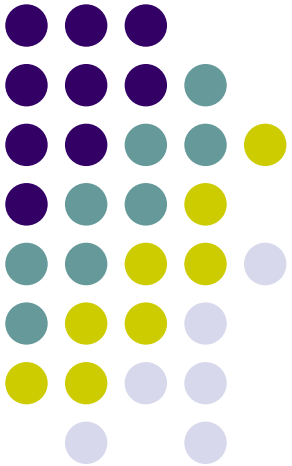
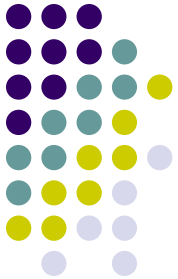
VIRAL HEPATITIS

V.Bodnar

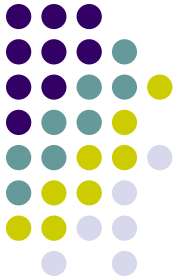


ETIOLOGY



- **HBV:** hepatitis B virus; partially double stranded DNA virus, enveloped, hepadnavirus
- **HCV**: hepatitis C virus; ssRNA, enveloped, flavivirus
- **HDV**: hepatitis D virus; ssRNA, associated with HBV, a viriod

Several antigens can be found in the blood at various times during viral infection

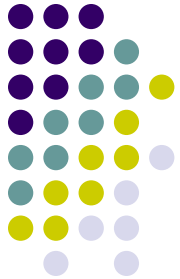


- **HBsAg or Australia antigen** - includes 3 glycoproteins (L, M, and S). HBsAg is an envelope protein eliciting neutralizing antibodies in the patient. This antigen is composed of a group (*a*) and type specific (termed *d* or *y* and *w* or *r*) determinants. Eight different subtypes of HBV exists. The most common combination of HBV surface antigens is either *adw* or *ady*. These type specific determinants are useful in epidemiology.
- **Other antigens:** Incomplete viral particles that may be present in the patient's serum include:
  - HBcAg: HBV core antigen
  - HBeAg: HBV soluble antigen = a minor component of the virion. HBeAg and HBcAg have nearly identical amino acid sequences. HBeAg is processed differently by the cell, is primarily secreted into the serum, does not self assemble like an HBcAg, and expressed different antigenic determinants.
  - viral DNA
  - DNA polymerase
  - protein kinase

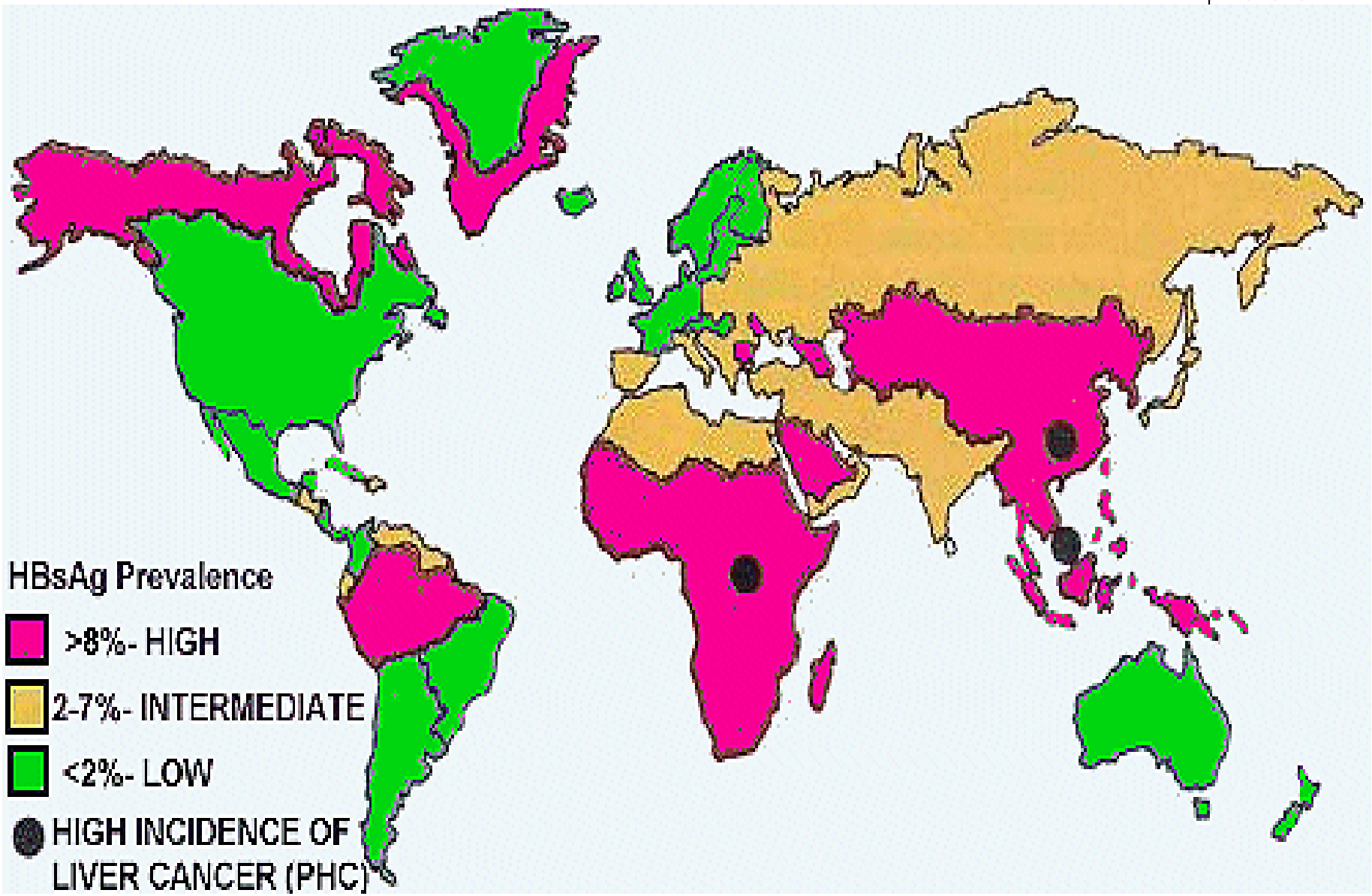
EPIDEMIOLOGY

- Distribution is worldwide, but uneven. Hepatitis B virus (HBV) infection is a serious global health problem, with 2 billion people infected worldwide, and 350 million suffering from chronic HBV infection. Approximately 15-40% of infected patients will develop cirrhosis, liver failure, or hepatocellular carcinoma (HCC). It is the 10th leading cause of death worldwide, HBV infections result in 500,000 to 1.2 million deaths per year due to chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC). HCC accounts for 320,000 deaths per year.
- Acute viral hepatitis in the US and Europe has been well characterized. About 55% is caused by HAV, 32% by HBV, and 12% by HCV. HBV and HCV play some role in 64% of patients with chonic liver disease. 80% of all cases of Primary Hepatocellular Carcinoma (HPC) is attributed to chronic HBV infections.
- Estimated 1-1.25 million Americans are chronically infected with HBV. HBV costs the American people an estimated $700 million (1991 dollars)/yr (medical and work loss).

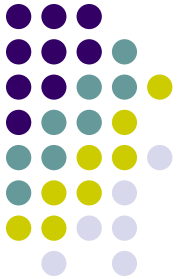
EPIDEMIOLOGY



- There are 36,000 new HCV infections/yr with 25-30% being symptomatic. Chronic infection occurs in >85% of persons infected with HCV. 70% of persons infected with HCV develop chronic liver disease. Deaths from chronic liver disease: 8,000-10,000/yr.
- Infection with HCV is the leading infectious indication for liver transplantation. About 3.9 million (1.8%) Americans have been infected with HCV of whom 2.7 million are chronically infected. HCV infections cost the American people an estimated $600 million (1991 dollars)/year (medical and work loss, excluding transplantation).
- HDV infection can be acquired either as a coinfection with HBV or as a superinfection of patients with chronic HBV infection. Patients with HBV-HDV coinfection may have more severe acute disease and a higher risk of fulminant hepatitis (2%-20%) compared with those infected with HBV alone. However, chronic HBV infection appears to occur less frequently in persons with HBV-HDV coinfection. Chronic HBV carriers who acquire HDV superinfection usually develop chronic HDV infection. In long-term studies of chronic HBV carriers with HDV superinfection, 70%-80% have developed evidence of chronic liver diseases with cirrhosis compared with 15%-30% of patients with chronic HBV infection alone.

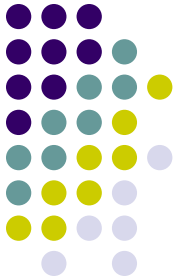

HBsAg Prevalence
>8%- HIGH
2-7%- INTERMEDIATE
<2%- LOW
HIGH INCIDENCE OF LIVER CANCER (PHC)

HBV Transmission



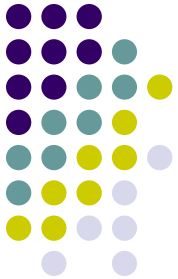
- Hepatitis B virus is present in the blood, saliva, semen, vaginal secretions, menstrual blood, and to a lesser extent, perspiration, breast milk, tears, and urine of infected individuals. A highly resilient virus, HBV is resistant to breakdown, can survive outside the body. It is easily transmitted through contact with infected body fluids. In areas of high endemicity, the most common route of transmission is perinatal or the infection is acquired during the preschool years. The route of transmission has important clinical implications, because there is a very high probability of developing chronic hepatitis B (CHB) if the infection is acquired perinatally or in the preschool years.
- The virus can be spread by percutaneous routes (e.g. needle sharing, acupuncture, ear piercing, tattooing, transfusions, receiving blood products) and through very close personal contact involving the exchange of blood or secretions (e.g. sex, child birth).

HBV Transmission



- The pattern of transmission of HBV varies with chronic HBV prevalence. In areas where chronic infections (chronic hepatitis) are highly endemic (East and Southeast Asia and Sub-Saharan Africa), transmission is usually perinatal (from a carrier mother to her newborn) or by close contact between children (horizontal transmission). Perinatal transmission of HBV usually occurs during or soon after delivery following contact of the infant with maternal blood and other body fluids. In areas of low endemicity (Western Europe and North America), perinatal transmission is less common and transmission occurs mainly through blood and by sexual contact between adults.
- There is no evidence that breastfeeding from a chronically infected mother poses an additional risk of HBV infection to her infant, even without immunization. However, damage to the breast as a result of breastfeeding, such as cracked or bleeding nipples or lesions with serous exudates, could however expose the infants to infectious doses of HBV. Therefore, neonates born to chronically infected women should be given hepatitis B immunoglobulin at birth along with the first dose of the hepatitis B recombinant vaccine. The remaining doses of vaccine should be given at 1 and 6 months of age.

At high risk for HBV infection:



- intravenous drug users
- patients undergoing blood transfusions or hemodialysis lab
- personnel in contact with blood and blood products
- individuals with multiple sexual contacts (heterosexual and homosexual)
- immunosuppressed individuals
- infants born to mothers with chronic HBV
- residents and staff members of institutions for the mentally handicapped
- people from endemic regions (i.e., China, parts of Africa, Alaska, Pacific Islands)

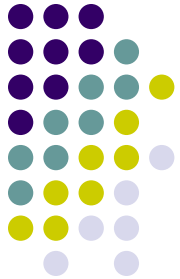
HCV Transmission

- **HCV** infections are mainly associated with injecting drug use (60%).
- HCV can also be transmitted by sexual contact (15%) however the efficiency of sexual transmission is quite low. People with increased risk factors for sexual transmission of HCV are those that participate in unprotected sex with multiple sexual partners, begin sexual activity at an early age, have an infected sexual partner, have a history of other STD's, and/or experience sex with trauma.
- HCV is the most common infectious reason patients need liver transplants; 2.7 million people are chronic carriers of HCV.

HDV Transmission

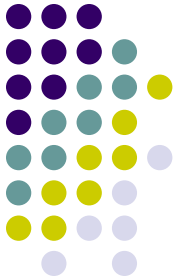
- **HDV** infections are usually due to percutaneous exposures. Most commonly found in IV drug users. Sexual transmission of HDV is less efficient than for HBV. Perinatal HDV transmission is rare.

PATHOGENESIS



- HBV replicates within liver cells, within 3 days following bloodstream acquisition. Replication of the virus is not cytopathic; symptoms may not be observed for 45 days or longer, depending on the dose of HBV, the route of infection, and the individual.
- HBV genomes integrate into host chromosomes during replication; the basis of latent infections. Large amounts of HBsAg are released into the blood as well as complete virions.
- Immune complexes formed by HBsAg and specific antibody are responsible for hypersensitivity reactions seen as arthritis, rash, liver damage, vasculitis, arthralgia (acute paroxysmic joint pain), or kidney problems.
- Liver parenchyma degeneration results from cellular swelling and necrosis. Resolution of the infection allows the liver parenchyma to regenerate.
- Fulminant infections, activation of chronic infections, or coinfection with the delta agent can lead to permanent liver damage or cirrhosis.

PATHOGENESIS



- Resolution of disease: Both cell mediated immunity and inflammation are responsible for the resolution of HBV infection and its symptoms.
- Acute cases of HBV disease are usually of short duration with significant symptomology.
- Chronic Hepatitis B infection or CHB is the presence of Hepatitis S antigen (HbsAg) in the bloodstream following infection by Hepatitis B virus for at least 6 months. The early phase of chronic Hepatitis B virus (CHB) infection is characterized by the presence of hepatitis B e antigen (HBeAg) and high serum levels of HBV DNA (referred to as HBeAg-positive CHB).
- After infection the CHB patient's immune system attempts to clear the HBV by destroying infected hepatocytes. This leads to increasing circulatory blood levels of alanine aminotransferase (ALT). Most patients will clear HBeAg (and produce anti-HBe antibodies) and achieve a state of nonreplicative infection, characterized by low or undetectable serum levels of HBV DNA and normal ALT levels.
- High HBV DNA and ALT levels may persist in some anti-HBe-positive patients (referred to as HBeAg-negative CHB) because of the presence of an HBV variant that is unable to produce HBeAg (HBeAg-negative variant, also called HBV precore stop codon mutant). Severe disease progresses quickly with HBeAg-negative HBV; 60% of patients with this form of disease develop cirrhosis within 6 years.

PATHOGENESIS

- Over time, 25% of persons who acquire HBV as children will develop primary liver cancer or cirrhosis as adults. Cirrhosis may develop as a consequence of repeated immune system attacks. Once established, cirrhosis cannot be cured; however, its progress may be stopped if the cause (in this case, HBV infection) is removed.
- Without treatment, the typical progression is from compensated cirrhosis to decompensated cirrhosis. The latter is characterized by cessation of enzymatic processes in the liver and subsequent severe clinical complications such as fluid retention in the abdomen (ascites), jaundice, internal bleeding, and hepatic encephalopathy. Patients with decompensated cirrhosis are candidates for liver transplantation, without which death results from end-stage liver disease.

MANIFESTATIONS

Incubation period: 7 to 160 days.

Anicteric infections. about 65% of the time.

Acute Infection - about 25% of time with HBV;

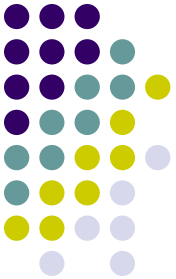
- less severe in children than adults.
- early symptoms
- fatigue
- anorexia; recovery follows regaining appetite.
- nausea pain and fullness in the upper right quadrant
- fever
- loss of fever signifies recovery.

Later symptoms arthritis and rash, cholestasis; symptoms tend to be more severe those seen in HAV infections.

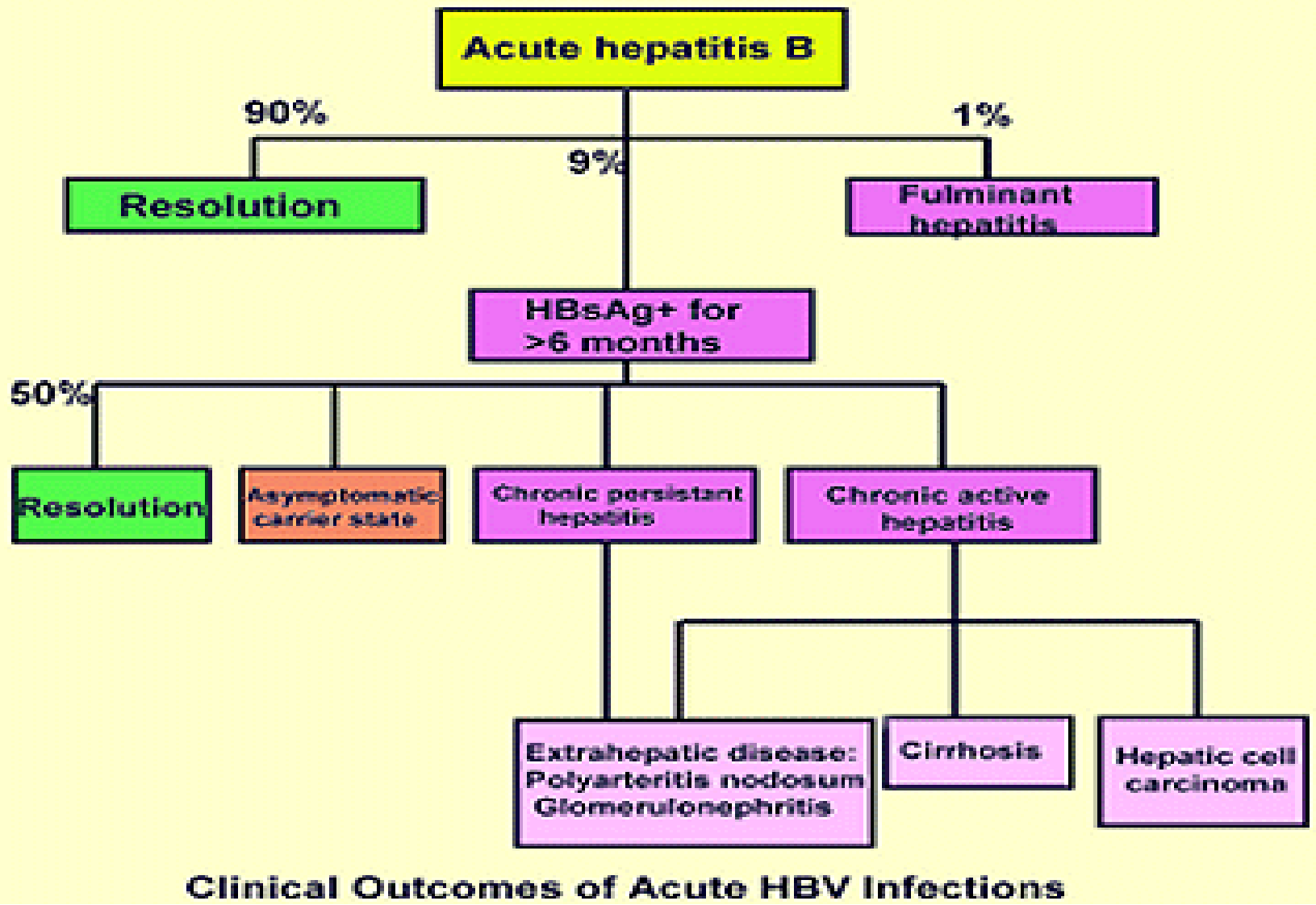
Fulminant hepatitis.

- occurs in 1% of acutely infected individuals; more likely if HBV and HDV coinfect.
- more severe symptoms, can be fatal.
- severe liver damage: ascites and bleeding;
- liver shrinkage rather than hepatomegaly.

MANIFESTATIONS



- **Chronic infection** more common with HCV (50-70% of acutely ill patients) Occurs in 5-10% of HBV infections. Usually follows mild or inapparent initial disease. Usually detected by elevated liver enzyme levels on a routine blood analysis. 10% of chronic hepatitis HBV patients suffer from liver cirrhosis and liver failure. Chronic HBV infections are the major reservoir.
- HBV and HDV can infect a person at the same time (coinfection). HDV can also infect a person after they have been infected with HBV (superinfection). Chonic HBV patients are more likely to develop fulminant hepatitis or a more severe hepatitis when superinfected by HDV.
- 20% of chronic HCV patients suffer from liver cirrhosis and 20% of these cirrhotic patients have liver failure.
- **Primary hepatocellular carcinoma.** Chronic HBV infection is associated with 80% of cases of liver carcinoma (one of the three most common causes of cancer mortality, worldwide). Liver carcinoma follows HBV infection after 9-35 years. Chronic HCV infection can also result in hepatocellular carcinoma.



Clinical Outcomes of Acute HBV Infections

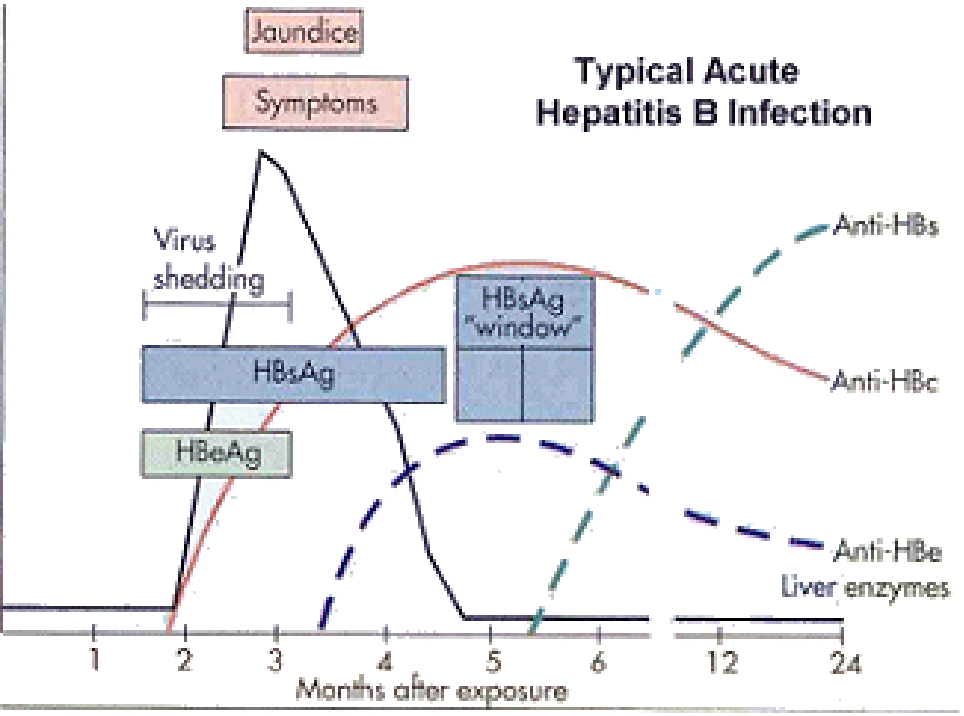
DIAGNOSIS

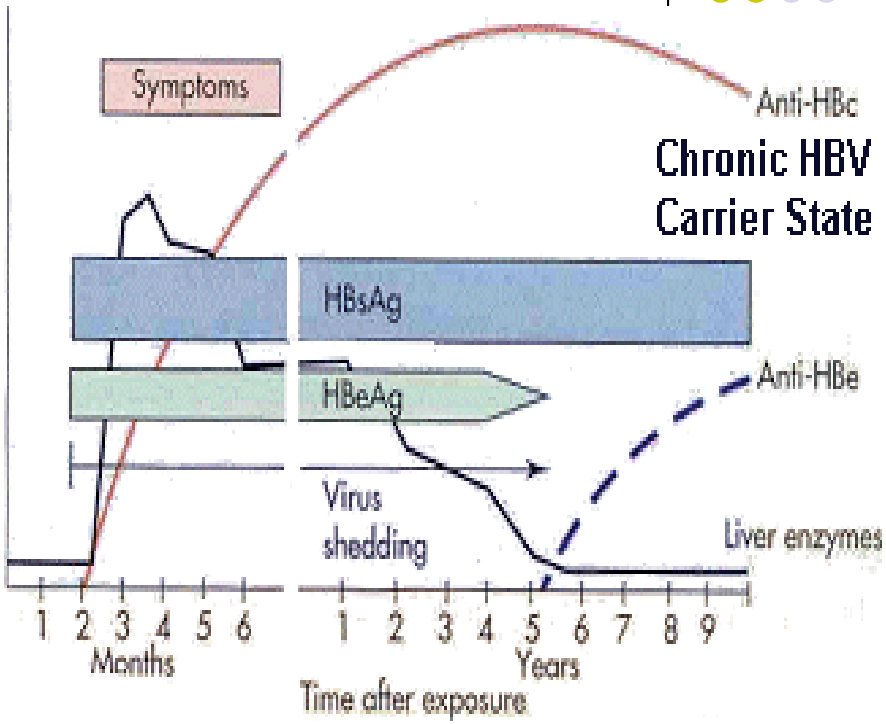
Initial diagnosis

- Cholestasis
- Altered liver enzyme profiles in the blood; ALT, AST
- Alkaline phosphatase elevated
- bilirubin elevated

Confirmatory diagnosis

- HBsAg and HBeAg are detectable by clinical laboratory assays.
- HBsAg only: predicts minimal liver damage
- HBsAg and HBeAg predicts more liver damage, cirrhosis.
- IgM for HBcAg and/or HBsAg is usually the best indication of an acute HBV infection.
- IgM or IgG specific for delta antigen indicate HDV infection. Occasionally delta antigen, itself is tested for.
- Antibodies for HCV are also detectable.
- PCR DNA HBV or RNA HCV

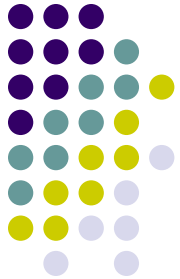

Jaundice
Symptoms
Typical Acute
Hepatitis B Infection
Virus
shedding
HBsAg
HBeAg
HBsAg
"window"
Anti-HBs
Anti-HBc
Anti-HBe
Liver enzymes
1
2
3
4
5
6
12
24
Months after exposure


Symptoms
Anti-HBc
Chronic HBV
Carrier State
HBsAg
HBeAg
Anti-HBe
Virus
shedding
Liver enzymes
1 2 3 4 5 6
Months
1 2 3 4 5 6 7 8 9
Years
Time after exposure

THERAPY

- Human interferon alpha 2b (IFNa-2b), lamivudin and adefovir may be used to treat chronic HBV. IFNa-2b has immunostimulatory activity as well as antiviral activity. lamivudin and adefovir are nucleoside/nucleotide analogues that suppress HBV replication through inhibition of HBV DNA polymerase.
- HbeAg positive chronic hepatitis patients usually respond better to therapy than HbeAg negative chronic hepatitis patients. Treatment with conventional IFNα not only results in loss of viremia and normalization of liver enzymes, but also improves long-term outcomes and survival, and alters the natural history of the disease.

PREVENTION



For HBV and HDV.

- **Active immunization.** There are two HBV vaccines available.
- The most commonly used vaccine Energix-B or Recombivax HB are HBs antigen produced in yeast. The vaccines are given to all children at 0-2 month, 1 to 4 months, and 6 to 18 months (three different immunizations).
- **Passive immunization.** HBV Immune Globulin prepared from plasma with a high titer of HBs antibody, but no detectable HBsAg. This treatment is often used in combination with vaccination for infants born to HBV positive mothers and for persons who were accidentally exposed to HBV as above.
- **Protection of neonates born from mothers with chronic HBV.** Neonates should be given hepatitis B immunoglobulin at birth along with the first dose of the hepatitis B recombinant vaccine. The remaining doses of vaccine should be given at 1 and 6 months of age.