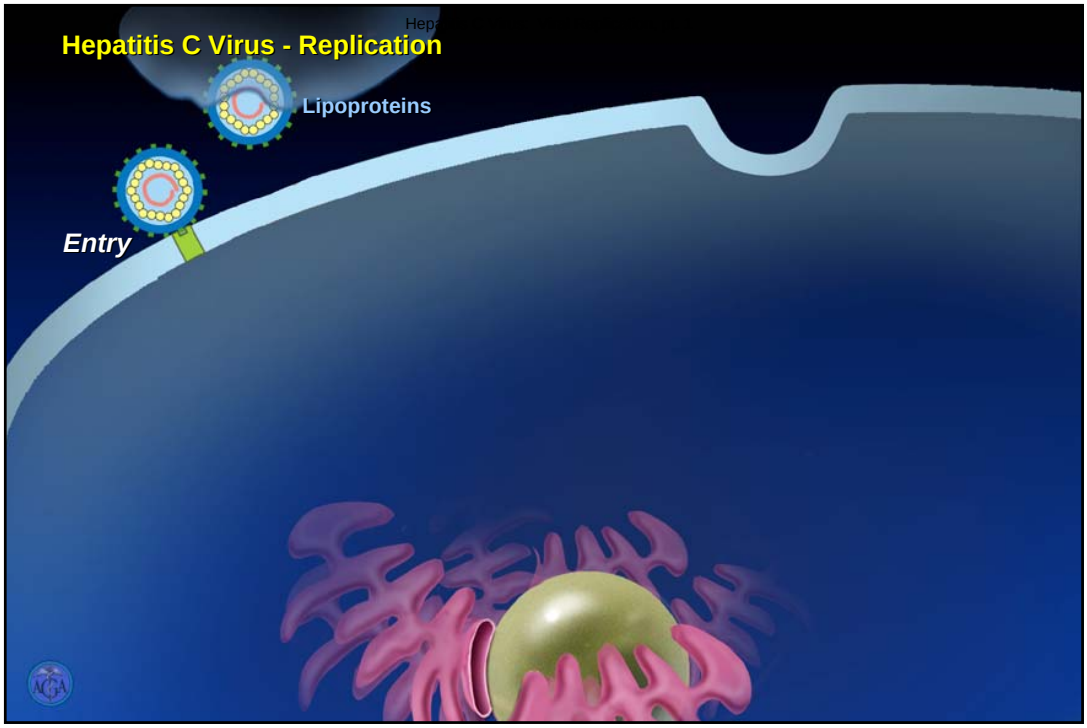


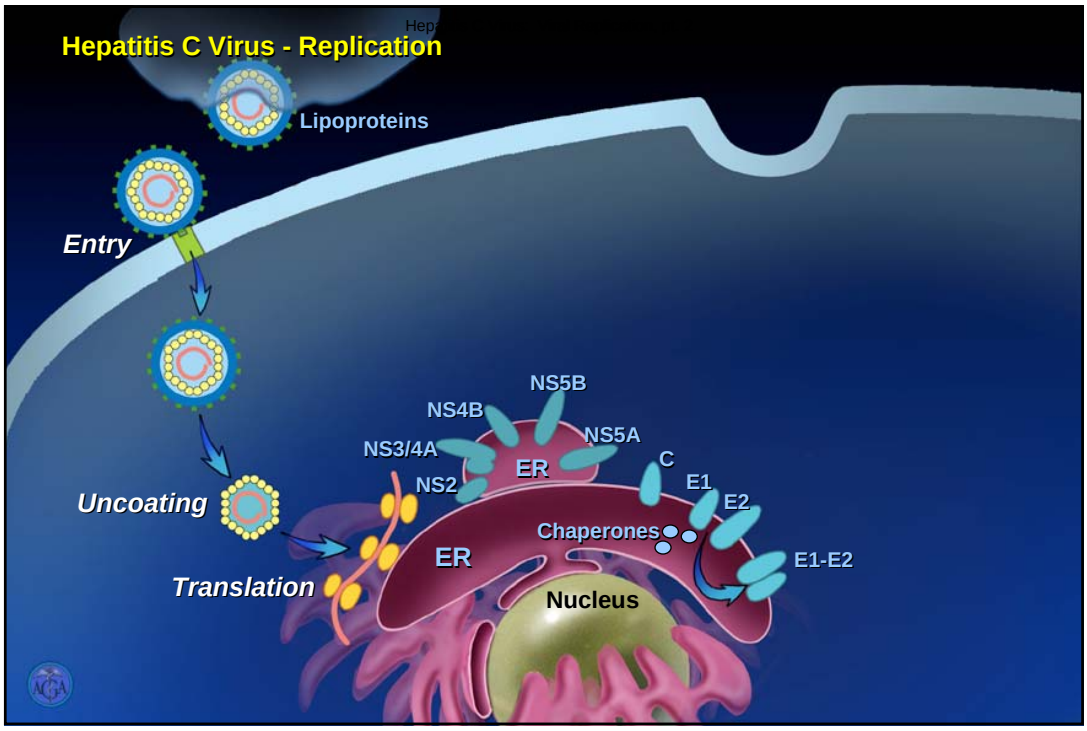


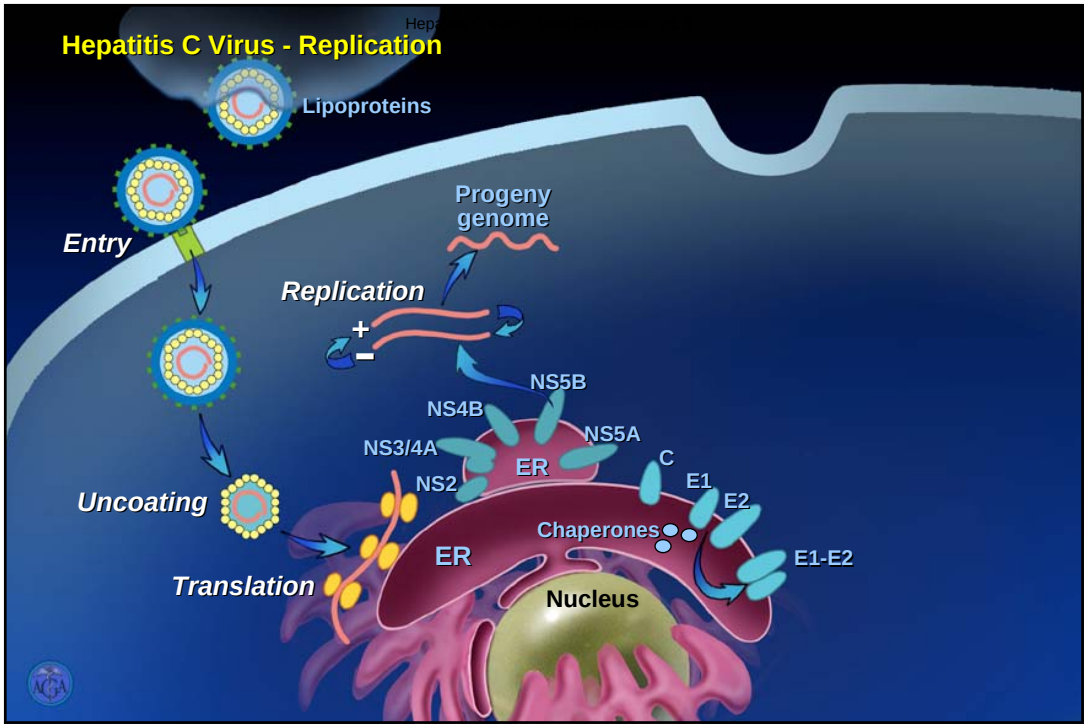
Hepatitis C Virus

Gene Products and Functions

Core (C)	Nucleocapsid
E1 and E2	Envelope proteins hypervariable region in E2
p7	Nonstructural, ion channel (?)
NS 2	NS 2-3 protease
NS 3	Protease, nucleotide triphosphatase, and RNA helicase
NS 4	Cofactor for NS 3 protease activity
NS 4B	Formation of membranous web
NS 5A	Interferon sensitivity sequence
NS 5B	RNA-dependent RNA polymerase




Hepatitis C Virus - Replication
Lipoproteins
Entry
Uncoating
Translation
NS5B
NS4B
NS5A
NS3/4A
NS2
ER
C
E1
E2
Chaperones
E1-E2
ER
Nucleus


Hepatitis C Virus - Replication
Lipoproteins
Entry
Progeny genome
Replication
+
−
Uncoating
Translation
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NS4B
NS5A
NS3/4A
NS2
ER
C
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E2
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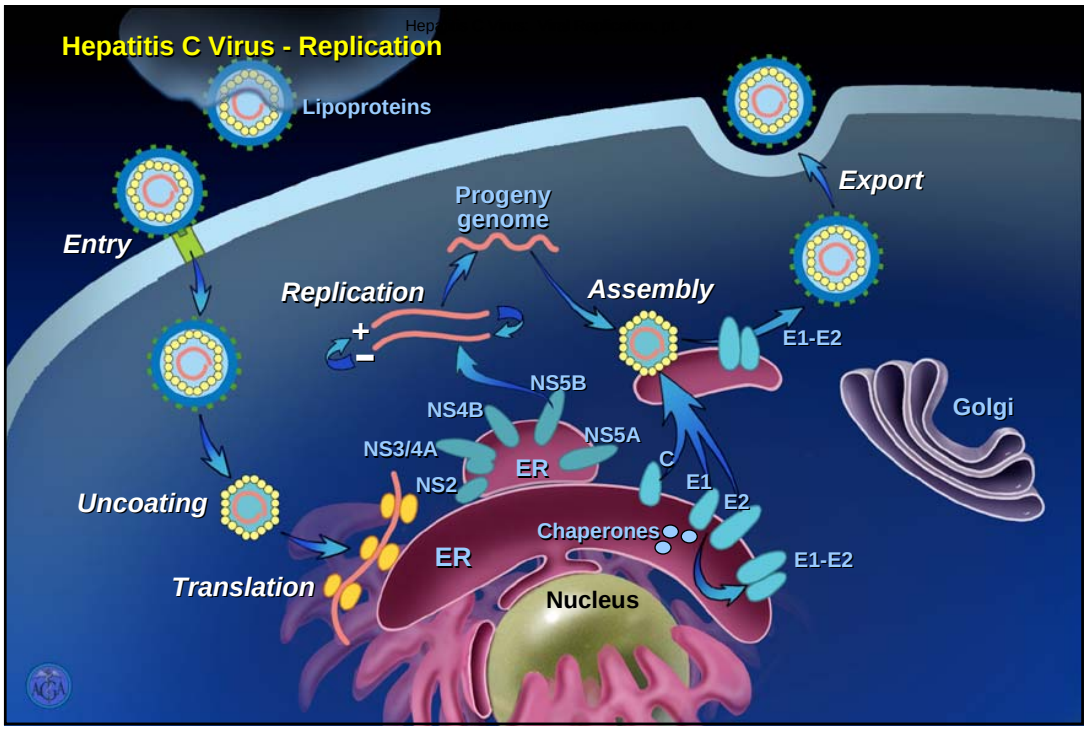
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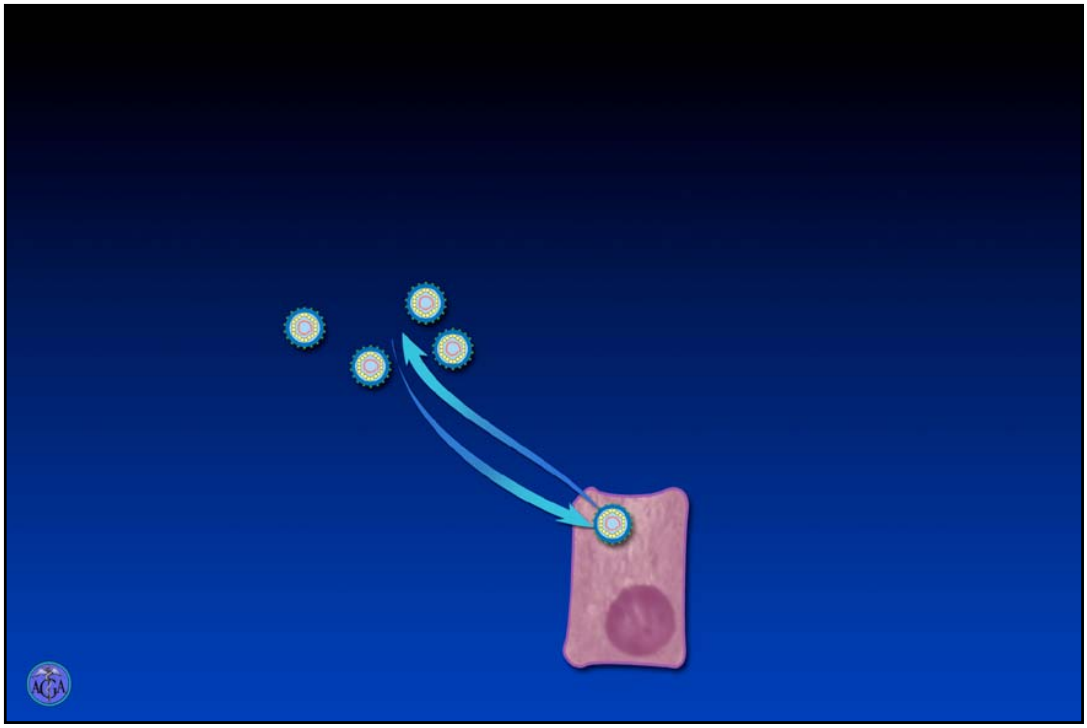
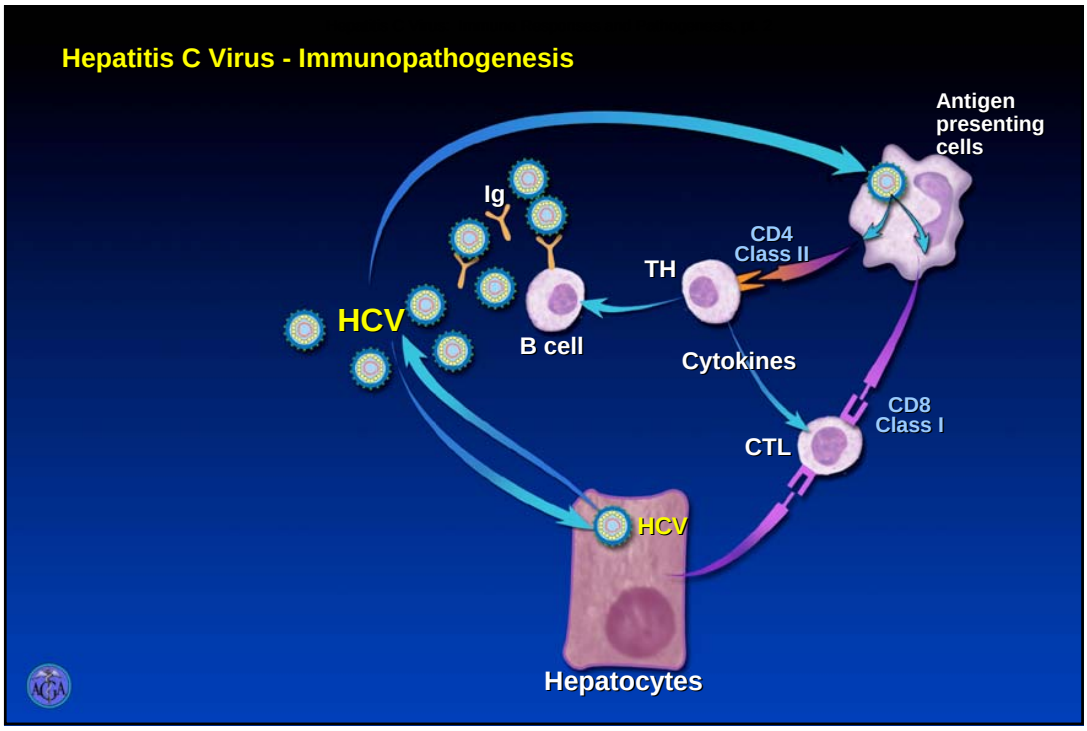
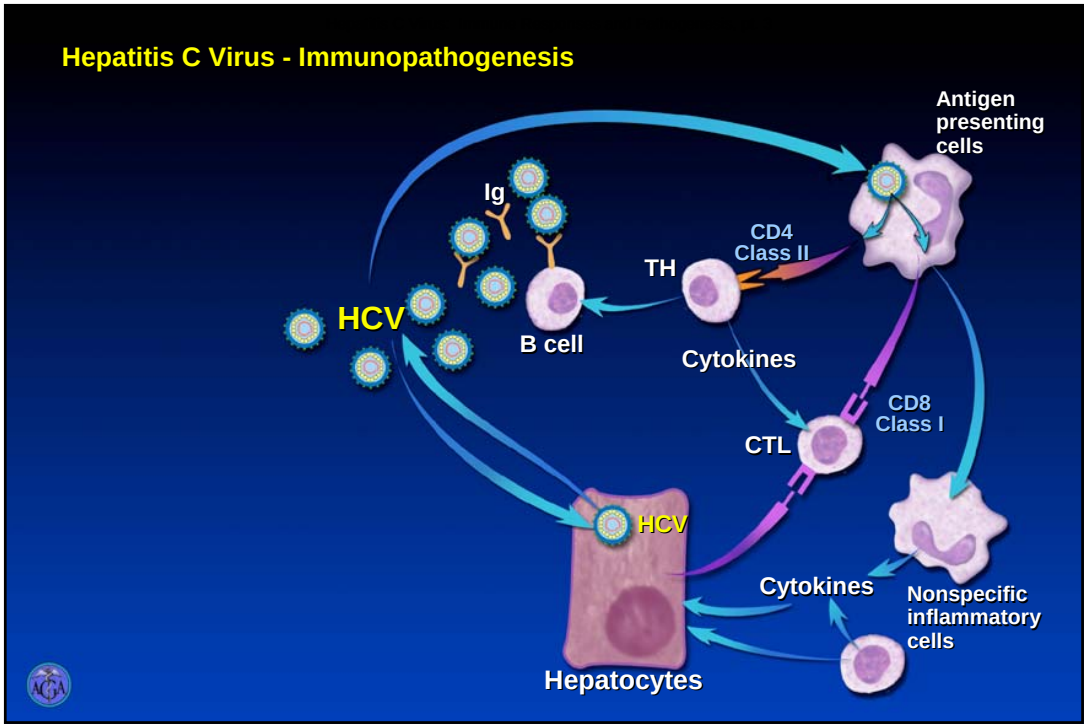
E2
NS2
Golgi
Uncoating
Chaperones
ER
E1-E2
Translation
Nucleus




Hepatitis C Virus - Immunopathogenesis
Antigen presenting cells
Ig
CD4 Class II
TH
HCV
B cell
Cytokines
CD8 Class I
CTL
HCV
Hepatocytes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B cell
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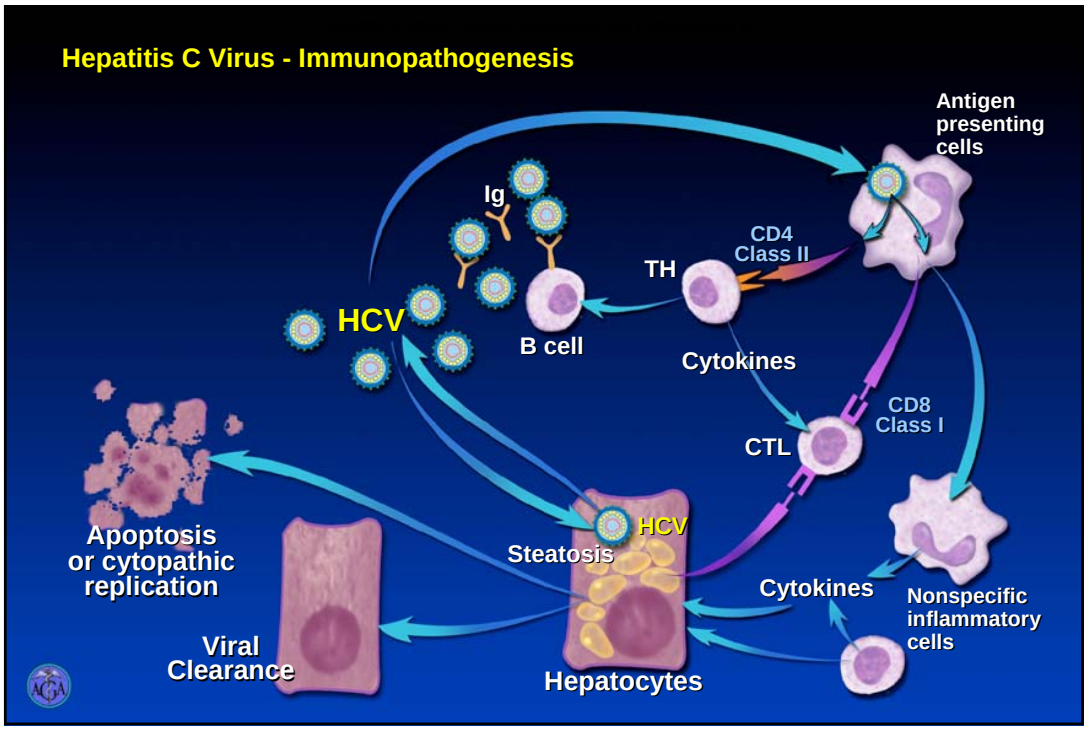
CTL
HCV
Cytokines
Nonspecific inflammatory cells
Hepatocytes


Hepatitis C Virus - Immunopathogenesis
Antigen presenting cells
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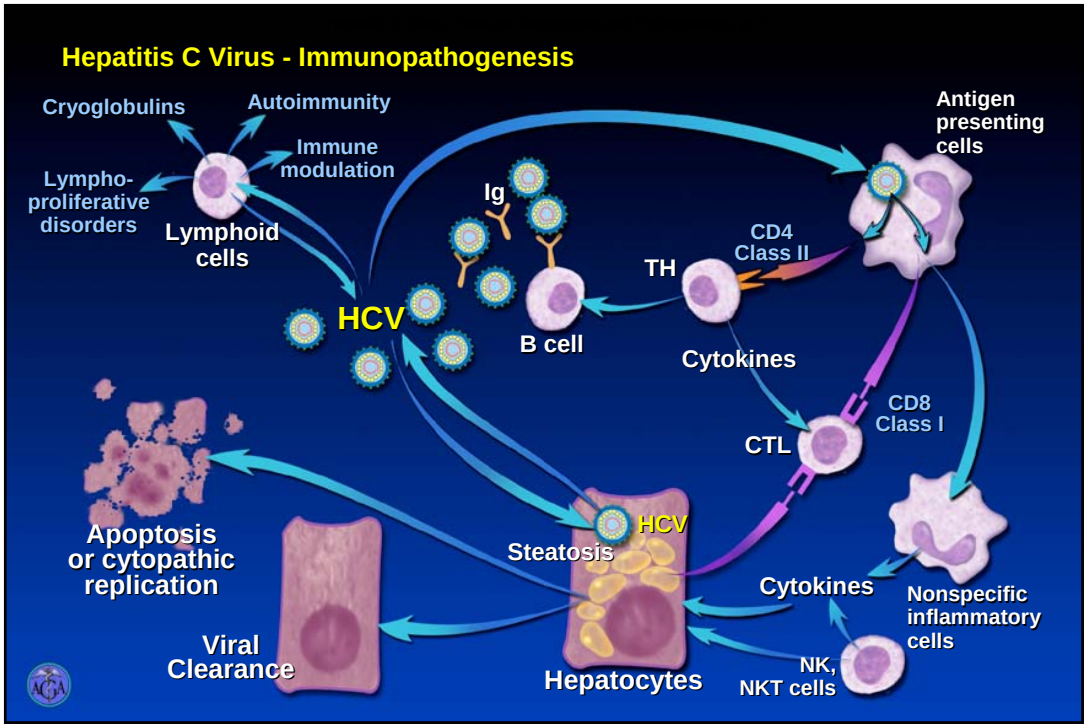
CD4 Class II
TH
HCV
B cell
Cytokines
CD8 Class I
CTL
Apoptosis or cytopathic replication
HCV
Steatosis
Cytokines
Nonspecific inflammatory cells
Viral Clearance
Hepatocytes

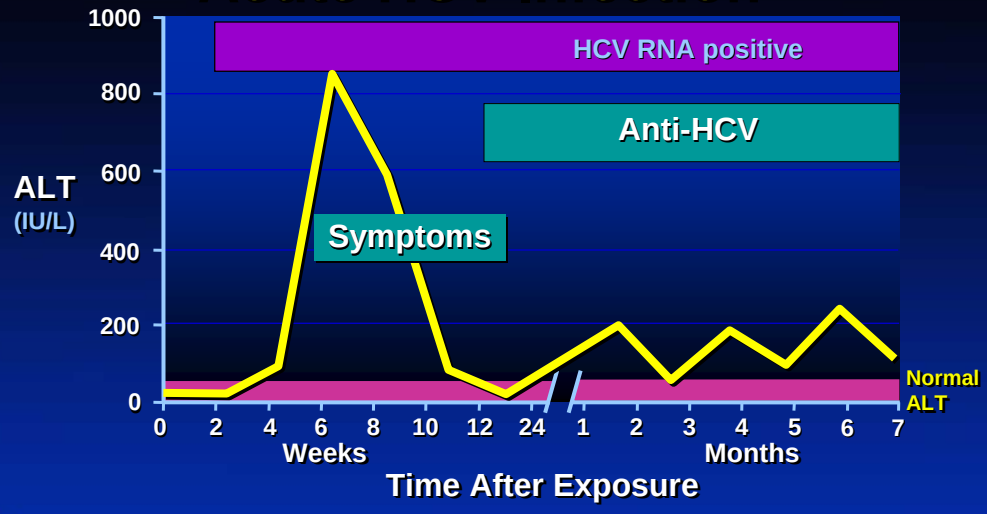

Hepatitis C Virus - Immunopathogenesis
Cryoglobulins
Autoimmunity
Immune modulation
Lympho-proliferative disorders
Lymphoid cells
Antigen presenting cells
Ig
CD4 Class II
TH
HCV
B cell
Cytokines
CD8 Class I
CTL
Apoptosis or cytopathic replication
HCV
Steatosis
Cytokines
Nonspecific inflammatory cells
Viral Clearance
Hepatocytes
NK, NKT cells

HEPATITIS C CLINICAL

- Most common cause of chronic hepatitis in USA
- 1.5% of population in USA carries the virus
- Parenteral transmission – blood, sexual
- 6-8 week incubation period
- Acute infection generally mild
- 80% of acute develop chronic disease
- No vaccine available
- Treatment – 40-80% cure rate

HCV - Diagnosis

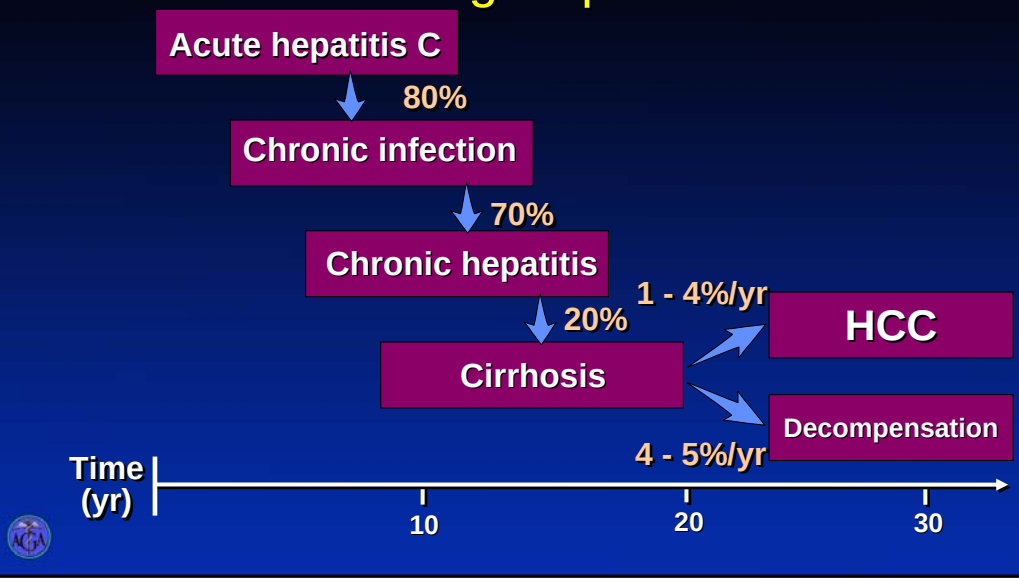
Acute HCV Infection



Hoofnagle JH, Hepatology 1997; 26:15S

HCV - Natural History

Outcome Following Hepatitis C Infection



HEPATITIS D AND E

- HEPATITIS D
  - Also known as delta agent
  - Uses the HBsAg protein coat
  - Hepatitis B must be present – coinfection or preexist
- HEPATITIS E
  - Water borne virus resembling hepatitis A
  - Rarely seen in USA

CHRONIC HEPATITIS

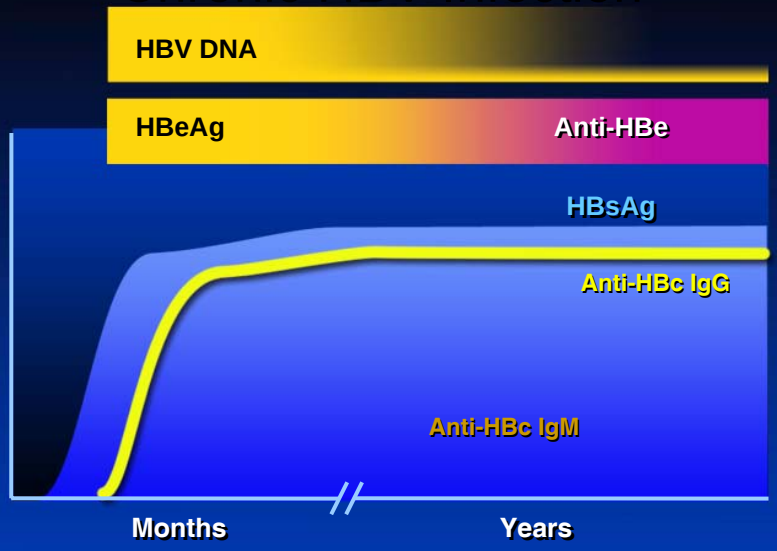
- Fatty liver
- Viral – B and C
- Autoimmune
- Drugs
- Alcohol
- Metabolic
- Others – CHF, hemochromatosis, vasculitis, IBD, celiac disease, neoplasia, etc.

CHRONIC HEPATITIS B AND C

- Cirrhosis develops in 20% of patients
- Liver failure and hepatoma develop in about ½ of cirrhotics
- Diagnosis of chronic hepatitis made on basis of:
  - chronic AST and ALT elevations
  - positive serology
  - positive DNA or RNA in blood
  - some patients have normal liver enzymes
- Treatment available with varying success rates

HBV - Diagnosis

Chronic HBV Infection

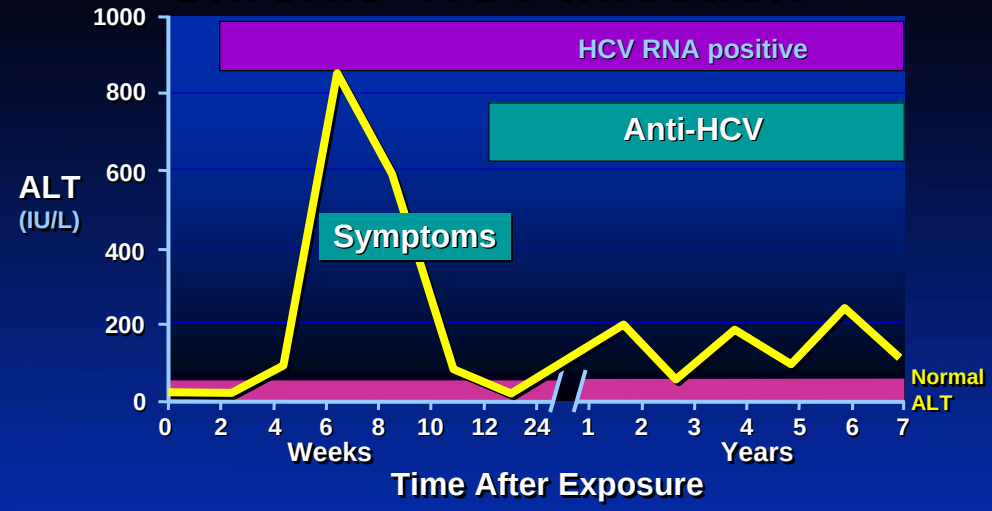


Serologic events in HBV infection

	HBsAg	anti-HBs	HBeAg	Anti-Hbe	Anti-HBc IgG	anti-HBc IgM	HBV DNA	ALT
Acute HBV Infection	+	-	+	-	+	+	+	↑↑
Vaccine Responder	-	+	-	-	-	-	-	Normal
Exposure with Immunity	-	+	-	+/-	+	-	-	Normal
Chronic HBV (Wild Type)	+	-	+	-	+	-	+	↑ / N
Chronic HBV (Precore Mutant)	+	-	-	+	+	-	+	↑ /N
Inactive Carrier	+	-	-	+	+	-	-/+	Normal

HCV - Diagnosis

Chronic HCV Infection



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AUTOIMMUNE HEPATITIS

- Genetically predisposed host exposed to an environmental agent triggering an autoimmune response directed at liver antigens leading to a necroinflammatory response
- Associated with other autoimmune diseases - thyroid disease, colitis, hemolytic anemia, ITP, diabetes, celiac disease, polymyositis, pericarditis, SLE, MCTD

AUTOIMMUNE HEPATITIS

- Clinical presentation – generally female, fatigue, jaundice, hypergammaglobulinemia, elevated AST and ALT
- Presence of associated autoantibodies – ANA, thyroid antiboides, LKM, smooth muscle
- Diagnostic liver biopsy – interface hepatitis and plasma cell infiltration
- Treatment - steroids and immunosuppressants

END