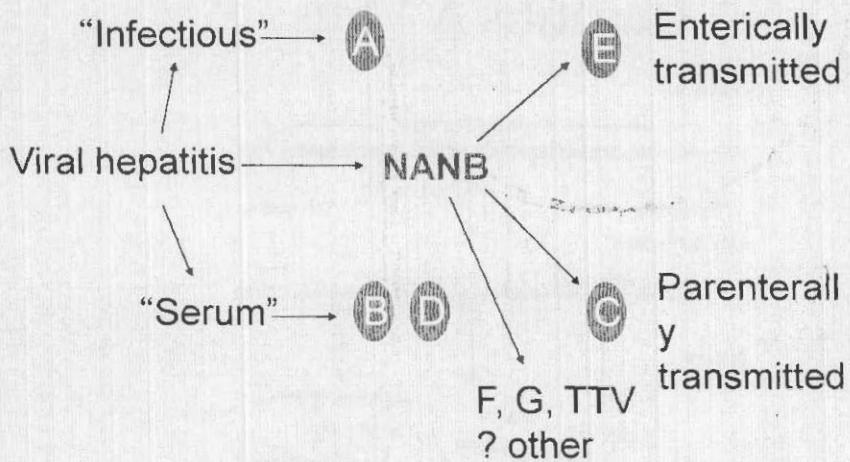


Hepatitis Viruses A-E

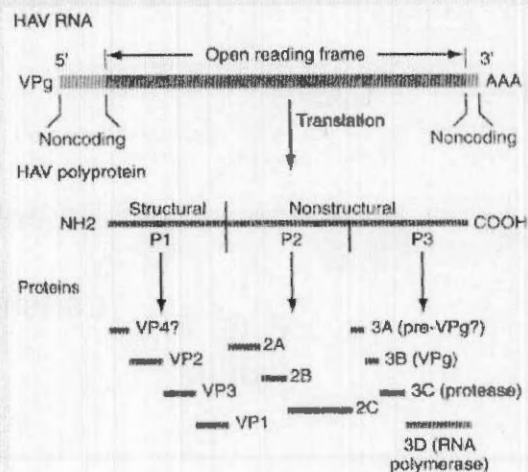
Viral Hepatitis - Historical Perspective



Types of Viral Hepatitis

	A	B	C	D	E
Source of virus	feces	blood/ blood-derived body fluids	blood/ blood-derived body fluids	blood/ blood-derived body fluids	feces
Route of transmission	fecal-oral	percutaneous permucosal	percutaneous permucosal	percutaneous permucosal	fecal-oral
Chronic infection	no	yes	yes	yes	no
Prevention	pre/post- exposure immunization	pre/post- exposure immunization	blood donor screening; risk behavior modification	pre/post- exposure immunization; risk behavior modification	ensure safe drinking water

Hepatitis A Virus



Genomic organization of hepatitis A virus (HAV). VP, viral protein.

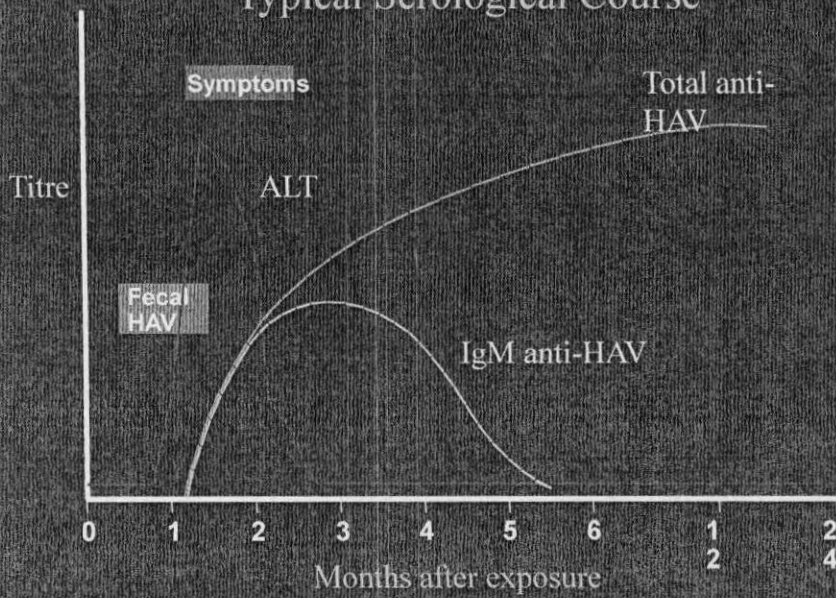
Hepatitis A - Clinical Features

- Incubation period: Average 30 days
Range 15-50 days
- Jaundice by age group: <6 yrs, <10%
6-14 yrs, 40%-50%
>14 yrs, 70%-80%
- Complications: Fulminant hepatitis
Cholestatic hepatitis
Relapsing hepatitis
- Chronic sequelae: None

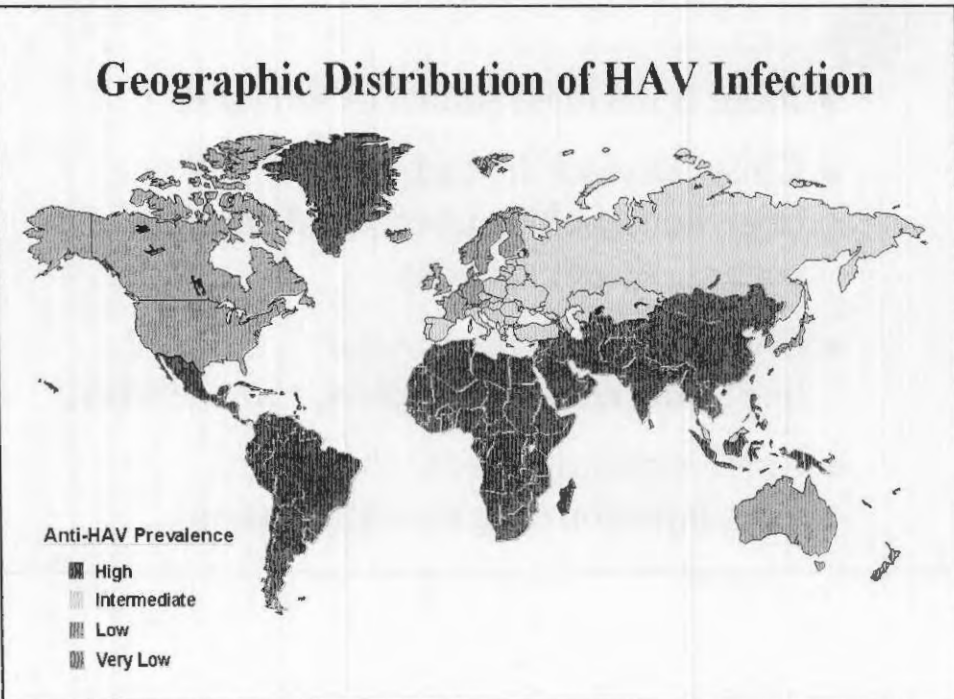
Hepatitis A Virus Transmission

- Stool is the main source of infection.
- Close personal contact
(e.g., household contact, child day care centers, sexual contact)
- Contaminated food or water
(e.g., infected food handlers, raw shellfish)
- Blood exposure (rare)
(e.g., injection drug use, transfusion)

Hepatitis A Infection Typical Serological Course



Geographic Distribution of HAV Infection



Global Patterns of Hepatitis A Virus Transmission

Endemicity	Disease Rate	Peak Age of Infection	Transmission Patterns
High	Low to High	Early childhood	Person to person; outbreaks uncommon
Moderate	High	Late childhood/ young adults	Person to person; food and waterborne outbreaks
Low	Low	Young adults	Person to person; food and waterborne outbreaks
Very low	Very low	Adults	Travelers; outbreaks uncommon

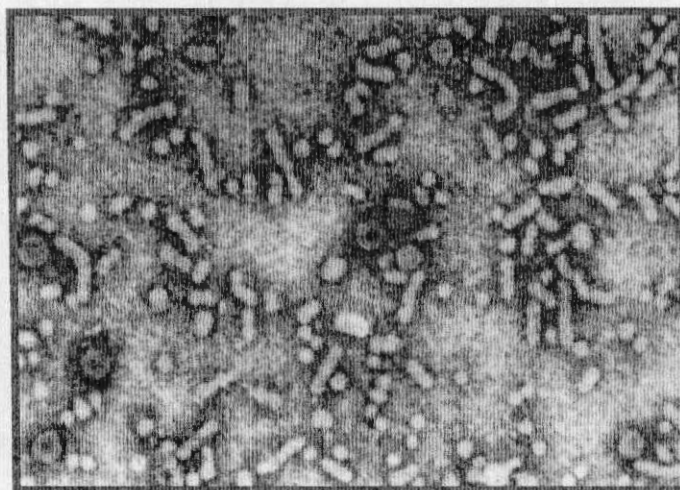
Laboratory Diagnosis

- Acute infection is diagnosed by the detection of HAV-IgM in serum by EIA.
- Past Infection i.e. immunity is determined by the detection of HAV-IgG (total anti-HAV) by EIA.

HAV Treatment and Prevention

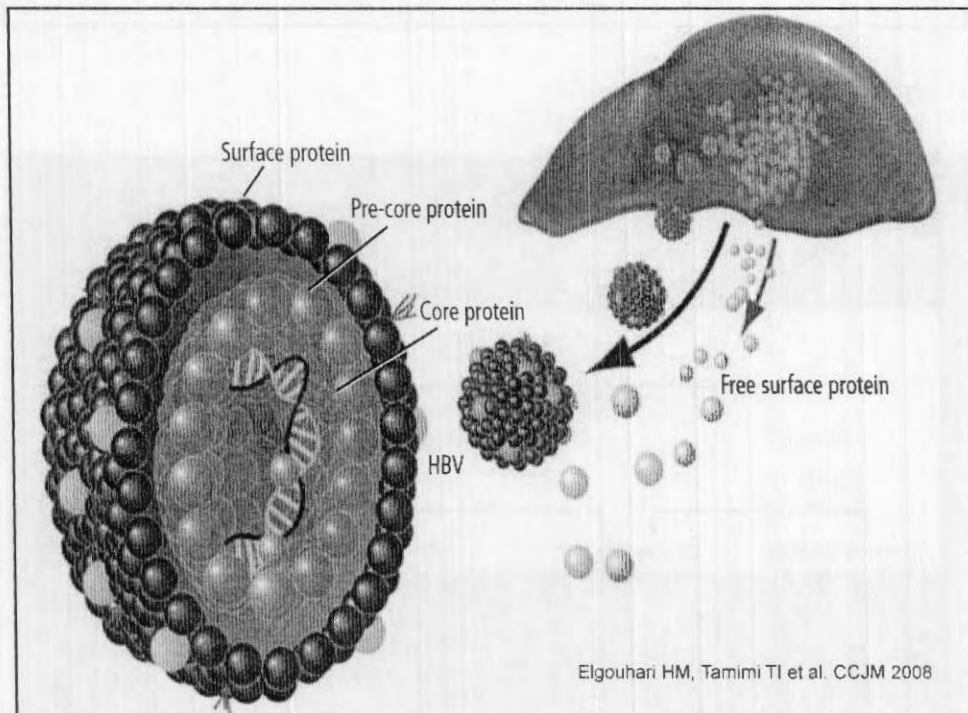
- Symptomatic treatment is the rule. No specific medications.
- Attention to sanitation.
- Pre-exposure HAV vaccine administered to high-risk groups e.g. travelers to endemic areas.
- Post-exposure HAV vaccine or IG within 2 weeks of exposure.

Hepatitis B Virus



Hepatitis B Virus

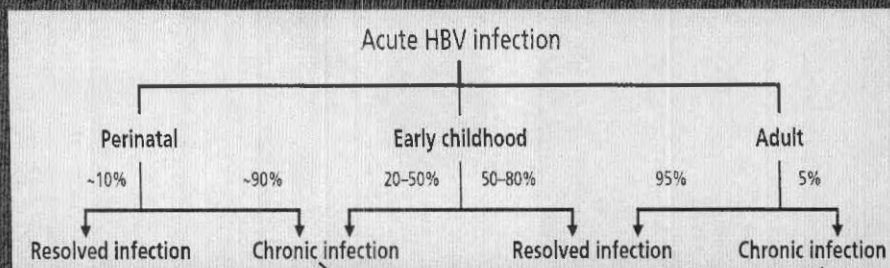
- DNA virus of the Hepadnaviridae family
- Genome is double-stranded, 4 genes:
 - S gene → the viral envelope HBsAg
 - C gene → both the nucleocapsid (core) antigen and the pre-core (e) antigen
 - X gene → two regulatory proteins required for HBV replication
 - P gene → DNA polymerase



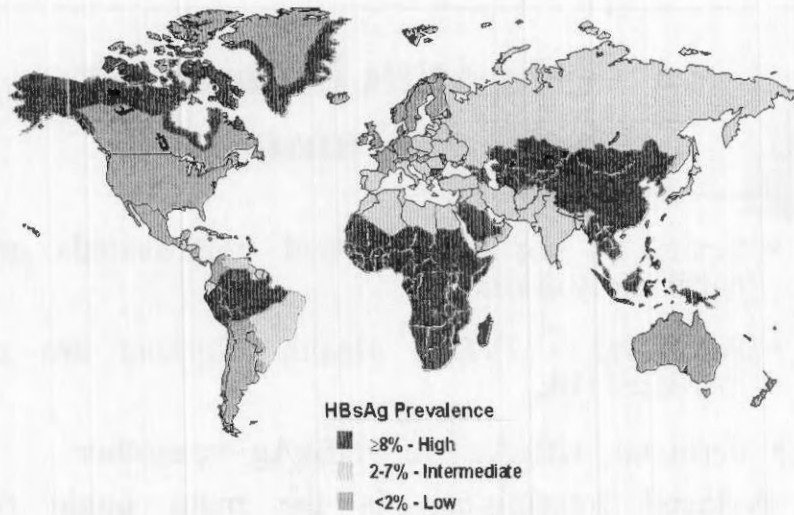
Hepatitis B - Clinical Features

- Incubation period: Average 60-90 days
Range 45-180 days
- Clinical illness (jaundice): <5 yrs, <10%
>5 yrs, 30%-50%
- Acute case-fatality rate: 0.5%-1%
- Chronic infection: <5 yrs, 30%-90%
>5 yrs, 2%-10%
- Premature mortality from chronic liver disease: 15%-25%

Hepatitis B- Clinical Features



Geographic Distribution of Chronic HBV Infection



Concentration of Hepatitis B Virus in Various Body Fluids

High	Moderate	Low/Not Detectable
blood	semen	urine
serum	vaginal fluid	feces
wound exudates	saliva	sweat
		tears
		breast milk

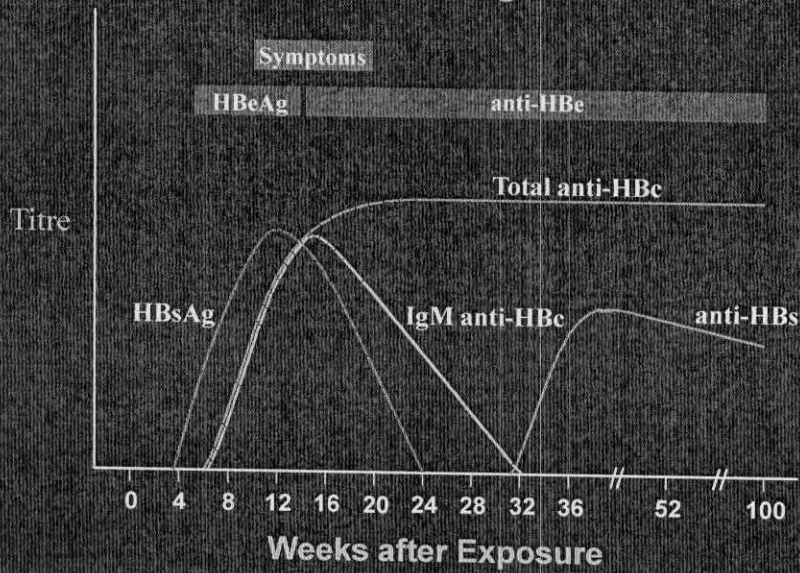
Hepatitis B Virus Modes of Transmission

- Sexual - sex workers and homosexuals are particularly at risk.
- Parenteral - IVDA, Health Workers are at increased risk.
- Perinatal - HBeAg +ve > HBeAg -ve mother
Perinatal transmission is the main mode of transmission in high prevalence populations.

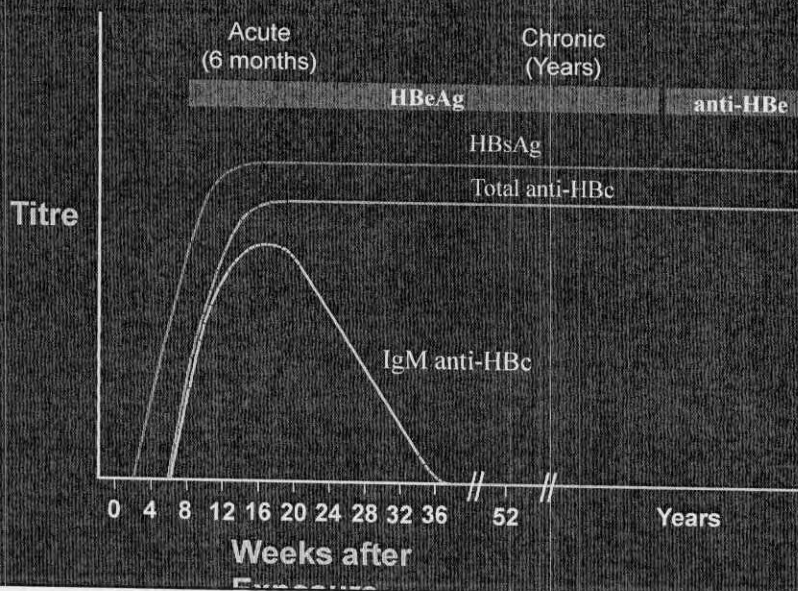
Global Patterns of Chronic HBV Infection

- High ($\geq 8\%$): 45% of global population
 - lifetime risk of infection >60%
 - early childhood infection is common
- Intermediate (2%-7%): 43% of global population
 - lifetime risk of infection 20%-60%
 - infection occurs in all age groups
- Low (<2%): 12% of global population
 - lifetime risk of infection <20%
 - most infections occur in adult risk groups

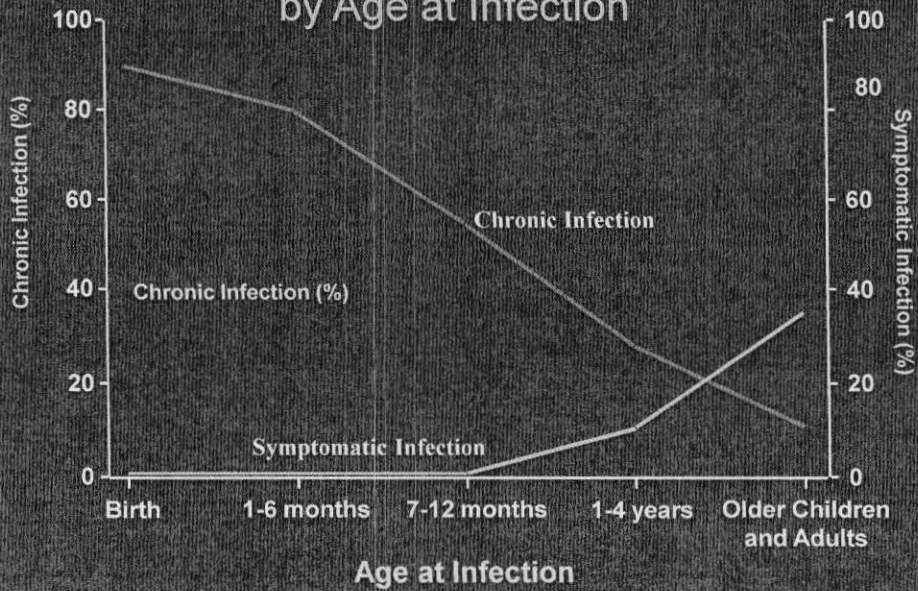
Acute Hepatitis B Virus Infection with Recovery Typical Serologic Course



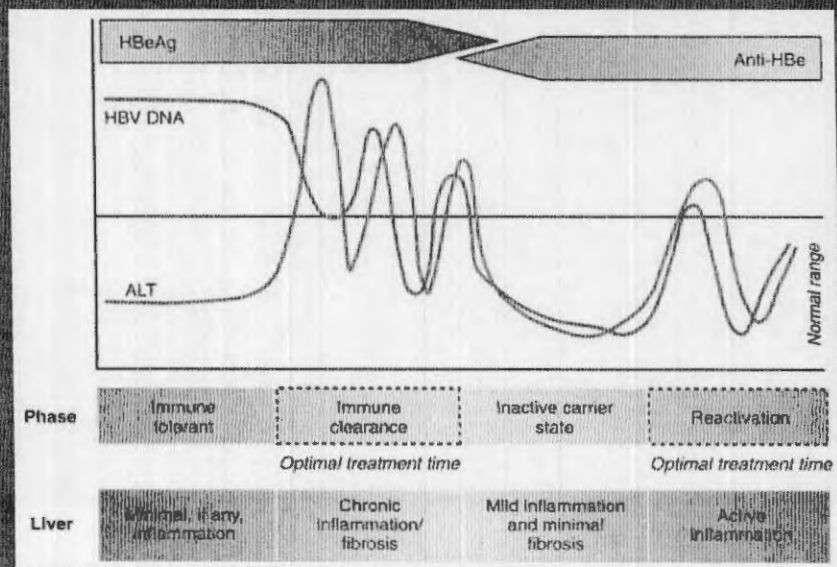
Progression to Chronic Hepatitis B Virus Infection Typical Serologic Course



Outcome of Hepatitis B Virus Infection by Age at Infection



Phases of Chronic HBV



Immune Clearance = Immune-Active CHB

Sliesenger and Fordtran's 9th Edition

Phases of Chronic HBV

TABLE 2

Phases of chronic hepatitis B virus infection

PHASE	E ANTIGEN	E ANTIBODY	HBV DNA	ALT	LIVER BIOPSY FINDINGS
Immune tolerance	Positive	Negative	High	Normal	Normal or nonspecific
Immune clearance	Positive	Negative	Moderately high	Elevated	Chronic hepatitis
Inactive carrier	Negative	Positive	Absent or low	Normal	Nonsignificant hepatitis (usually)
Reactivation	Negative or positive	Positive or negative	Moderate	Elevated	Chronic hepatitis

Egouhari HM, Tamimi TI et al. CCJM 2008

Interpretation of Screening Tests for HBV

TABLE 4. Interpretation of Screening Tests for HBV Infection

Screening Test Results			Interpretation	Management
HBsAg	Anti-HBc	Anti-HBs		
+	+	-	Chronic hepatitis B	Additional testing and management needed
-	+	+	Past HBV infection, resolved	No further management unless immunocompromised or undergoing chemotherapy or immunosuppressive therapy
-	+	-	Past HBV infection, resolved or false-positive	HBV DNA testing if immunocompromised patient
-	-	+	Immune	No further testing
-	-	-	Uninfected and not immune	No further testing

AASLD Guidelines 2018

Diagnosis

- A battery of serological tests are used for the diagnosis of acute and chronic hepatitis B infection.
- HBsAg - used as a general marker of infection.
- HBsAb - used to document recovery and/or immunity to HBV infection.
- Anti-HBc IgM - marker of acute infection.
- Anti-HBc IgG - past or chronic infection.
- HBeAg - a marker of HBV replication and infectivity.
- Anti-HBe - virus is no longer replicating. However, the patient can still be positive for HBsAg which is made by integrated HBV.
- HBV-DNA - indicates active replication of virus, more accurate than HBeAg especially in cases of escape mutants. Used mainly for monitoring response to therapy.

Treatment

- In general, no specific treatment for acute HBV.
- Chronic HBV:
 - Interferon
 - Nucleos(t)ide analogs: Preferred agents include Entecavir and Tenofovir

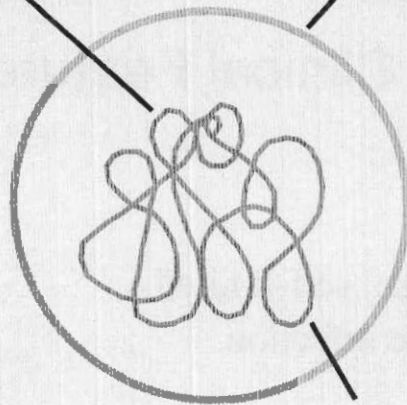
Prevention

- Vaccination
 - Those at increased risk of HBV infection such as health care workers.
 - Given routinely to neonates as universal vaccination in many countries.
- Hepatitis B Immunoglobulin HBIG
 - Used to protect persons who are exposed to hepatitis B. Particularly efficacious within 48 hours of the incident.
 - Neonates born to HBsAg positive mothers (+ HBV vaccine).
- Other measures - screening of blood donors; blood and body fluid precautions.

Hepatitis D (Delta) Virus

δ antigen

HBsAg



RNA





Hepatitis D Virus Modes of Transmission

- Percutaneous exposures
 - injection drug use
- Permucosal exposures
 - sexual contact

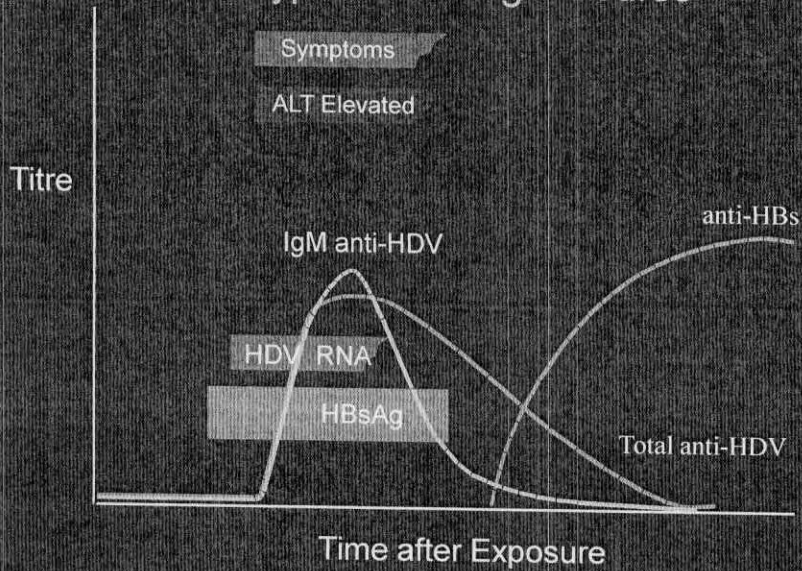


Hepatitis D - Clinical Features

- Coinfection
 - Severe acute disease; self-limited.
 - Low risk of chronic infection.
- Superinfection
 - May present as an acute hepatitis.
 - High risk of decompensation of chronic liver disease.
 - Usually develops chronic HDV infection.

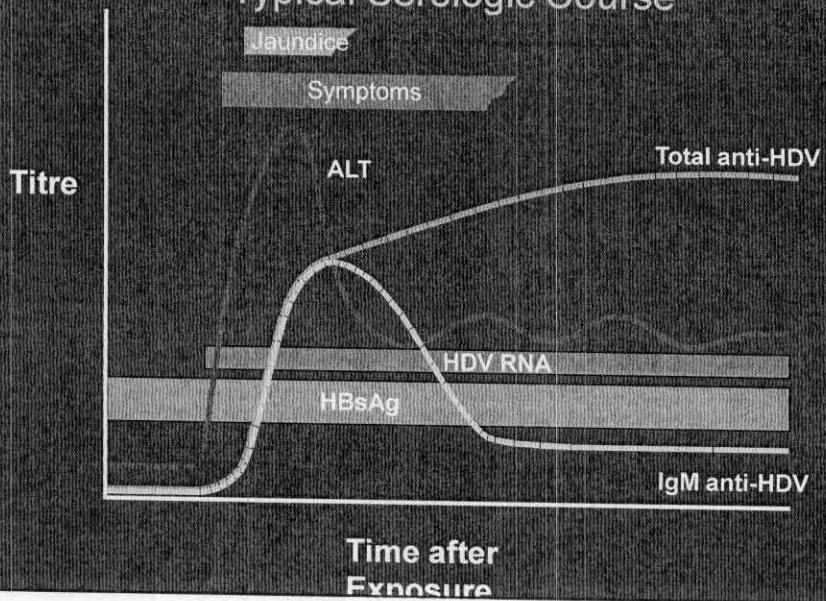
HBV - HDV Coinfection

Typical Serologic Course

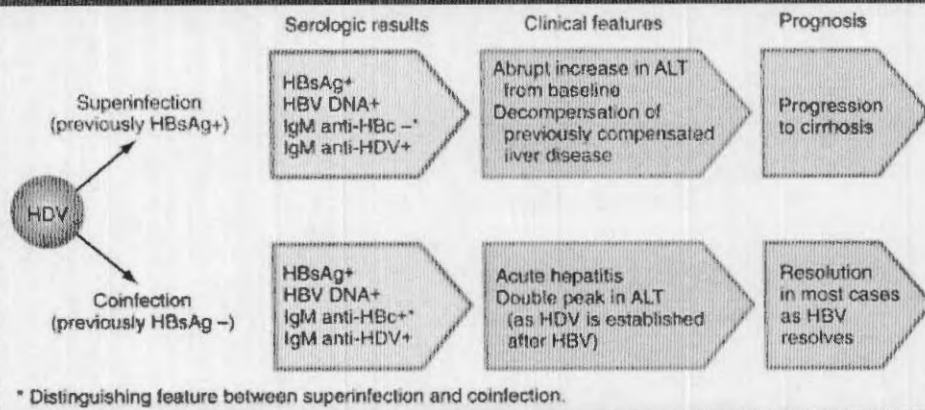


HBV - HDV Superinfection

Typical Serologic Course

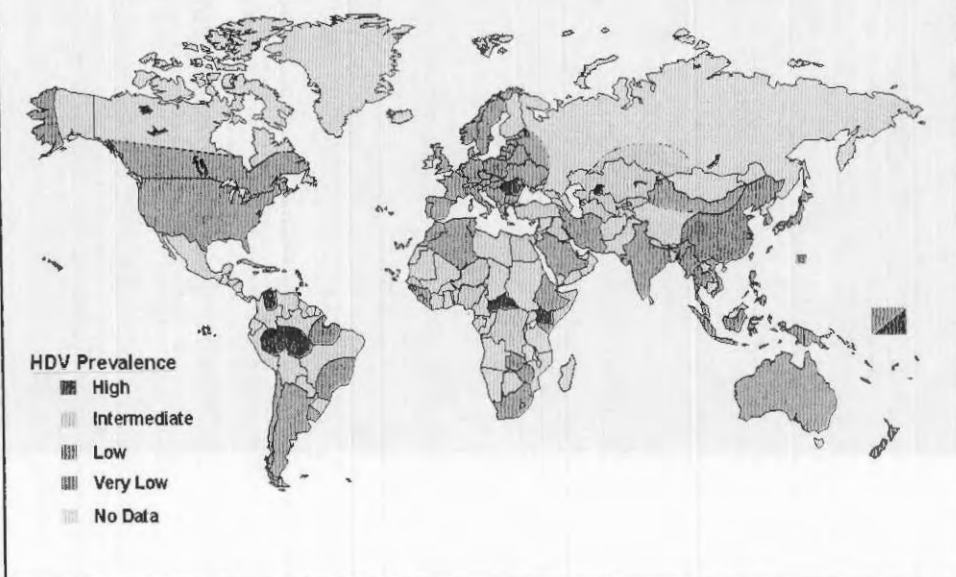


Serology, Clinical Features and Prognosis of HDV Infection



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Geographic Distribution of HDV Infection



Treatment of HDV-HBV Infection

- Interferon alpha: pegylated better than conventional; duration 48 to 72 weeks
- Nucleos(t)ide analogs are not effective in HDV infection.

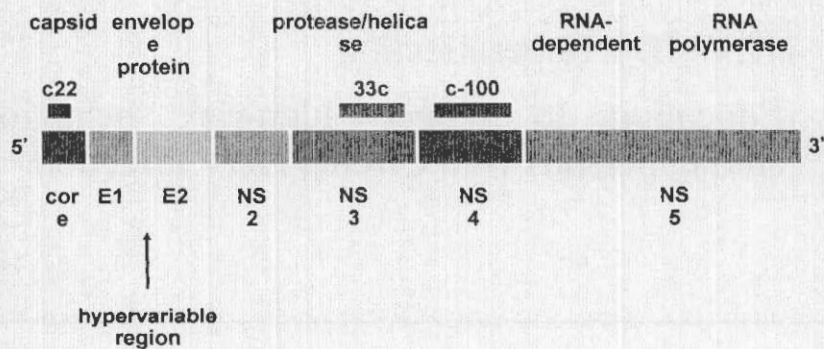
Hepatitis D - Prevention

- HBV-HDV Coinfection
Pre or postexposure prophylaxis to prevent HBV infection.
- HBV-HDV Superinfection
Education to reduce high-risk behaviors among persons with chronic HBV infection.

Hepatitis C Virus

- Single-stranded RNA virus
- Flaviviridae family
- 6 major genotypes

Hepatitis C Virus Polyprotein





HCV Modes of Transmission

- Percutaneous: blood transfusion and needlestick inoculation
- Sexual contact
- Perinatal exposure



Risk Factors Associated with Transmission of HCV

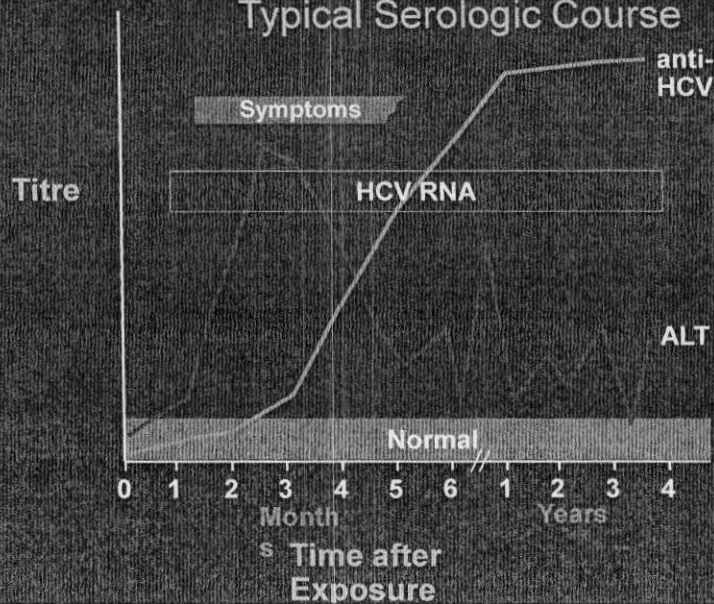
- Injection drug use
- Transfusion or transplant from infected donor
- Hemodialysis (years on treatment)
- Accidental injuries with needles/sharps
- Sexual/household exposure to anti-HCV-positive contact
- Multiple sexual partners
- Birth to HCV-infected mother

Hepatitis C - Clinical Features

Incubation period:	Average 6-7 wks Range 2-26 wks
Clinical illness (jaundice):	30-40% (20-30%)
Chronic hepatitis:	70%
Persistent infection:	85-100%
Immunity:	No protective antibody response identified

Hepatitis C Virus Infection

Typical Serologic Course



Prevalence of HCV Infection Among Blood Donors*



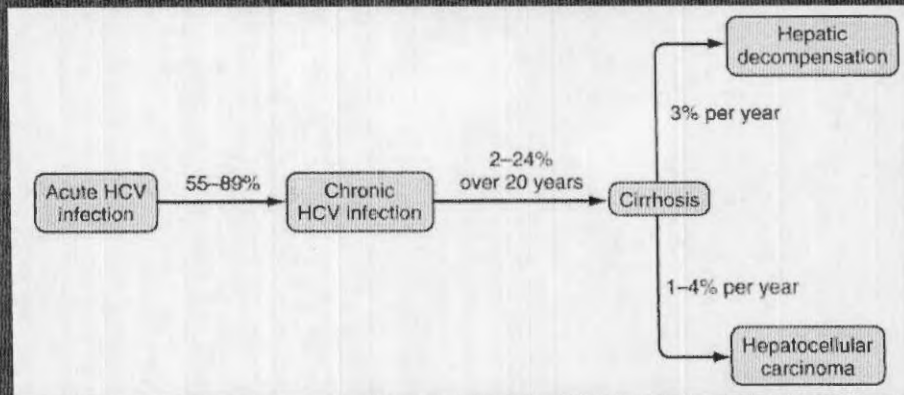
* Anti-HCV prevalence by EIA-1 or EIA-2 with supplemental testing; based on data available in January, 1995.

CDC

HCV Diagnosis

- HCV antibody:
 - EIA
 - Detectable at 4 - 8 weeks after infection
 - Used as a screening test; positive with any history of HCV infection (whether active or cleared)
- HCV RNA: qualitative and *quantitative*
 - Positive within 1- 3 weeks of acute infection
 - Indicates active viremia

Natural History of HCV Infection



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Treatment

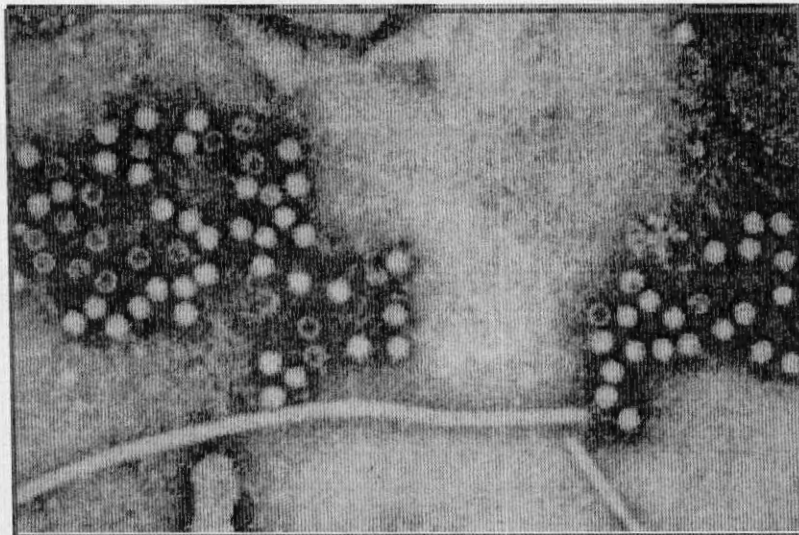
■ DIRECT-ACTING ANTIVIRALS (DAAs)

NS3/4A Protease Inhibitors	NS5A Inhibitors	NS5B Polymerase Inhibitors
Boceprevir	Daclatasvir	Dasabuvir
Glecaprevir	Elbasvir	Sofosbuvir
Grazoprevir	Ledipasvir	
Paritaprevir	Ombitasvir	
Simeprevir	Pibrentasvir	
Telaprevir	Velpatasvir	
Voxilaprevir		

Prevention of Hepatitis C

- Screening of blood, organs, tissue donors
- High-risk behavior modification
- Blood and body fluid precautions

Hepatitis E Virus



Hepatitis E - Clinical Features

- Incubation period: Average 40 days
Range 15-60 days
- Case-fatality rate: Overall, 1%-3%
Pregnant women,
15%-25%
- Illness severity: Increases with age
- Chronic sequelae: None identified

Geographic Distribution of Hepatitis E

Outbreaks or Confirmed Infection in >25% of Sporadic Non-ABC Hepatitis



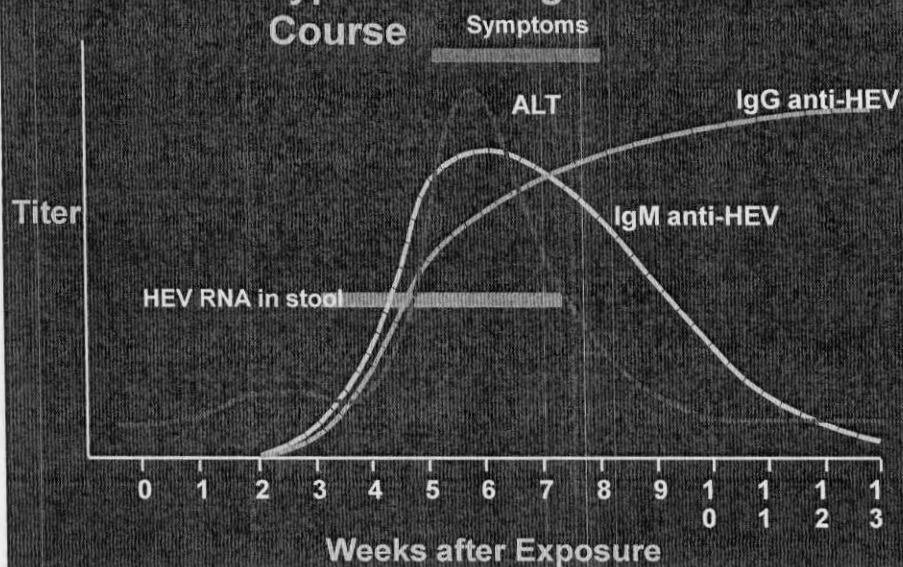
Epidemiologic Features of Hepatitis E

- Large outbreaks involving several thousand persons in developing countries
- Sporadic cases
- Frequent in endemic areas
- Uncommon in nonendemic areas (occur mainly among travelers to endemic areas)
- Fecal-oral transmission, usually through contaminated water
- Highest attack rates among young adults aged 15 to 40 years, with relative sparing of children
- Infrequent person-to-person transmission
- No evidence of parenteral or sexual transmission
- High attack rates in pregnant women, particularly in second and third trimesters
- High mortality rates (15% to 25%) in pregnant women, especially in the third trimester
- Mother-to-newborn (transplacental) transmission is likely

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Hepatitis E Virus Infection

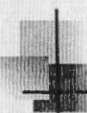
Typical Serologic Course





Treatment

- Acute HEV usually is self-limited.
- Supportive care.



Prevention and Control Measures for Travelers to HEV-Endemic

Regions

- Avoid drinking water (and beverages with ice) of unknown purity
- Avoid eating uncooked shellfish, and uncooked fruits/vegetables not peeled or prepared by traveler
- ?Vaccine?