Digestive System

University of Jordan

Faculty of Medicine

Batch of 2013-2019

Medical Committee
The University of Jordan

● Slide ○ Sheet ○ Handout ○ Other

☐ Anatomy ☐ Embryology

☐ Physiology ☐ Histology

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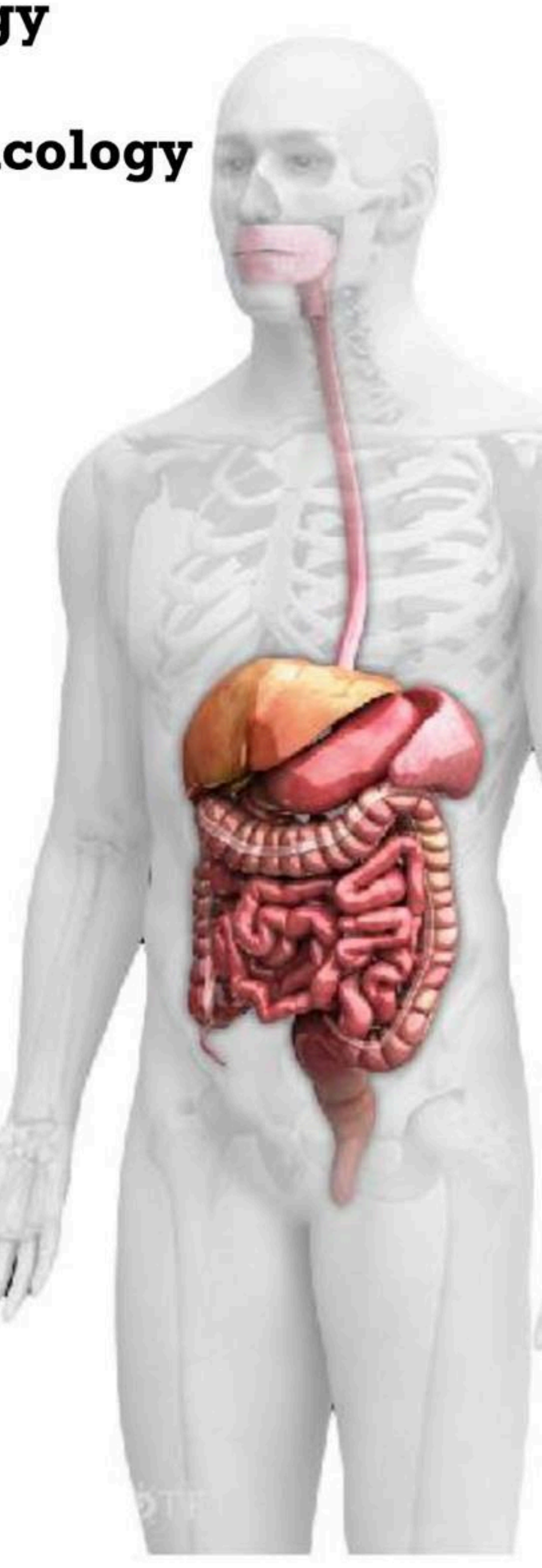

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Date: 21-3-2015

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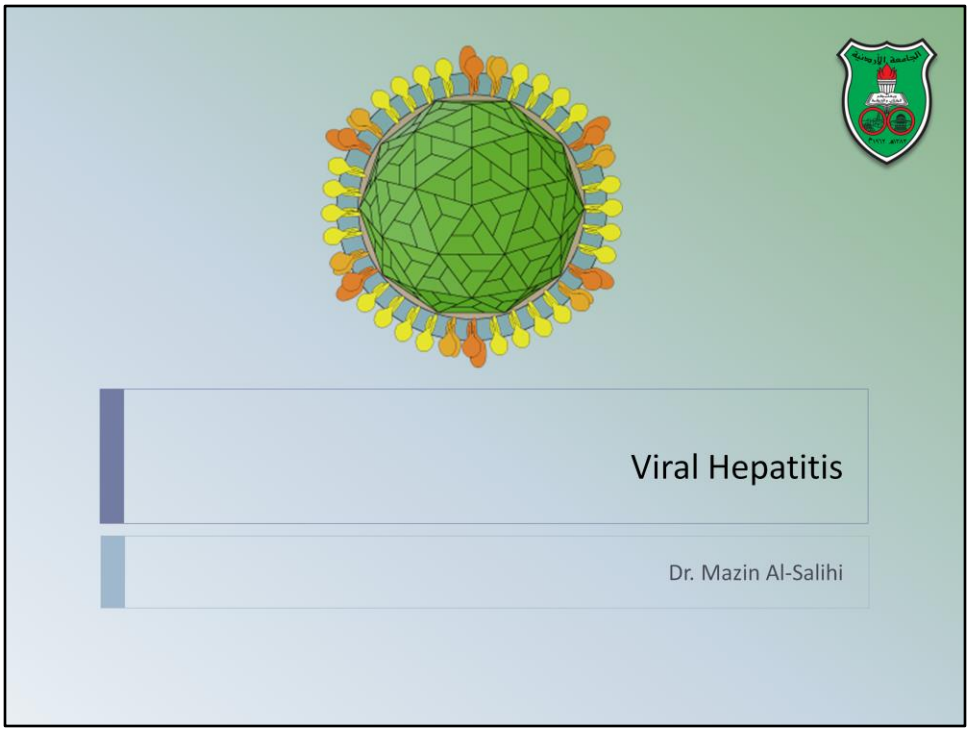
DESIGNED BY: TAMER ALTAMIMI "SMILE"



The liver has enormous functional reserve, and regeneration occurs in all but the most fulminant of hepatic diseases. Surgical removal of 60% of the liver in a normal person is followed by minimal and transient hepatic impairment, with restoration of most of its mass by regeneration within
4 to 6 weeks. In persons who have sustained massive hepatic necrosis, almost perfect restoration may occur if the patient can survive the metabolic insult of liver failure. The functional reserve and the regenerative capacity of the liver mask to some extent the clinical impact of early liver damage.

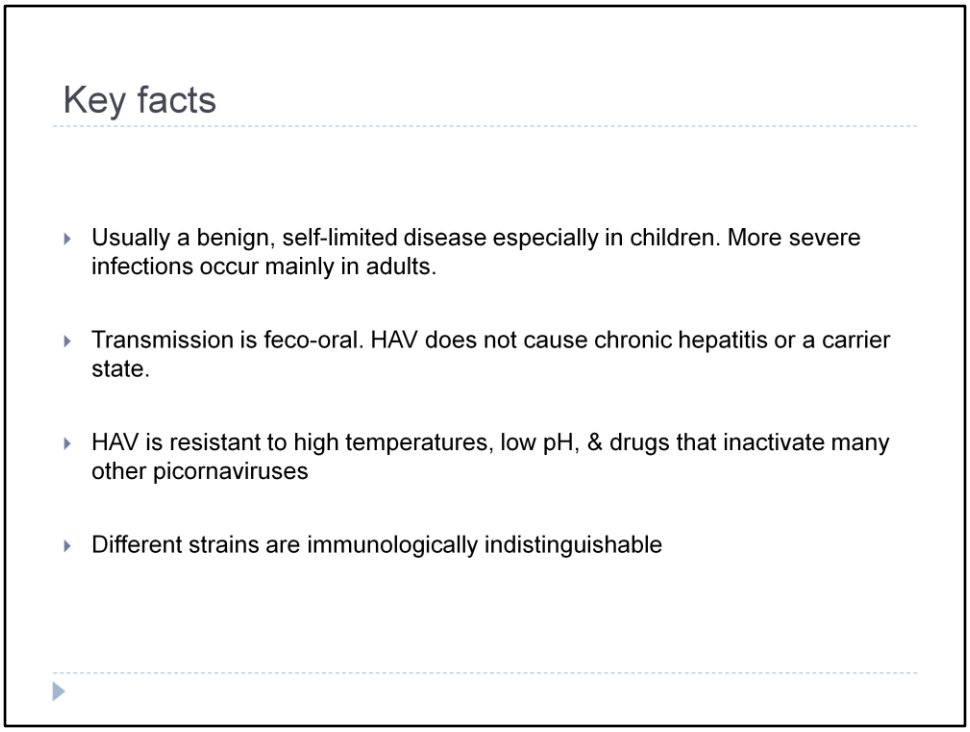
The Hepatitis Viruses

Virus	Hepatitis A	Hepatitis B	Hepatitis C	Hepatitis D	Hepatitis E
Type of virus	ssRNA	Partially dsDNA	ssRNA	Circular defective ssRNA	ssRNA
Viral family	Hepatovirus; related to picornavirus	Hepadnavirus	Flaviridae	Subviral particle in Deltaviridae family	Hepevirus
Route of transmission	Fecal-oral (contaminated food or water)	Parenteral, sexual contact, perinatal	Parenteral; intranasal cocaine use is a risk factor	Parenteral	Fecal-oral
Incubation period	2–6 weeks	4–26 weeks	2–26 weeks	Same as for HBV	2–8 weeks
Frequency of chronic liver disease	Never	10%	~80%	5% (coinfection); ≤70% for superinfection	Never
Laboratory diagnosis	Detection of serum IgM antibodies	Detection of HBsAg or antibody to HBcAg	PCR assay for HCV RNA; 3rd-generation ELISA for antibody detection	Detection of IgM and IgG antibodies; HDV RNA serum; HDAg in liver	PCR assay for HEV RNA; detection of serum IgM and IgG antibodies

Almost all cases of acute viral hepatitis are caused by one of five viral agents: hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), the HBV-associated delta agent or hepatitis D virus (HDV), and hepatitis E virus (HEV). Other transfusion-transmitted agents (e.g., “hepatitis G” virus and “TT” virus, have been identified but do not cause hepatitis). All these human hepatitis viruses are RNA viruses, except for hepatitis B, which is a DNA virus. Although these agents can be distinguished by their molecular and antigenic properties, all types of viral hepatitis produce clinically similar illnesses. These range from asymptomatic and inapparent to fulminant and fatal acute infections common to all types, on the one hand, and from subclinical persistent infections to rapidly progressive chronic liver disease with cirrhosis and even hepatocellular carcinoma, common to the bloodborne types (HBV, HCV, and HDV), on the other.

These viruses are readily spread because infected people are contagious before, or even without, showing symptoms.

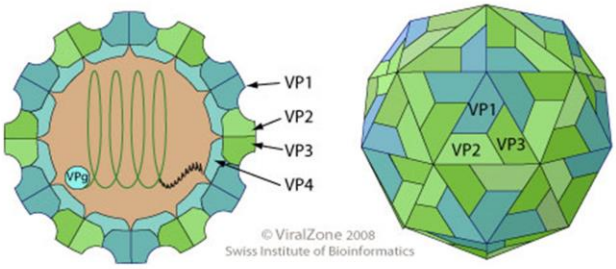
Hepatitis A

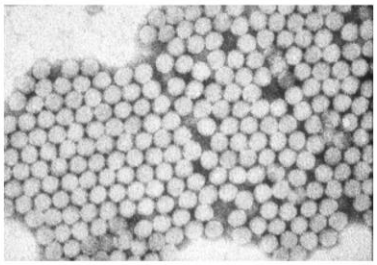


Improved sanitation has resulted in a paradoxical increase in the number of cases observed in adults as they escape early childhood infection where disease manifestations are mild, and transition to adulthood where clinical disease is more overt and severe.

HAV has been found to survive for days to months in experimentally contaminated food and water. Inactivation of viral activity can be achieved
by boiling for 1 minute, by contact with formaldehyde and chlorine, or by ultraviolet irradiation.

Despite nucleotide sequence variation of up to 20% among isolates of HAV, and despite the recognition of four genotypes affecting humans, all strains of this virus are immunologically indistinguishable and belong to one serotype.





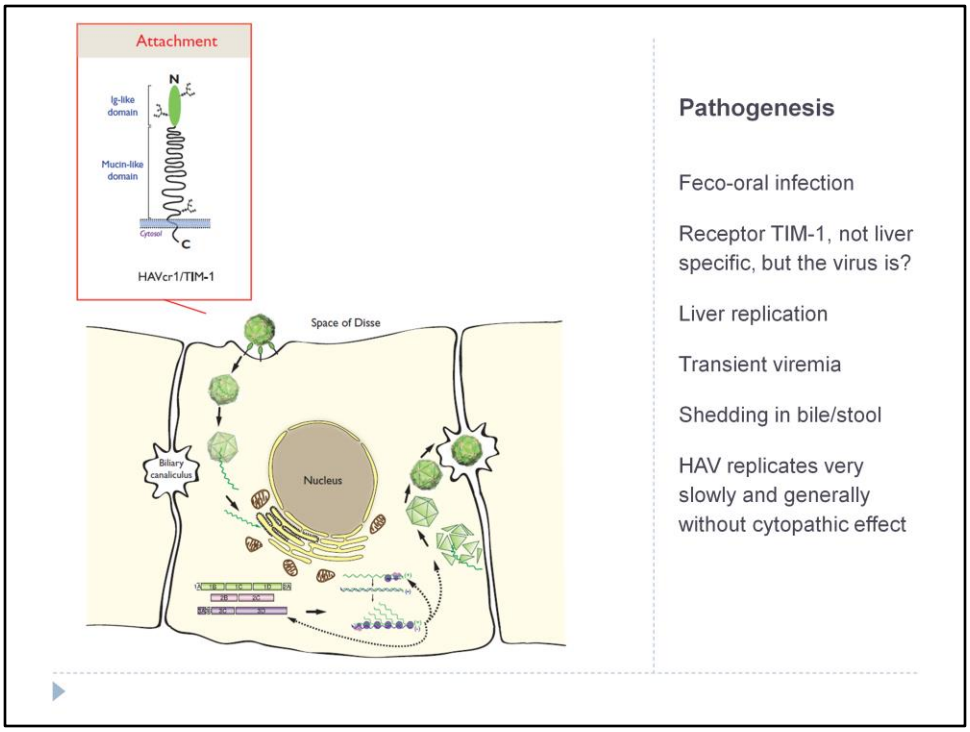
Molecular Biology

Picornaviridae family

Non-enveloped

+ve ssRNA produces a single polyprotein cleaved to form the 4 capsid proteins

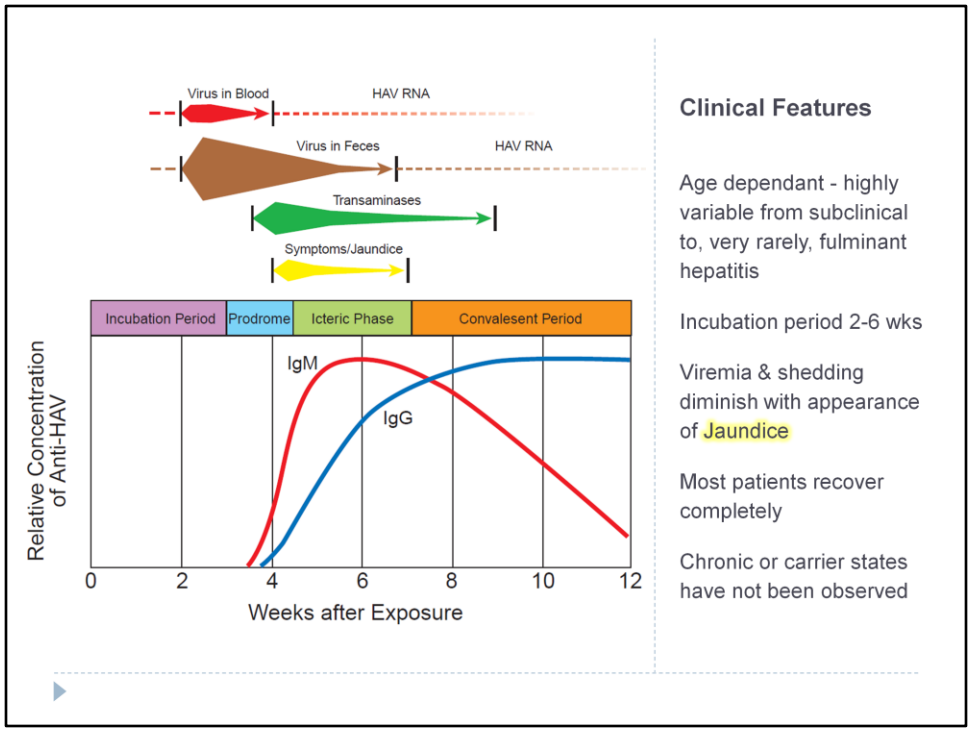
VP1/3 antigenic



Natural infection with HAV usually follows ingestion of virus from material contaminated with feces containing HAV

The T-cell immunoglobulin mucin (TIM) gene family, particularly TIM-1, are cell surface receptors that are important in T-cell regulation and Th-cell differentiation. TIM-1 is widely distributed in different tissues; thus, the tropism of HAV for the liver remains an enigma waiting to be resolved

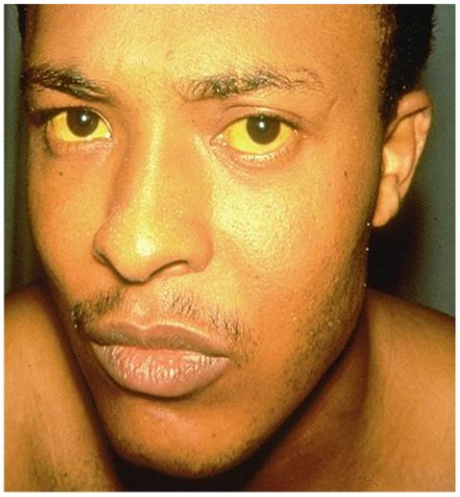
The virus itself does not seem to be toxic to hepatocytes, and hence the liver injury seems to result from T cell–mediated damage of infected hepatocytes. Cellular injury appears to arise from the induction of apoptotic pathways leading to programmed cell Death



While HAV replication is limited to the liver, the virus is present in the liver, bile, stools, and blood during the late incubation period
and acute preicteric phase of illness. Despite persistence of virus in the liver, viral shedding in feces, viremia, and infectivity diminish rapidly once jaundice becomes apparent.

The mortality rate for fulminant hepatitis is higher in older adults and is also considerably higher among patients with chronic hepatitis B or C
who are superinfected with HAV, primarily when the underlying liver disease is advanced.

The damaged hepatic tissue is usually restored within 8-12 weeks.



Clinical Features

Incubation: asymptomatic

Prodrome: typical quick transition with fever

Icteric: Bilirubinuria, pale stools

Complications:
Fulminant hepatitis**
Cholestatic hepatitis
Relapsing hepatitis

** Reduction in liver size in a deteriorating patient is a bad sign

During the incubation phase, the patient remains asymptomatic despite active replication of the virus.

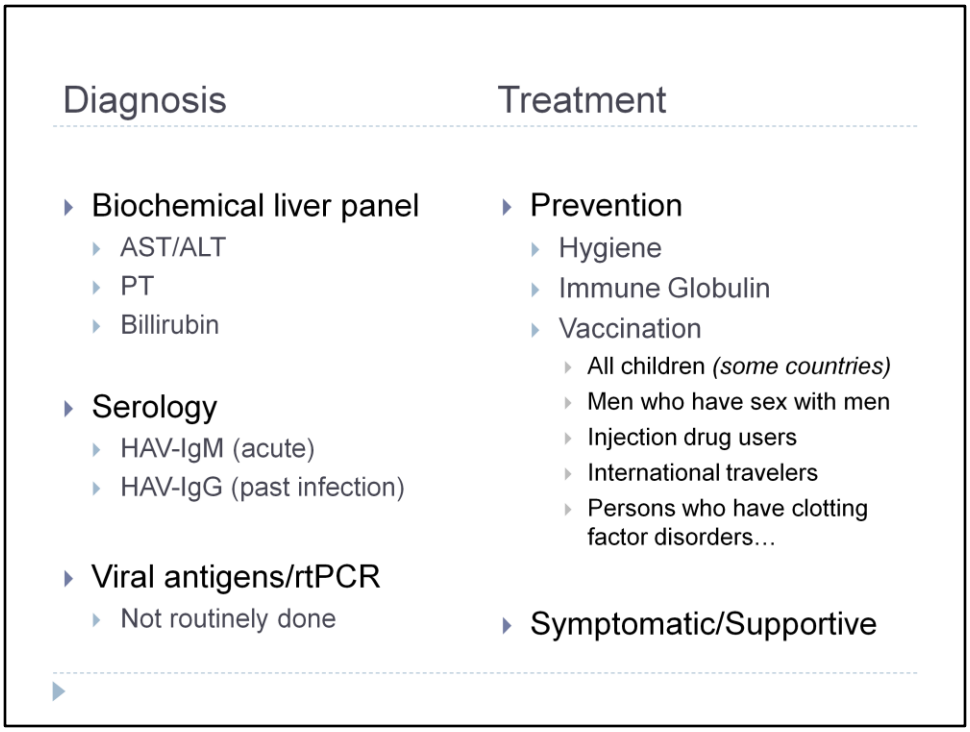
A short prodromal or preicteric phase precedes the onset of jaundice. In more than half of patients, the prodromal state typically is characterized by anorexia, fever, fatigue, malaise, myalgia, nausea, and vomiting. In hepatitis A, the transition from well-being to acutely ill
occurs abruptly (within a period of 24 hours) in more than 60% of the cases, whereas the onset is more insidious in hepatitis B. Fever higher
than 38°C is more common in acute hepatitis A than in acute hepatitis B. Diarrhea, nausea, and vomiting are more frequent in children than in adults. Older children and adults often complain of right upper quadrant pain or discomfort as a consequence of hepatomegaly.

The icteric phase of acute viral hepatitis is ushered in by the appearance of golden-brown urine caused by bilirubinuria, followed one to several days later by pale stools and yellowish discoloration of the mucous membranes, conjunctivae, sclerae, and skin. Fever usually subsides a few
days after start of jaundice.

Physical examination of the patient with a typical case of acute disease reveals the presence of jaundice accompanied by tenderness to palpation or percussion of the

liver, which may be enlarged. Measurement by percussion is essential, because a reduction in size in a patient whose condition is deteriorating often heralds massive necrosis.

A small proportion of patients with hepatitis A experience *relapsing hepatitis* weeks to months after apparent recovery from acute hepatitis. Relapses are characterized by recurrence of symptoms, aminotransferase elevations, occasionally jaundice, and fecal excretion of HAV. Another unusual variant of acute hepatitis A is *cholestatic hepatitis*, characterized by protracted cholestatic jaundice and pruritus. Rarely, liver test abnormalities persist for many months, even up to a year. Even when these complications occur, hepatitis A remains self-limited and does not progress to chronic liver disease.



Measurement of the prothrombin time (PT) is important in patients with acute viral hepatitis, for a prolonged value may reflect a severe hepatic synthetic defect, signify extensive hepatocellular necrosis, and indicate a worse prognosis.

In most instances, the total bilirubin is equally divided between the conjugated and unconjugated fractions. In certain patients with underlying hemolytic anemia, however, such as glucose-6-phosphate dehydrogenase deficiency and sickle cell anemia, a high serum bilirubin level is common, resulting from superimposed hemolysis.

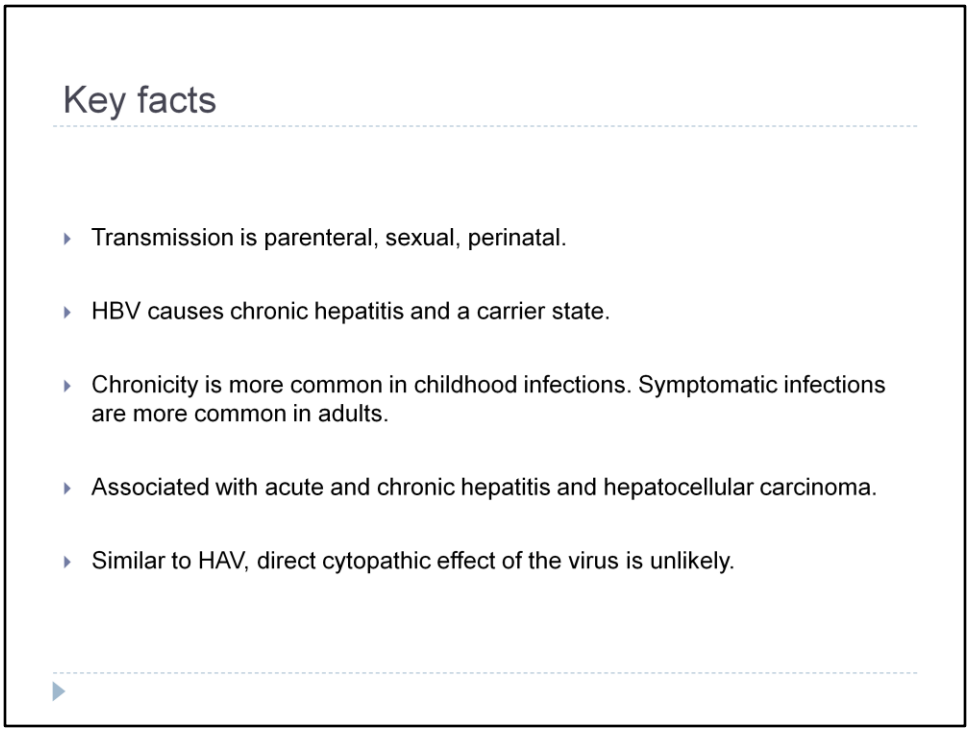
No specific treatment for acute viral hepatitis exists, and hospitalization is not ordinarily indicated. Therapy should be supportive and aimed at maintaining comfort and adequate nutritional balance. For most jaundiced patients, strict bed rest and prolonged confinement are probably not indicated. Intravenous feeding is necessary in the acute stage if the patient has persistent vomiting and cannot maintain oral intake. Drugs capable of producing adverse reactions such as cholestasis and drugs metabolized by the liver should be avoided. If severe pruritus is present, the use of the bile salt-sequestering resin cholestyramine is helpful. Glucocorticoid therapy has no value in acute viral hepatitis. Physical isolation of patients with hepatitis to a single room and bathroom is rarely necessary except in the case of fecal incontinence for hepatitis A.

Formalin-inactivated vaccines made from strains of HAV attenuated in tissue culture have been shown to be safe, immunogenic, and effective in preventing hepatitis A. Hepatitis A vaccines are approved for use in persons who are at least one year old and appear to provide adequate protection beginning 4 weeks after a primary inoculation. If it can be given within 4 weeks of an expected exposure, such as by travel to an endemic area, hepatitis A vaccine is the preferred approach to pre-exposure immunoprophylaxis. If travel is more imminent, IG should be administered at a different injection site, along with the first dose of vaccine. Because vaccination provides long-lasting protection (protective levels of anti-HAV should last 20 years after vaccination), persons whose risk will be sustained (e.g., frequent travelers or those remaining in endemic areas for prolonged periods) should be vaccinated, and vaccine should supplant the need for repeated IG injections.

Other groups considered to be at increased risk for HAV infection and who are candidates for hepatitis A vaccination include military personnel, populations with cyclic outbreaks of hepatitis A, employees of day-care centers, primate handlers, laboratory workers exposed to hepatitis A or fecal specimens, and patients with chronic liver disease.

Although IGIM may not interfere with the immune response to inactivated vaccines or to oral poliovirus or yellow fever vaccine, it may interfere with the response to other live attenuated vaccines such as measles, mumps, rubella, and varicella. Therefore, IG should be delayed at least 2 weeks after such immunizations, or, if IG is administered initially for hepatitis A prophylaxis, at least 3 months should pass before these other vaccines are administered.

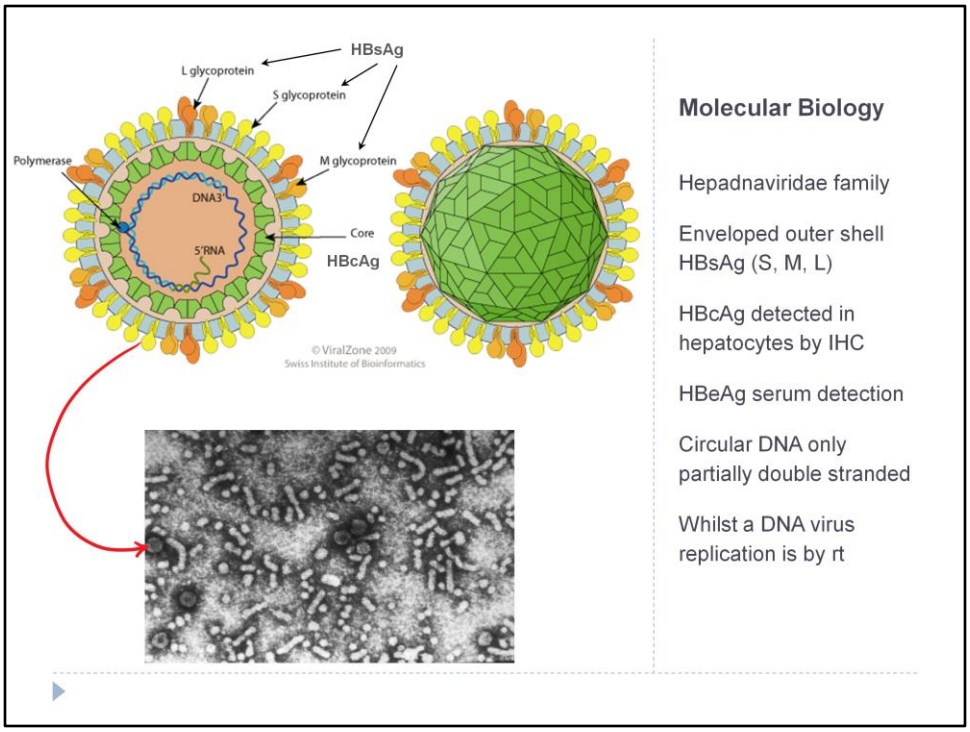
Hepatitis B



Hepatic and extrahepatic lesions of the disease are likely produced by host immune response.

The fact that patients with defects in cellular immune competence are more likely to remain chronically infected rather than to clear HBV supports the role of cellular immune responses in the pathogenesis of hepatitis B–related liver injury.

An important distinction should be drawn between HBV infection acquired at birth, common in endemic areas, such as the Far East, and infection acquired in adulthood, common in the west. Infection in the neonatal period is associated with the acquisition of immunologic tolerance to HBV, absence of an acute hepatitis illness, but the almost invariable establishment of chronic, often lifelong infection. While after adulthood acquired infection, chronicity is uncommon, and the risk of hepatocellular carcinoma is very low.

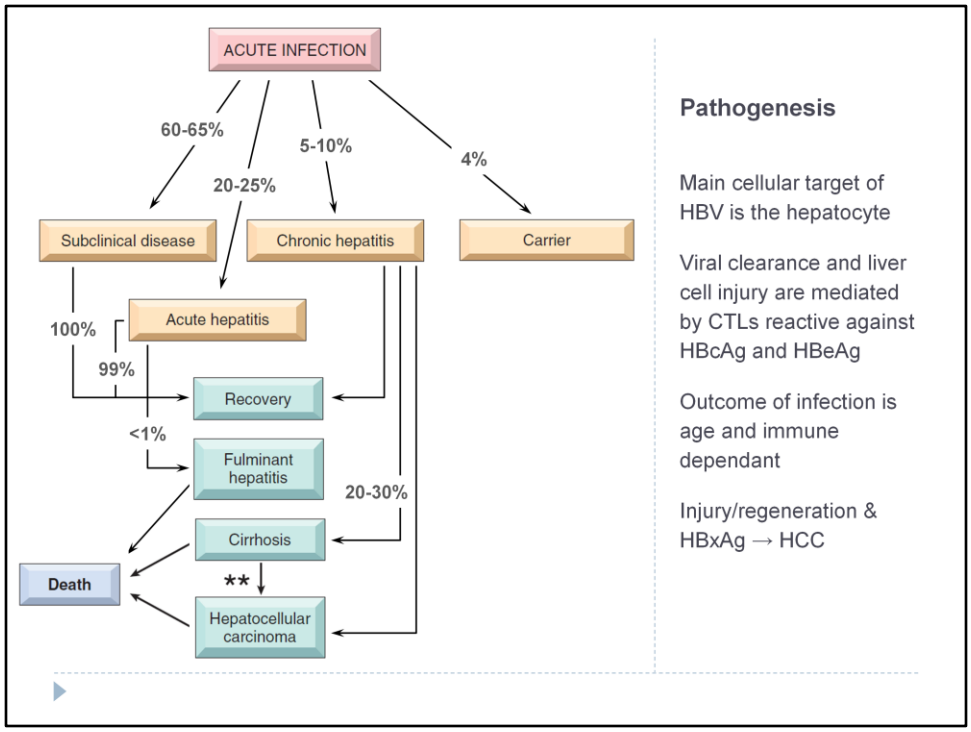


This is the least common form in the serum, the two other forms are antigenically indistinguishable (HBsAg -S -M). They are smaller spheres or tubules. Their exact role in the HBV life cycle is not known. One possibility is that, by adsorbing virus neutralizing antibodies, they facilitate virus spread and maintenance in the host.

The capsid is covered with a lipoprotein membrane made up of three forms of the viral envelope protein HBsAg, large (L), middle (M) and small (S). The shortest, the S protein, is the most abundant envelope protein in virions and in the subviral spheres and rods. It contains the major antigenic determinants of Australia antigen, which led to the discovery of HBV and provided the reagent for the development of diagnostic tools for the detection of HBV infections and of vaccines against HBV infections. The L protein provides the primary ligand for the viral receptor.

HBcAg naked core particles do not circulate in the serum. The secreted nucleocapsid protein, HBeAg, provides a convenient, readily detectable, qualitative marker of HBV replication and relative infectivity.

These are the only DNA viruses of animals known to replicate their DNA by reverse transcription of a viral RNA



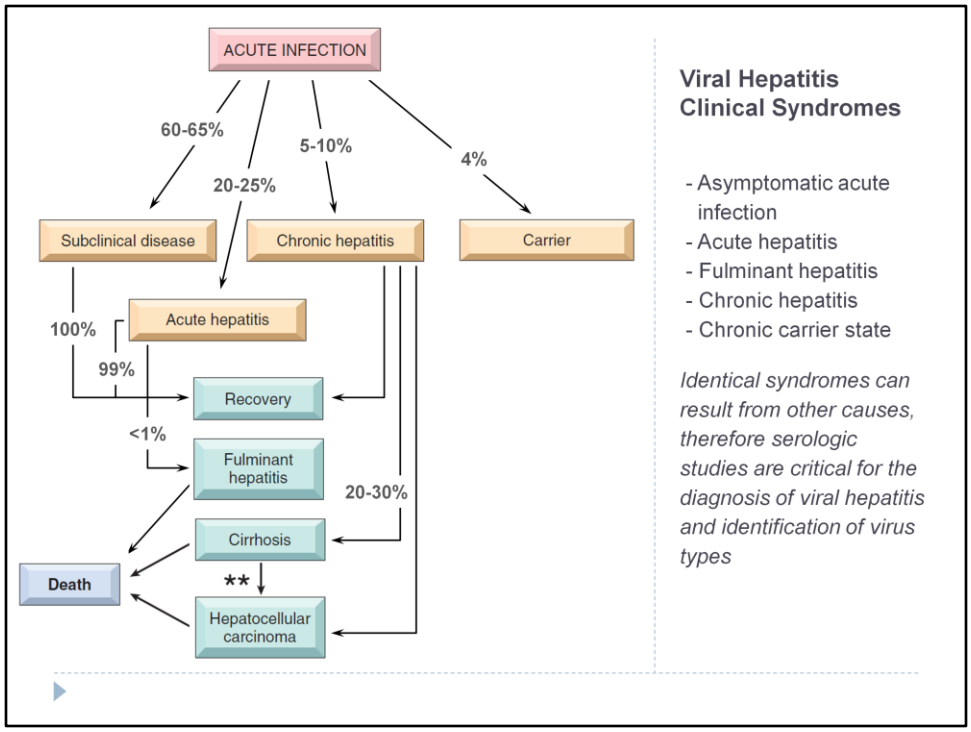
The belief that other cells replicate the virus in humans has persisted, despite a lack of conclusive evidence.

Nucleocapsid proteins (HBcAg and possibly HBeAg), present on the cell membrane in minute quantities, are the viral target antigens that, with host antigens, invite cytolytic T cells to destroy HBV-infected hepatocytes.

Differences in the robustness and broad polyclonality of CD8+ cytolytic T cell responsiveness and in the elaboration of antiviral cytokines by T cells have been invoked to explain differences in outcomes between those who recover after acute hepatitis, and those who progress to chronic hepatitis, or between those with mild and those with severe (fulminant) acute HBV infection.

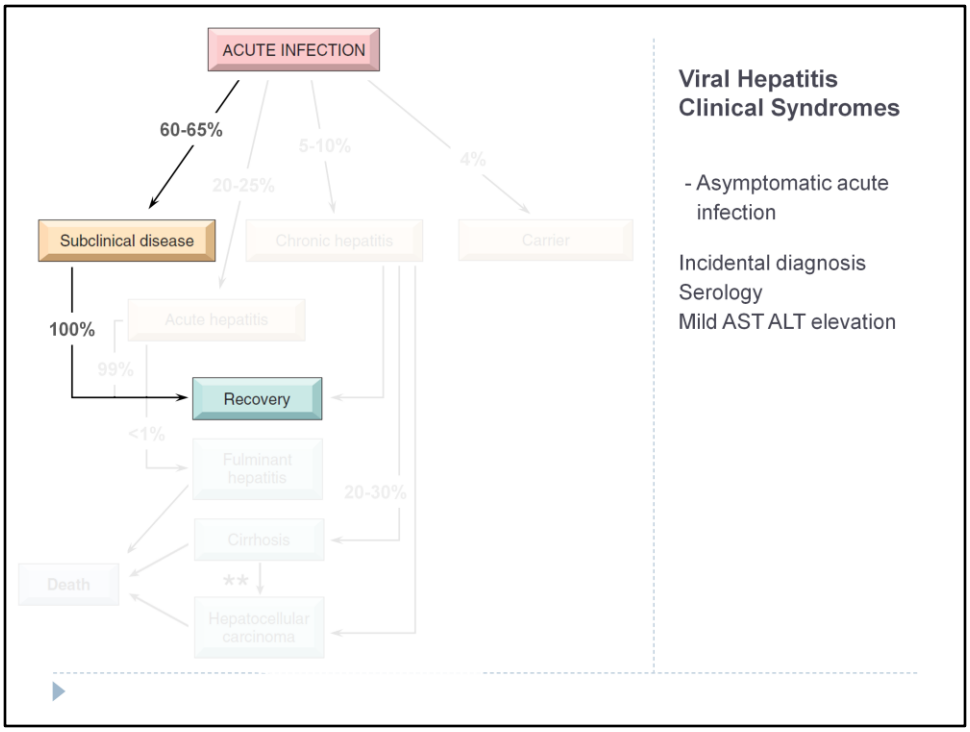
HBeAg, which is sufficiently small to traverse the placenta, induces T cell tolerance to both nucleocapsid proteins. This may explain why, when infection occurs so early in life, immunologic clearance does not occur, and protracted, lifelong infection ensues.

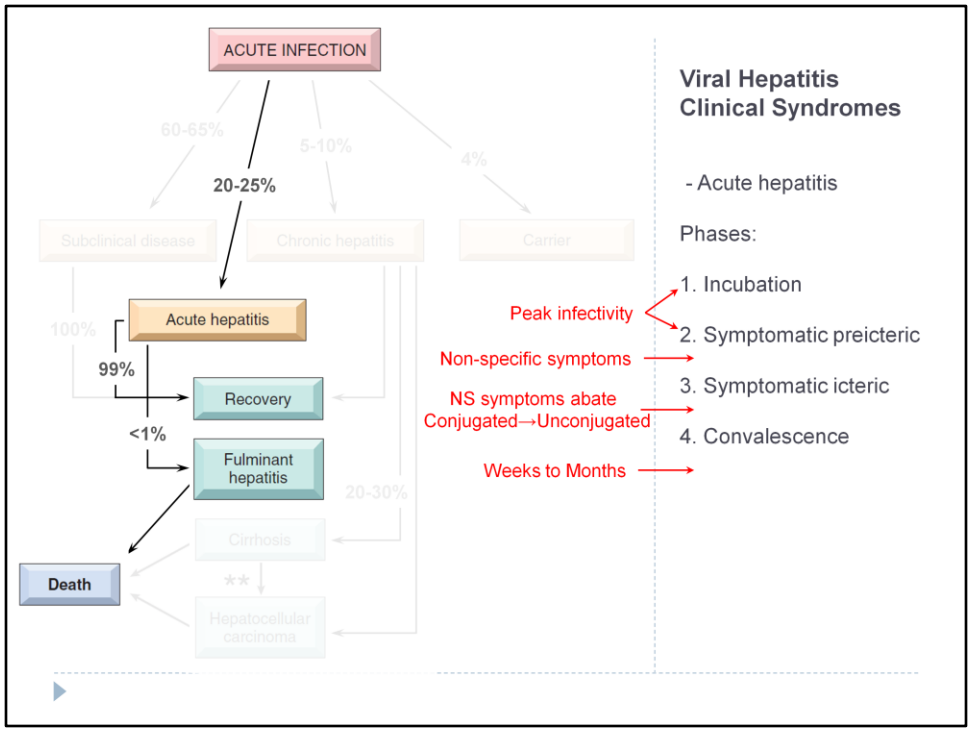
hepatitis B x antigen (HBxAg) is capable of transactivating the transcription of both viral and cellular genes. Remember pathogenesis of hepatocellular carcinoma from last semester.



I'm using HepB as an example here to show all clinical syndrome types

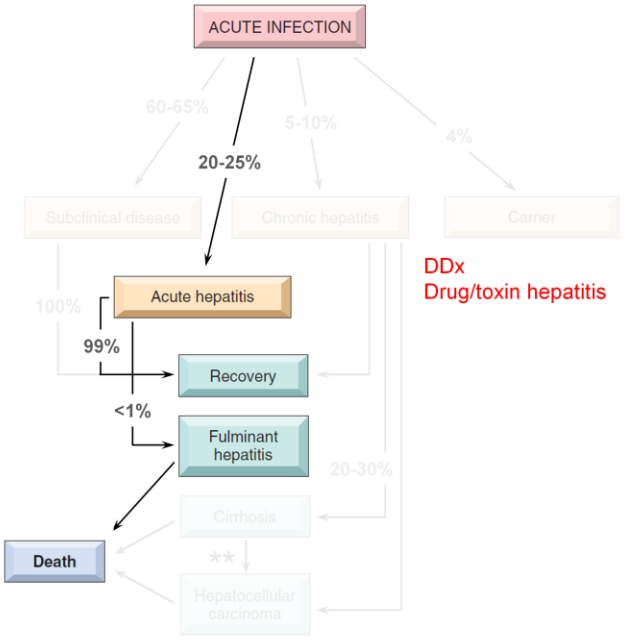
- *Asymptomatic acute infection*: serologic evidence only
- *Acute hepatitis*: anicteric or icteric
- *Fulminant hepatitis*: submassive to massive hepatic necrosis with acute liver failure
- *Chronic hepatitis*: with or without progression to cirrhosis
- *Chronic carrier state*: asymptomatic without apparent disease


ACUTE INFECTION
60-65%
5-10%
4%
20-25%
Subclinical disease
Chronic hepatitis
Carrier
Acute hepatitis
100%
99%
Recovery
<1%
Fulminant hepatitis
20-30%
Cirrhosis
Death
**
Hepatocellular carcinoma
Viral Hepatitis
Clinical Syndromes
- Asymptomatic acute infection
Incidental diagnosis
Serology
Mild AST ALT elevation



Malaise is followed in a few days by general fatigability, nausea, and loss of appetite. Weight loss, low-grade fever, headaches, muscle and joint aches, vomiting, and diarrhea are inconstant symptoms. About 10% of patients with acute hepatitis B develop a serum sickness–like syndrome consisting of fever, rash, and arthralgias, attributed to circulating immune complexes. The hepatitis-related origin of all of these symptoms is suggested by elevated serum aminotransferase levels. Physical examination reveals a mildly enlarged, tender liver. In some patients the nonspecific symptoms are more severe, with higher fever, shaking chills, and headache sometimes accompanied by right upper quadrant pain
and tender liver enlargement.

The jaundice is caused predominantly by conjugated hyperbilirubinemia, which produces dark-colored urine. With hepatocellular damage and consequent defect in bilirubin conjugation, unconjugated hyperbilirubinemia also can occur. The stools may become light-colored, and the retention of bile salts may cause pruritus. An icteric phase is usual in adults (but not children) infected with HAV, present in about half of the cases involving HBV, and absent in most cases of HCV infection.



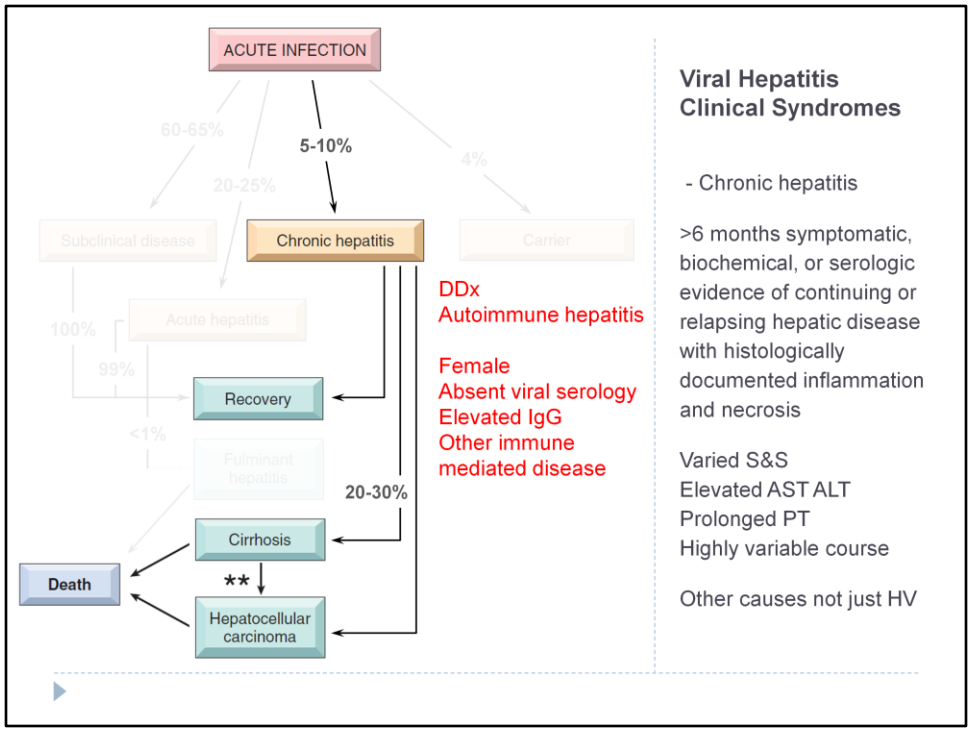
DDx
Drug/toxin hepatitis

Viral Hepatitis Clinical Syndromes

- Fulminant hepatitis

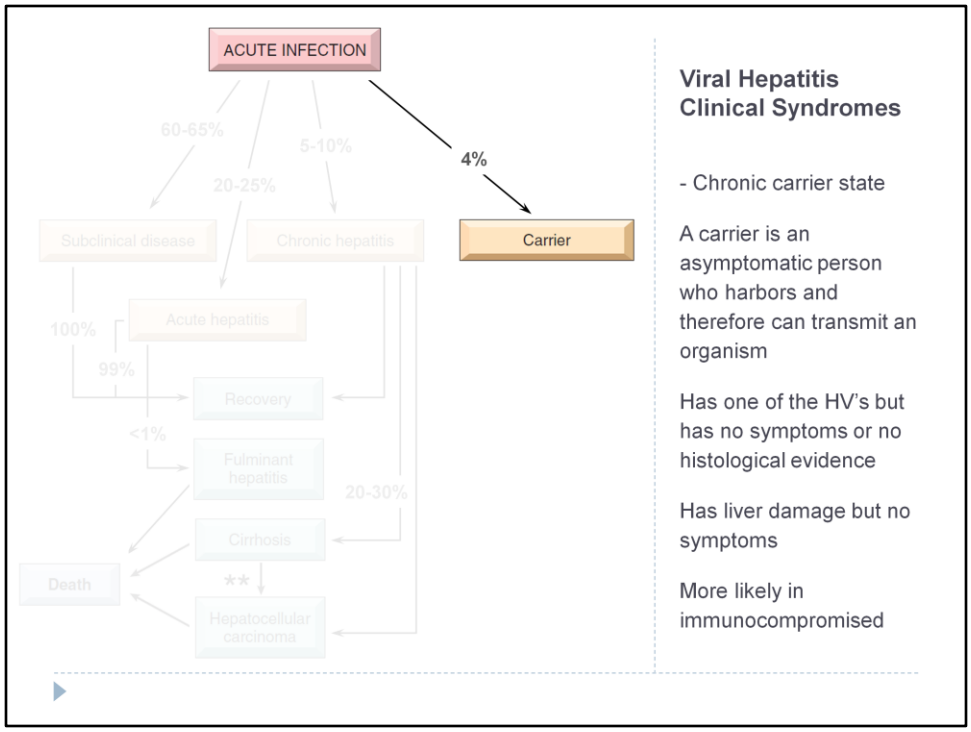
Massive hepatic necrosis
A,B,D,E

With the exception of immunosuppressed individuals, HCV almost never causes acute liver failure



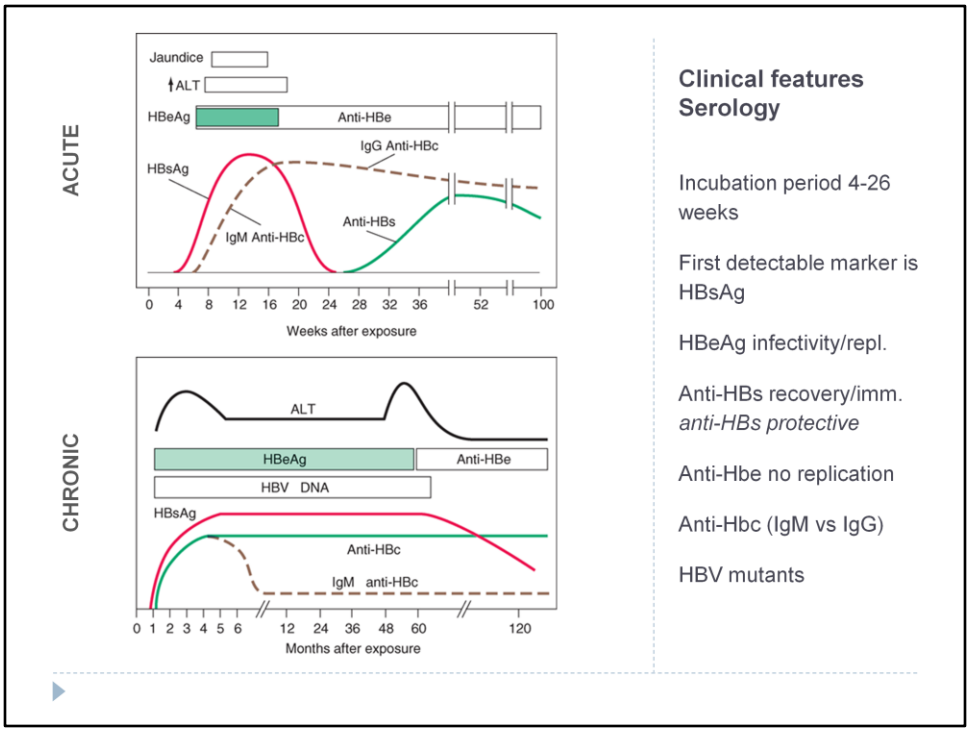
Although the hepatitis viruses are responsible for most cases, there are many causes of chronic hepatitis, such as autoimmunity, drugs/toxins, Wilson disease, and α1-antitrypsin (AAT) deficiency. Etiology rather than the histologic pattern is the most important determinant of the probability of developing progressive chronic hepatitis. In particular, HCV is notorious for causing a chronic hepatitis evolving to cirrhosis, regardless of histologic features at the time of initial evaluation.

In patients with chronic hepatitis B, other types of immune-complex disease may also be seen. Glomerulonephritis with the nephrotic syndrome
is observed occasionally; HBsAg, immunoglobulin, and C3 deposition has been found in the glomerular basement membrane. Polyarteritis nodosa has also been reported but is rare.



HBV infection early in life, particularly through vertical transmission during childbirth, produces a carrier state 90% to 95% of the time. By contrast, only 1% to 10% of HBV infections acquired in adulthood yield a carrier state.

HCV & HDV there's also a carrier state



HBsAg-positive serum containing HBeAg is more likely to be highly infectious and to be associated with the presence of hepatitis B virions than HBeAg-negative or anti-HBe-positive serum.

After a person is infected with HBV, the first virologic marker detectable in serum within 1–12 weeks, usually between 8–12 weeks, is HBsAg. Circulating HBsAg precedes elevations of serum aminotransferase activity and clinical symptoms by 2–6 weeks and remains detectable during the entire icteric or symptomatic phase of acute hepatitis B and beyond. In typical cases, HBsAg becomes undetectable 1–2 months after the onset
of jaundice and rarely persists beyond 6 months. After HBsAg disappears, antibody to HBsAg (anti-HBs) becomes detectable in serum and remains detectable indefinitely thereafter. Because HBcAg is intracellular and, when in the serum, sequestered within an HBsAg coat, naked core particles do not circulate in serum and, therefore, HBcAg is not detectable routinely in the serum of patients with HBV infection. By contrast, anti-HBc is readily demonstrable in serum, beginning within the first 1–2 weeks after the appearance of HBsAg and preceding detectable levels of anti-HBs by weeks to months. Because variability exists in the time of appearance of anti-HBs after HBV infection, occasionally a gap of several weeks or longer may separate the disappearance of HBsAg and the appearance of anti-HBs. During this “gap” or “window” period (RARE), anti-HBc may represent the only serologic evidence of current or recent HBV infection.

HBsAg - used as a general marker of infection.
Anti- HBsAg - used to document recovery and/or immunity to HBV infection.

anti- HBcAg IgM - marker of acute infection.
anti- HBcAg IgG - past or chronic infection. These two are not always reliably to distinguish between acute and chronic hepatitis B infection because high-titer IgM anti-HBc can reappear during acute exacerbations of chronic hepatitis B. In such cases, patient history is invaluable.

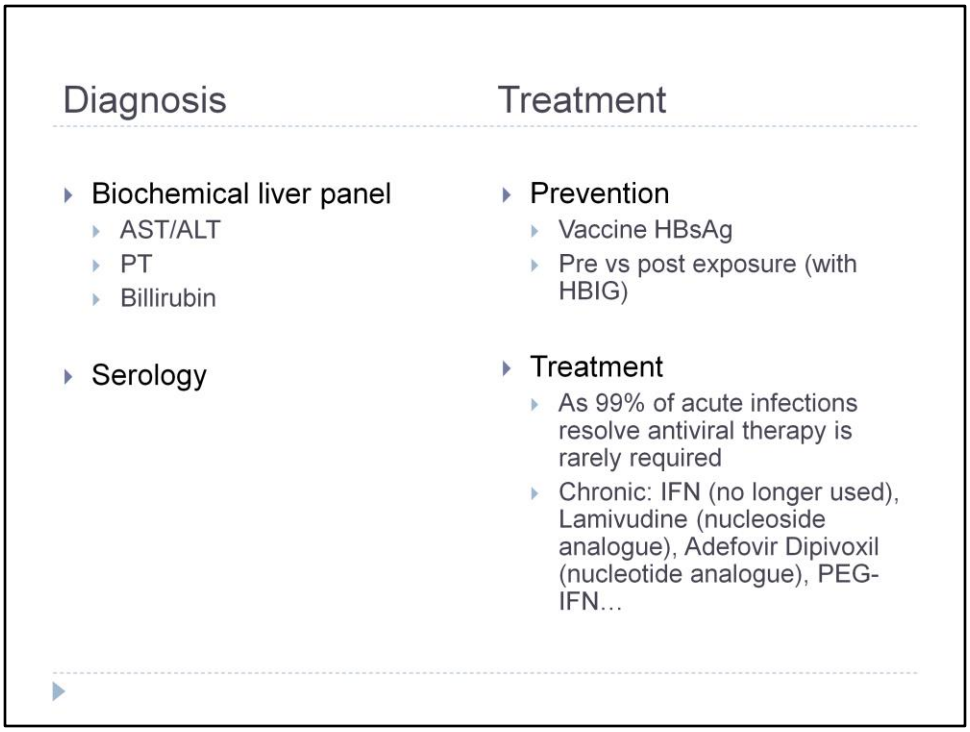
HBeAg - indicates active replication of virus and therefore infectiveness.
Anti-HBeAg - virus no longer replicating. However, the patient can still be positive for HBsAg which is made by integrated HBV.

HBV-DNA - indicates active replication of virus, more accurate than HBeAg. Used mainly for monitoring response to therapy.

Generally, in persons who have recovered from hepatitis B, anti-HBs and anti-HBc persist indefinitely.

Seroconversion from HBeAg-positive to anti-HBe-positive in chronic infections coincides with a transient, acute hepatitis-like elevation in aminotransferase activity, believed to reflect cell-mediated immune clearance of virus-infected hepatocytes.

Two categories of naturally occurring HBV variants have attracted the most attention. One of these was identified initially in Mediterranean countries among patients with an unusual serologic clinical profile. They have severe chronic HBV infection and detectable HBV DNA but with anti-HBe instead of HBeAg. These patients were found to be infected with an HBV mutant that contained an alteration in the precore region rendering the virus incapable of encoding HBeAg. The second important category of HBV mutants consists of *escape mutants*, in which a single amino acid substitution in HBsAg leads to a critical conformational change that results in a loss of neutralizing activity by anti-HBs. This specific HBV
mutant has been observed in two situations, active and passive immunization, in which humoral immunologic pressure may favor evolutionary change (“escape”) in the virus—in a small number of HB vaccine recipients who acquired HBV infection despite the prior appearance of neutralizing anti-HBs and in liver transplant recipients who underwent the procedure for hepatitis B and who were treated with a high-potency human monoclonal anti-HBs preparation. Although such mutants have not been recognized frequently, their existence raises a concern that may complicate vaccination strategies and serologic diagnosis.



A diagnosis of HBV infection can usually be made by detection of HBsAg in serum. Infrequently, levels of HBsAg are too low to be detected
during acute HBV infection, even with contemporary, highly sensitive immunoassays. In such cases, the diagnosis can be established by the presence of IgM anti-HBc.

After immunization with hepatitis B vaccine, which consists of HBsAg alone, anti-HBs is the only serologic marker to appear.

To date, seven drugs have been approved for treatment of chronic hepatitis B: injectable interferon (IFN) α pegylated interferon [long-acting IFN bound to polyethylene glycol (PEG), known as PEG IFN]; and the oral agents lamivudine, adefovir dipivoxil, entecavir, telbivudine, and tenofovir.

The first of the nucleoside analogues to be approved, the dideoxynucleoside lamivudine, inhibits reverse transcriptase activity of both HIV and HBV and is a potent and effective agent for patients with chronic hepatitis B. Although generally superseded by newer, more potent agents, lamivudine is still used in regions of the world where newer agents are not yet approved are or not affordable.

Adefovir Dipivoxil (nucleotide analogue), less likely to cause relapse at cessation or incur resistance than Lamivudine.

Once-a-week PEG IFN is more effective than the more frequently administered, standard IFN, and several large-scale trials of PEG IFN versus oral nucleoside analogues have been conducted with mixed recommendations.

Newer analogues are showing even better success. For current recommendations see Harrison's Table 306-4. Remember these may change by the time you start your clinical practice! Review accordingly.

Successful response to treatment will result in the disappearance of HBsAg, HBV-DNA, and seroconversion to anti-HBe.