Digestive System

University of Jordan

Faculty of Medicine

Batch of 2013-2019

Medical Committee
The University of Jordan

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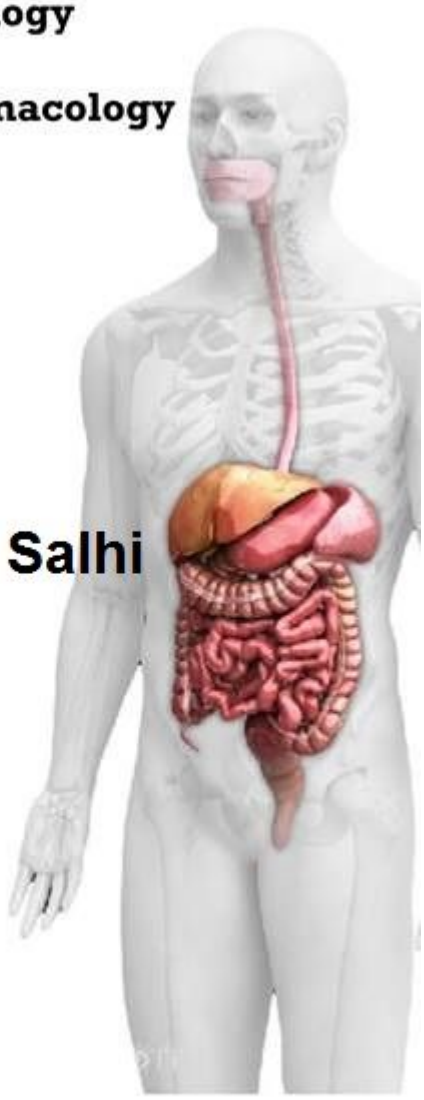

Lecture # : 3

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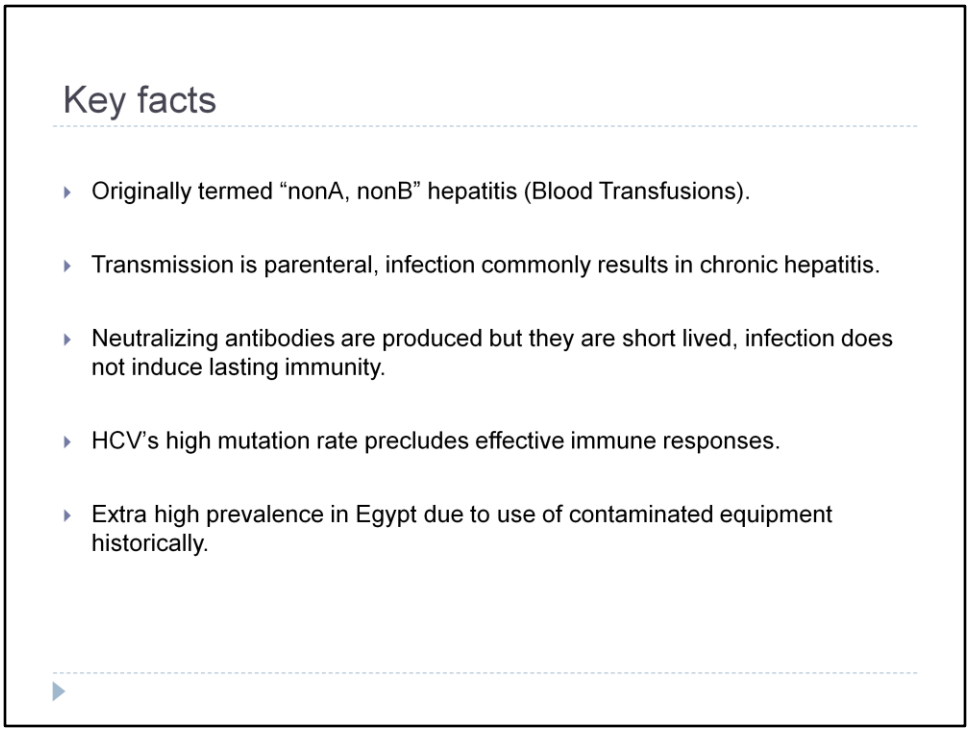
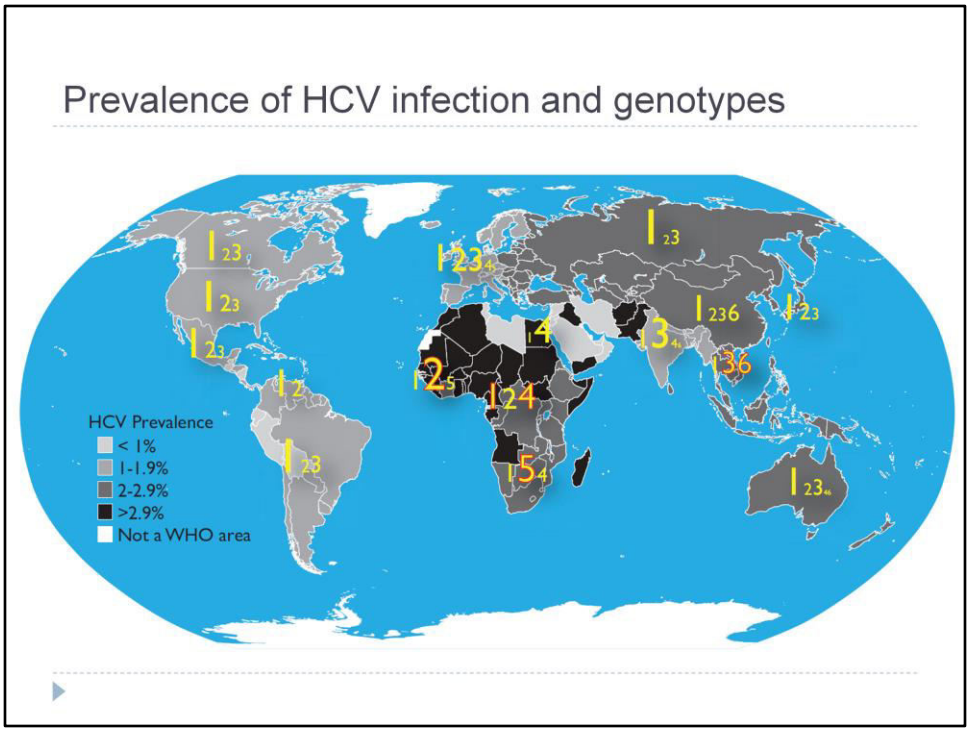
Hepatitis C



In addition to being transmitted by transfusion, hepatitis C can be transmitted by other percutaneous routes, such as injection drug use. In addition, this virus can be transmitted by occupational exposure to blood, and the likelihood of infection is increased in hemodialysis units. As a bloodborne infection, HCV potentially can be transmitted sexually and perinatally; however, both of these modes of transmission are inefficient. Breast-feeding does not increase the risk of HCV infection between an infected mother and her infant. Infection of health workers is not dramatically higher than among the general population; however, health workers are more likely to acquire HCV infection through
accidental needle punctures, the efficiency of which is ~3%.

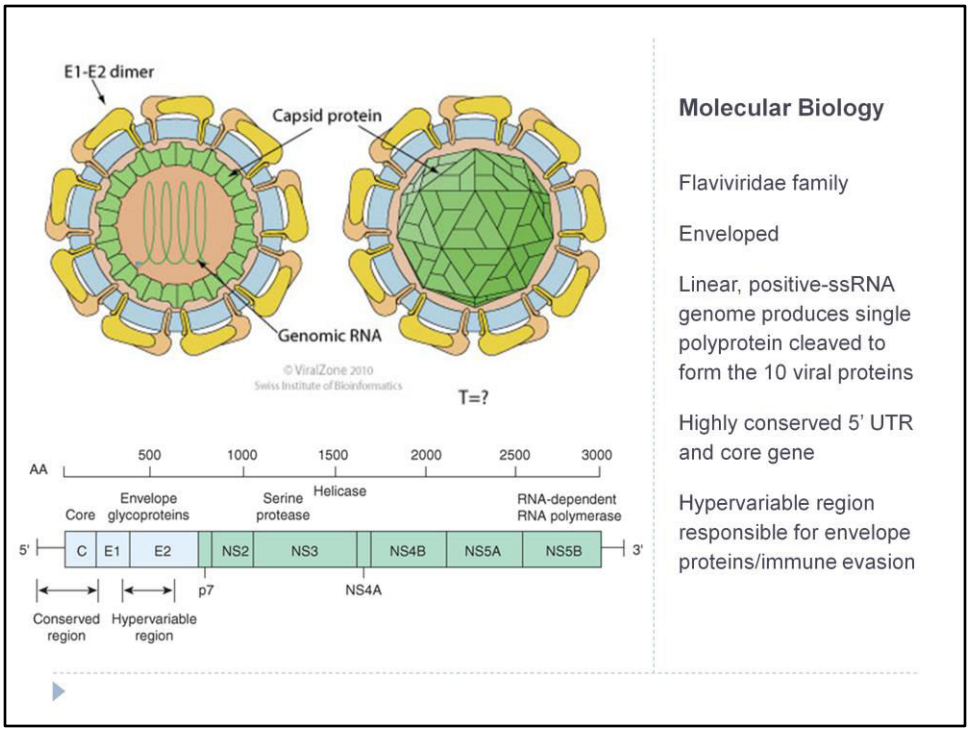
Genetic variability is one of the most remarkable features of HCV, contributing to evasion of host immune responses and complicating development of diagnostics, therapeutics, and effective vaccines.



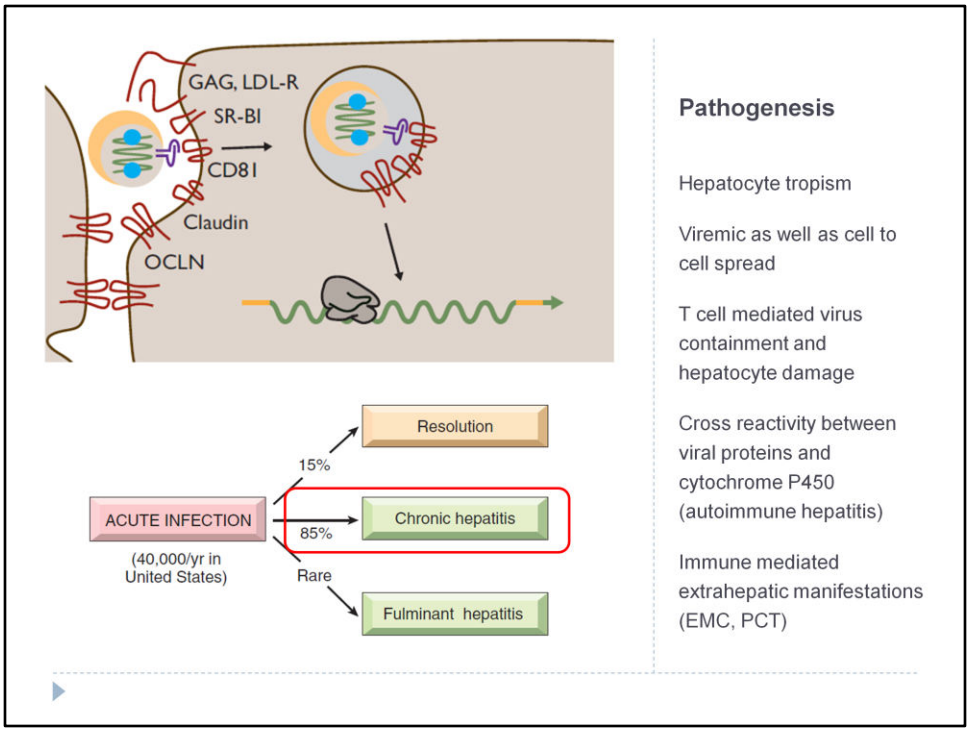
The distribution of HCV genotypes (of which there are 6) varies in different parts of the world. Worldwide, genotype 1 is the most common. Genotype 4 predominates in Egypt; genotype 5 is localized to South Africa, and genotype 6 to Hong Kong. Genotype dictates length of therapy and predicts therapeutic response. Genotype 1 requires longer therapy and has lower response.

Egypt appears to have the highest HCV prevalence, which is as high as 50% in persons born before 1960. From the 1950s to the 1980s, the Egyptian Ministry of Health embarked on a campaign to eradicate schistosomiasis infection by intravenously administering tartar emetic to
millions of citizens. The effort, commended at the time as a public health model, occurred before there was widespread appreciation for bloodborne transmission of infectious agents. HCV was transmitted extensively because of the widespread reuse of insufficiently cleaned injection equipment. Consequently, the prevalence of HCV infection can exceed 50% in persons alive during that campaign while being 1% to 2% in those born after.

It appears HCV was widely transmitted worldwide during the 1900s due to stepped-up production of syringes and their worldwide use both for conventional and illicit drugs.



Because HCV does not replicate via a DNA intermediate, it does not integrate into the host genome (unlike HBV).



HCV gains entry into the hepatocyte via the nonliver-specific CD81 receptor and the liver-specific tight junction protein claudin-1. Relying on the same assembly and secretion pathway as low-density lipoproteins (LPLs), HCV masquerades as a lipoprotein, which may limit its visibility to the adaptive immune system and which may explain its ability to evade immune containment and clearance.

The basis for this tropism is likely to be multifactorial:

1. entry facilitated by proteins expressed at particularly high levels on hepatocytes (e.g., low-density lipoprotein receptor [LDL-R] and scavenger receptor class B type I [SR-BI])
2. Dependence on liver-specific miR-122 for efficient replication
3. utilization of the liver's lipoprotein assembly pathway for virion production

Cell-mediated immune responses and elaboration by T cells of antiviral cytokines contribute to the containment of infection and pathogenesis of liver injury associated with hepatitis C. Perhaps HCV infection of lymphoid cells plays a role in moderating immune responsiveness to the virus, as well. Intrahepatic HLA class I restricted cytolytic T cells directed at nucleocapsid, envelope, and nonstructural viral protein antigens have been demonstrated in patients with chronic hepatitis C; however, such virus-specific cytolytic T cell responses do not correlate adequately with the degree of liver injury or with recovery. Yet, a consensus has emerged supporting a role in the pathogenesis of HCV-associated liver injury of virus-activated CD4 helper T cells that

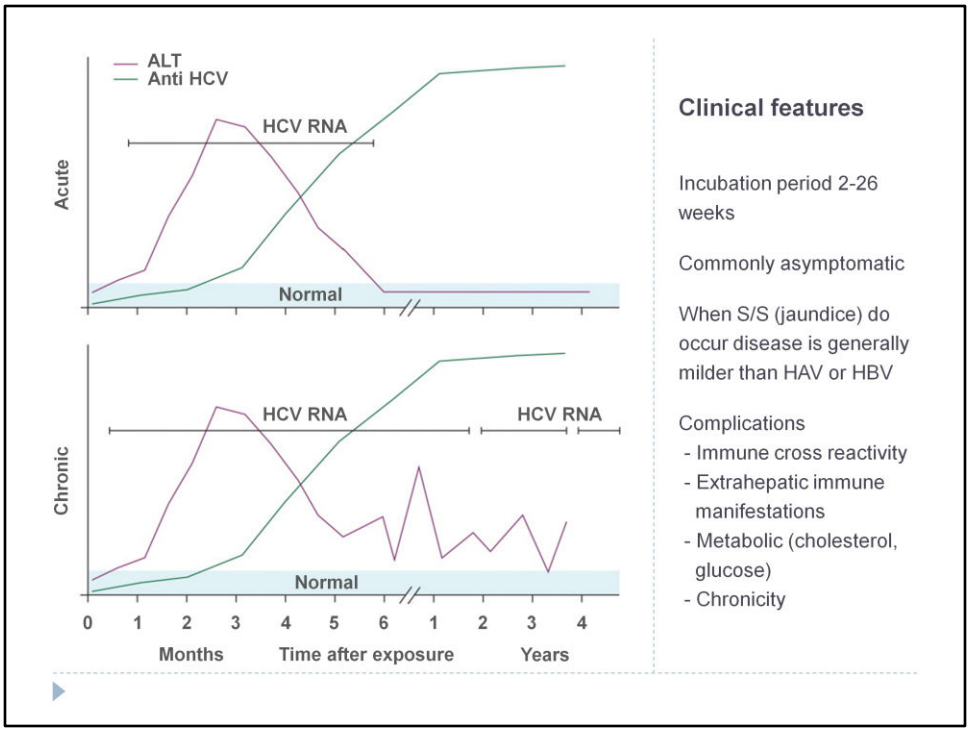
stimulate, via the cytokines they elaborate, HCV-specific CD8 cytotoxic T cells. These responses appear to be more robust (higher in number, more diverse in viral antigen specificity, more functionally effective, and more long lasting) in those who recover from HCV than in those who have chronic infection.

Also shown to contribute to limiting HCV infection are natural killer cells of the innate immune system that function when HLA class 1 molecules required for successful adaptive immunity are underexpressed. Of note, the emergence of substantial viral quasispecies diversity and HCV sequence variation allow the virus to evade attempts by the host to contain HCV infection by both humoral and cellular immunity.

Cross-reactivity between viral antigens (HCV NS3 and NS5A) and host autoantigens (cytochrome P450 2D6) has been invoked to explain the association between hepatitis C and a subset of patients with autoimmune hepatitis and antibodies to liver-kidney microsomal (LKM) antigen (anti-LKM).

An extrahepatic manifestation of viral hepatitis, essential mixed cryoglobulinemia (EMC), was reported initially to be associated with hepatitis B. The disorder is characterized clinically by arthritis; cutaneous vasculitis (palpable purpura); and, occasionally, with glomerulonephritis and serologically by the presence of circulating cryoprecipitable immune complexes of more than one immunoglobulin class. Many patients with this syndrome have chronic liver disease, but the association with HBV infection is limited; instead, a substantial proportion has chronic HCV infection, with circulating immune complexes containing HCV RNA. Immune-complex glomerulonephritis is another recognized extrahepatic manifestation of chronic hepatitis C.

Porphyria cutanea tarda (PCT), characterized primarily by disorders of the skin (blistering, hyperpigmentation) and nails (onycholysis) worsened by sun exposure and complicated by scarring, is associated with liver disease. It is a multifactorial disease, potentiated by mutations in the *HFE* gene (associated with hereditary hemochromatosis and found in 15% of persons with PCT), as well as HCV infection, alcohol, and estrogen use—all of which should be evaluated in persons presenting with PCT.



Clinical features of chronic hepatitis C are similar to those described above for chronic hepatitis B. Generally, fatigue is the most common symptom; jaundice is rare. In patients with hepatitis C, an episodic pattern of aminotransferase elevation is common.
Hepatitis C is less severe during the acute phase than hepatitis B and is more likely to be anicteric.

In relation to the reliance of HCV on lipoprotein secretion and assembly pathways and on interactions of HCV with glucose metabolism, HCV infection may be complicated by hepatic steatosis, hypercholesterolemia, insulin resistance (and other manifestations of the metabolic syndrome), and type 2 diabetes mellitus; both hepatic steatosis and insulin resistance appear to accelerate hepatic fibrosis and blunt responsiveness to antiviral therapy.

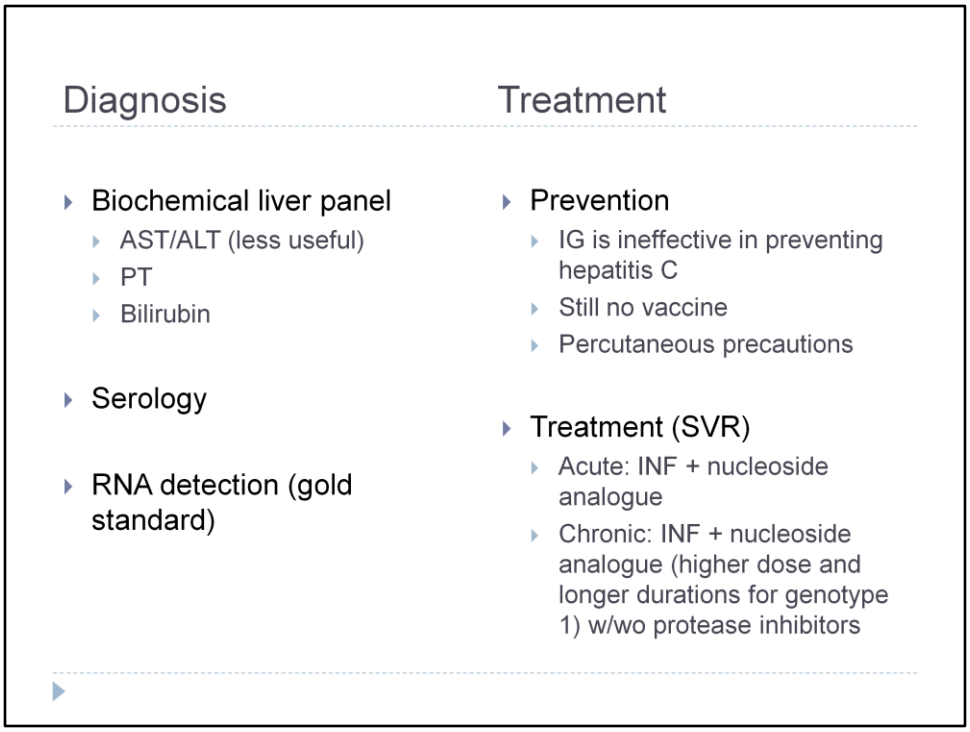
After acute HCV infection, the likelihood of remaining chronically *infected* approaches 85–90%. Although many patients with chronic hepatitis C have no symptoms, cirrhosis may develop in as many as 20% within 10–20 years of acute illness; in some series of cases reported by referral centers, cirrhosis has been reported in as many as 50% of patients with chronic hepatitis C. Although chronic hepatitis C accounts for at least 40% of cases of chronic liver disease and of patients undergoing liver transplantation for end-stage liver disease in the United States and Europe, in the

majority of patients with chronic hepatitis C, morbidity and mortality are limited during the initial 20 years after the onset of infection.

Progression of chronic hepatitis C may be influenced by age of acquisition, duration of infection, immunosuppression, coexisting excessive alcohol use, concomitant hepatic steatosis, other hepatitis virus infection, or HIV co-infection. In fact, instances of severe and rapidly progressive chronic hepatitis B and C are being recognized with increasing frequency in patients with HIV infection.

The risk of hepatocellular carcinoma is increased in patients with chronic hepatitis C, almost exclusively in patients with cirrhosis, and almost always after at least several decades, usually after 3 decades of disease. Unlike HBV, which is associated with a substantially elevated risk of HCC at all stages of infection, the association of HCC with HCV primarily arises after a person develops cirrhosis.

Despite this substantial rate of progression of chronic hepatitis C, and despite the fact that liver failure can result from end-stage chronic
hepatitis C, the long-term prognosis for chronic hepatitis C in a majority of patients is relatively benign.



A specific serologic diagnosis of hepatitis C can be made by demonstrating the presence in serum of anti-HCV. Anti-HCV can be detected in acute hepatitis C during the initial phase of elevated aminotransferase activity. This antibody may never become detectable in 5–10% of patients with acute hepatitis C, and levels of anti-HCV may become undetectable after recovery (albeit rare). In patients with chronic hepatitis C, anti-HCV is detectable in >95% of cases. Assays for HCV RNA are the most sensitive tests for HCV infection and represent the “gold standard” in establishing a diagnosis. HCV RNA can be detected even before acute elevation of aminotransferase activity and before the appearance of anti-HCV.
In addition, HCV RNA remains detectable indefinitely, continuously in most but intermittently in some, in patients with chronic hepatitis C (detectable as well in some persons with normal liver tests (i.e., inactive carriers). In the small minority of patients with hepatitis C who lack anti-HCV, a diagnosis can be supported by detection of HCV RNA. If all these tests are negative and the patient has a well-characterized case of hepatitis after percutaneous exposure to blood or blood products, a diagnosis of hepatitis caused by an unidentified agent can be entertained.

In typical cases of acute hepatitis C, recovery is rare, progression to chronic hepatitis is the rule, and meta-analyses of small clinical trials suggest that antiviral therapy with interferon alfa monotherapy is beneficial, reducing the rate of chronicity considerably by inducing sustained responses in 30–70% of patients.

Many authorities now opt for a 24-week course (beginning within 2–3 months after onset) of the best regimen identified for the treatment of chronic hepatitis C, long-acting pegylated interferon plus the nucleoside analogue ribavirin. 48 weeks for patients with genotype 1. Add on therapy using the protease inhibitors boceprevir and telaprevir (in combination with peginterferon and ribavirin at standard doses) resulted in approximately 70% SVR, compared with 40% SVR in those treated with the prior standard of care.

The primary goal of therapy is sustained virologic response (SVR), defined as undetectable HCV RNA 24 weeks after the end of treatment. Compared to chronic infection, acute HCV infection is more responsive to interferon-based treatment with overall SVR rates greater than 80%, and the response is significantly less genotype dependent than during chronic infection.

Physical isolation is rarely necessary except in the case of voluminous bleeding for hepatitis C (blood precautions, GLOVES!).

Diagnostic Algorithm for Acute Hepatitis

HBsAg	IgM Anti-HAV	IgM Anti-HBc	Anti-HCV	Diagnostic Interpretation
+	–	+	–	Acute hepatitis B
+	–	–	–	Chronic hepatitis B
+	+	–	–	Acute hepatitis A superimposed on chronic hepatitis B
+	+	+	–	Acute hepatitis A and B
–	+	–	–	Acute hepatitis A
–	+	+	–	Acute hepatitis A and B (HBsAg below detection threshold)
–	–	+	–	Acute hepatitis B (HBsAg below detection threshold)
–	–	–	+	Acute hepatitis C

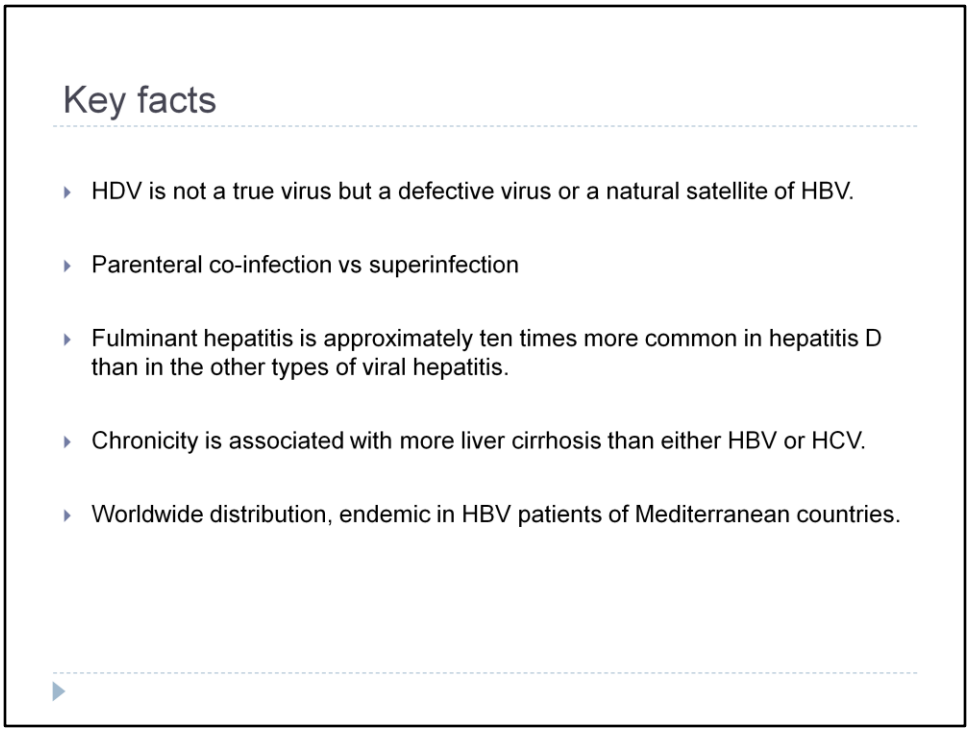
A diagnostic algorithm can be applied in the evaluation of cases of acute viral hepatitis. A patient with acute hepatitis should undergo four serologic tests, HBsAg, IgM anti-HAV, IgM anti-HBc, and anti-HCV.

The presence of HBsAg, with or without IgM anti-HBc, represents HBV infection. If IgM anti-HBc is present, the HBV infection is considered
acute; if IgM anti-HBc is absent, the HBV infection is considered chronic. A diagnosis of acute hepatitis B can be made in the absence of HBsAg when IgM anti-HBc is detectable. A diagnosis of acute hepatitis A is based on the presence of IgM anti-HAV. If IgM anti-HAV coexists with HBsAg, a diagnosis of simultaneous HAV and HBV infections can be made; if IgM anti-HBc (with or without HBsAg) is detectable, the patient has simultaneous acute hepatitis A and B, and if IgM anti-HBc is undetectable, the patient has acute hepatitis A superimposed on chronic HBV infection. The presence of anti-HCV supports a diagnosis of acute hepatitis C. Occasionally, testing for HCV RNA or repeat anti-HCV testing later during the illness is necessary to establish the diagnosis. Absence of all serologic markers is consistent with a diagnosis of “non-A, non-B, non-C” hepatitis, if the epidemiologic setting is appropriate.

In patients with chronic hepatitis, initial testing should consist of HBsAg and anti-HCV. Anti-HCV supports and HCV RNA testing establishes the diagnosis of chronic hepatitis C. If a serologic diagnosis of chronic hepatitis B is made, testing for HBeAg and anti-HBe is indicated to evaluate relative infectivity. Testing for HBV DNA in such patients

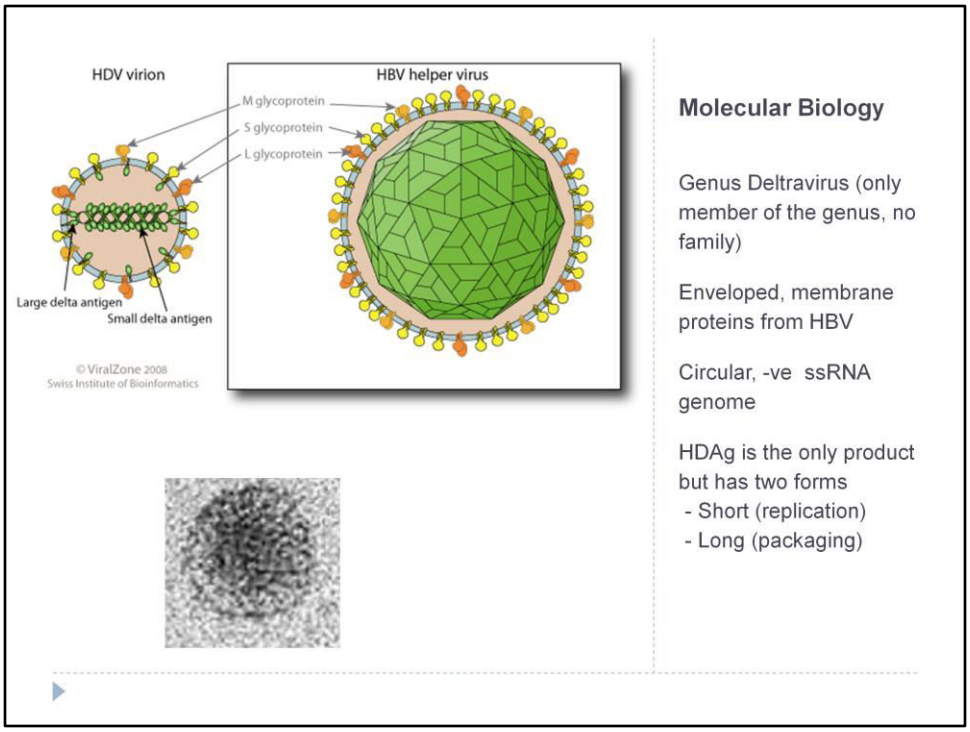
provides a more quantitative and sensitive measure of the level of virus replication and, therefore, is very helpful during antiviral therapy. In patients with chronic hepatitis B and normal aminotransferase activity in the absence of HBeAg, serial testing over time is often required to distinguish between inactive carriage and HBeAg-negative chronic hepatitis B with fluctuating virologic and necroinflammatory activity. In persons with hepatitis B, testing for anti-HDV is useful in those with severe and fulminant disease, with severe chronic disease, with chronic hepatitis B and acute hepatitis-like exacerbations, with frequent percutaneous exposures, and from areas where HDV infection is endemic.

Hepatitis D (delta)



The delta hepatitis agent, or HDV, the only member of the genus *Deltavirus*, is a defective RNA virus that coinfects with and requires the helper function of HBV (or other hepadnaviruses) for its replication and expression.

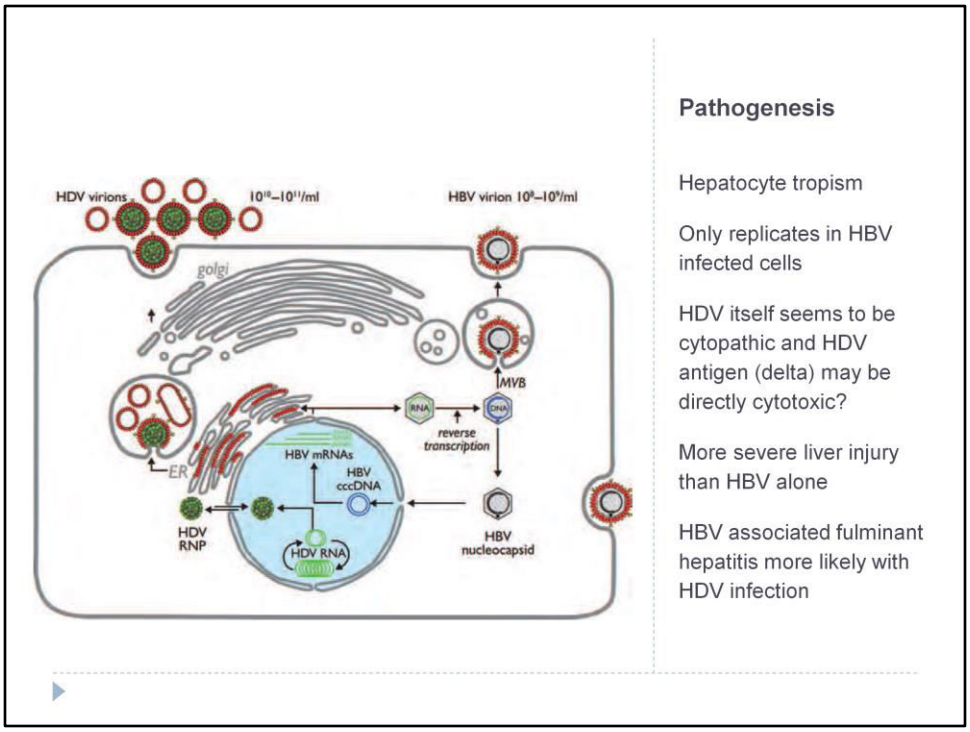
HDV can either infect a person simultaneously with HBV (*co-infection*) or superinfect a person already infected with HBV (*super-infection*). Because HDV relies absolutely on HBV, the duration of HDV infection is determined by the duration of (and cannot outlast) HBV infection.



HDV RNA contains many areas of internal complementarity; therefore, it can fold on itself by internal base pairing to form an unusual, very
stable, rodlike structure that contains a very stable, self-cleaving and self-ligating ribozyme.

HDV protein; HDAg exists in two forms: a small, 195-amino-acid species, which plays a role in facilitating HDV RNA replication, and a large, 214-amino-acid species, which appears to suppress replication but is required for assembly of the antigen into virions.

HDV antigen is expressed primarily in hepatocyte nuclei and is occasionally detectable in serum.



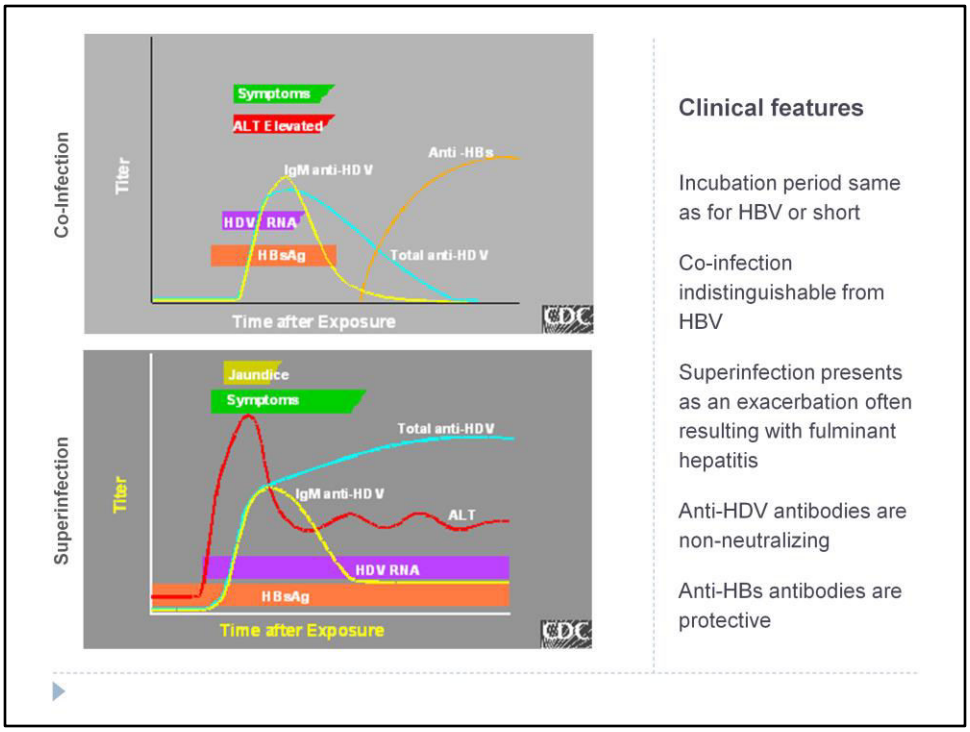
HDV nucleocapsids can be assembled using only HBV S, although such particles are not infectious. It is only when relatively small amounts of L are also present that the particles are infectious. M is not essential for assembly or infectivity. If one circumvents the viral entry process, the HDV genome can replicate in virtually any animal cell. Thus, the restriction of HDV is at the level of virus entry.

HBV uses the compartment known as the multivesicular body, whereas sub-viral particles (SVPs) are assembled using a secretory pathway. HDV assembly uses a secretory pathway like SVPs.

The pathogenesis of hepatitis D is still poorly understood. HDV is a highly pathogenic virus that causes the most severe forms of acute and chronic viral hepatitis. Controversy exists, however, regarding the relative role played by the direct pathogenic effects of HDV versus immune-mediated liver damage.

Concomitant HDV and HBV infections are associated with more severe liver injury than HBV infection.

LKM antibodies, similar to HCV infections, can also occur but can be distinguished from those with HCV and autoimmune hepatitis. These are a distinguishing serologic feature of chronic hepatitis D.



Infection with HDV can occur in the presence of acute or chronic HBV infection; the duration of HBV infection determines the duration of HDV infection.

When acute HDV and HBV infection occur simultaneously, clinical and biochemical features may be indistinguishable from those of HBV infection alone, although occasionally they are more severe. Co-infection usually results in an acute self-limited hepatitis, outcome is a complete recovery, as typically seen in acute hepatitis B.

As opposed to patients with *acute* HBV infection, patients with *chronic* HBV infection can support HDV replication indefinitely. HDV infection of an individual chronically infected with HBV (superinfection pattern) causes a generally severe acute hepatitis with a relatively short incubation period that may run to a fulminant course. In this setting, the pre-existing HBsAg status provides the biological background for the full expression of
the virulence of HDV. The acute hepatitis in the superinfection pattern is usually marked by an overt clinical illness and jaundice. Clinically, it may present as an exacerbation of a preexisting chronic hepatitis B leading to liver decompensation or as a new hepatitis in a previously
asymptomatic HBsAg carrier. If the HBsAg state is unknown, it may be misdiagnosed as acute hepatitis B. Superinfection with HDV is often associated with fulminant hepatitis.

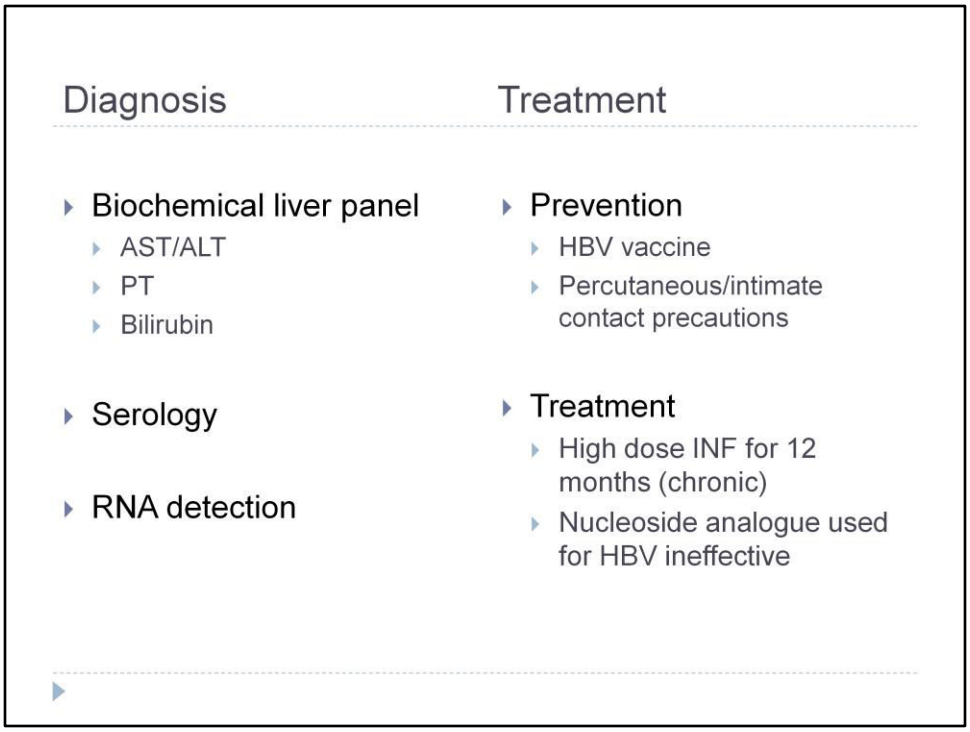
HDV elicits specific antibodies of immunoglobulin G (IgG) and immunoglobulin M (IgM) class against HDAg, which are typically detected during
the acute and chronic phase of infection. These antibodies do not have neutralizing activity because they are directed against the HDAg, the only protein encoded by the HDV genome, which is located in the interior of the virion. Because both HBV and HDV share the same envelope, HBsAg, antibodies to HBsAg (anti-HBs) confer protective immunity to both viruses.

During acute HDV infection, anti-HDV of the IgM class predominates, and 30–40 days may elapse after symptoms appear before anti-HDV can be detected.

In self-limited infection, anti-HDV is low-titer and transient, rarely remaining detectable beyond the clearance of HBsAg and HDV antigen. In chronic HDV infection, anti-HDV circulates in high titer, and both IgM and IgG anti-HDV can be detected. HDV antigen in the liver and HDV RNA
in serum and liver can be detected during HDV replication.

Patients with simultaneous acute hepatitis B and hepatitis D do not necessarily experience a higher mortality rate than do patients with acute hepatitis B alone; however, in several recent outbreaks of acute simultaneous HBV and HDV infection among injection drug users, the case
fatality rate has been ∼5%. In the case of HDV superinfection of a person with chronic hepatitis B, the likelihood of fulminant hepatitis and death is increased substantially. Although the case fatality rate for hepatitis D has not been defined adequately, in outbreaks of severe HDV superinfection in isolated populations with a high hepatitis B carrier rate, the mortality rate has been recorded in excess of 20%.

Although HDV and HBV infections are associated with severe liver disease, mild hepatitis and even inactive carriage have been identified in some patients, and the disease may become indolent beyond the early years of infection.



The presence of HDV infection can be identified by demonstrating intrahepatic HDV antigen or, more practically, an anti-HDV seroconversion (a rise in titer of anti-HDV or de novo appearance of anti-HDV). Circulating HDV antigen, also diagnostic of acute infection, is detectable only briefly, if at all. Because anti-HDV is often undetectable once HBsAg disappears, retrospective serodiagnosis of acute self-limited, simultaneous HBV and HDV infection is difficult.

When a patient presents with acute hepatitis and has HBsAg and anti-HDV in serum, determination of the class of anti-HBc is helpful in establishing the relationship between infection with HBV and HDV. Although IgM anti-HBc does not distinguish *absolutely* between acute and chronic HBV infection, its presence is a reliable indicator of recent infection and its absence a reliable indicator of infection in the remote past. In simultaneous acute HBV and HDV infections, IgM anti-HBc will be detectable, while in acute HDV infection superimposed on chronic HBV infection, anti-HBc will be of the IgG class.

Tests for the presence of HDV RNA are useful for determining the presence of ongoing HDV replication and relative infectivity.

In persons with hepatitis B, testing for anti-HDV is useful in those with severe and fulminant disease, with severe chronic disease, with chronic hepatitis B and acute hepatitis-like exacerbations, with frequent percutaneous exposures, and from areas

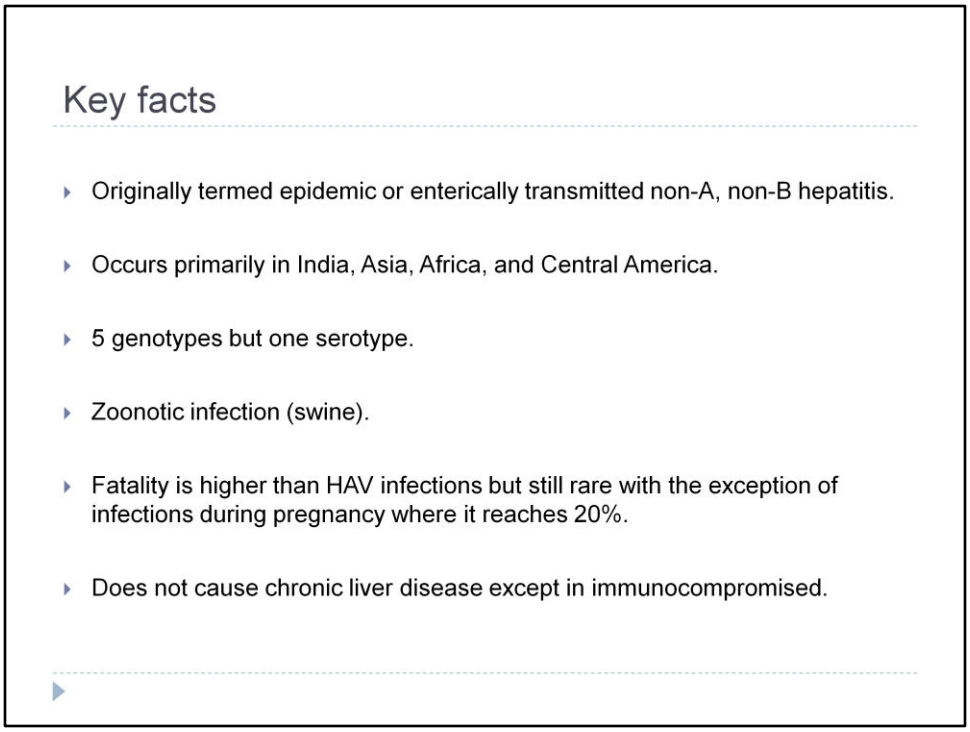
where HDV infection is endemic.

Infection with hepatitis D can be prevented by vaccinating susceptible persons with hepatitis B vaccine. No product is available for immunoprophylaxis to prevent HDV superinfection in HBsAg carriers; for them, avoidance of percutaneous exposures and limitation of intimate contact with persons who have HDV infection are recommended.

There is no evidence for benefit of IFN-a in acute hepatitis D, including fulminant hepatitis D. Patients with acute hepatitis D should be closely monitored to allow early detection of progression to fulminant hepatitis, for which liver transplantation remains the only valid therapeutic option.

Management for chronic HDV is not well defined. Glucocorticoids are ineffective and are not used. Preliminary experimental trials of IFN-α suggested that conventional doses and durations of therapy lower levels of HDV RNA and aminotransferase activity only transiently during treatment but have no impact on the natural history of the disease. In contrast, high-dose IFN-α (9 million units three times a week) for 12 months may be associated with a sustained loss of HDV replication and clinical improvement in up to 50% of patients.

Hepatitis E



HEV is an enterically transmitted virus that occurs primarily in India, Asia, Africa, and Central America; in those geographic areas, HEV is the most common cause of acute hepatitis.

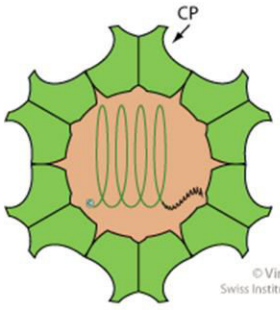
All HEV isolates appear to belong to a single serotype, despite genomic heterogeneity of up to 25% and the existence of five genotypes, only four of which have been detected in humans; genotypes 1 and 2 appear to be more virulent, while genotypes 3 and 4 are more attenuated and account for subclinical infections. Genotypes 1 and 2 infect only humans and primates. Genotypes 3 and 4 infect humans and primates as well; however, their main host is swine but have occasionally been isolated from deer and rabbits.

Contributing to the perpetuation of this virus are animal reservoirs, most notably in swine.

An epidemiologic feature that distinguishes HEV from other enteric agents is the rarity of secondary person-to-person spread from infected persons to their close contacts.

Survival of HEV in the intestinal tract suggests that the virus is relatively stable to acid and mild alkaline conditions. HEV is more heat labile than is HAV. Although not specifically tested, HEV is likely to be inactivated by the same

agents that inactivate HAV, and chlorination is suggested to inactivate HEV in water.



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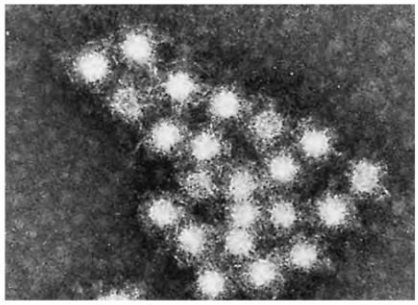
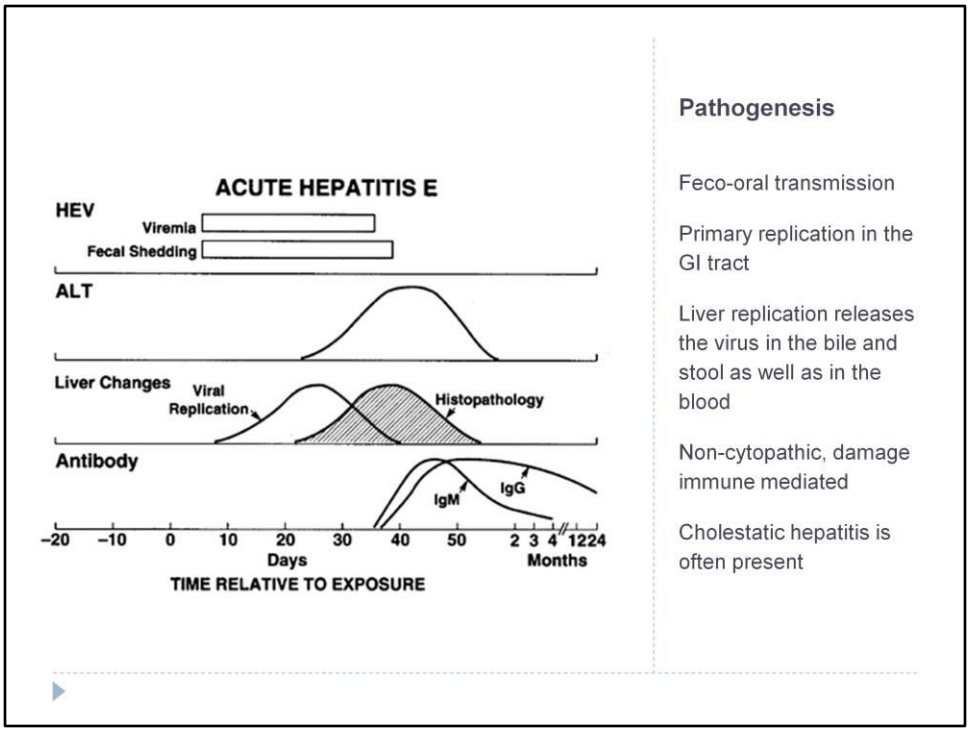


Molecular Biology

Hepeviridae family

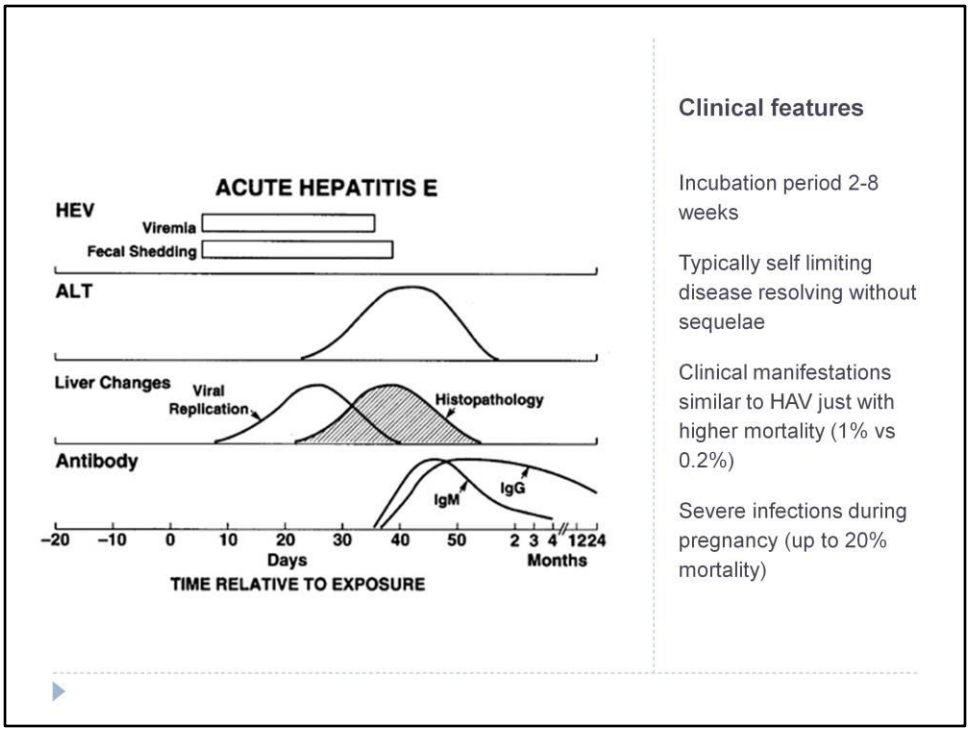
Non-enveloped

Linear, -ve ssRNA genome encodes 3 proteins (structural, replication, unknown)



The virus has been detected in stool, bile, and liver and is excreted in the stool during the late incubation period.

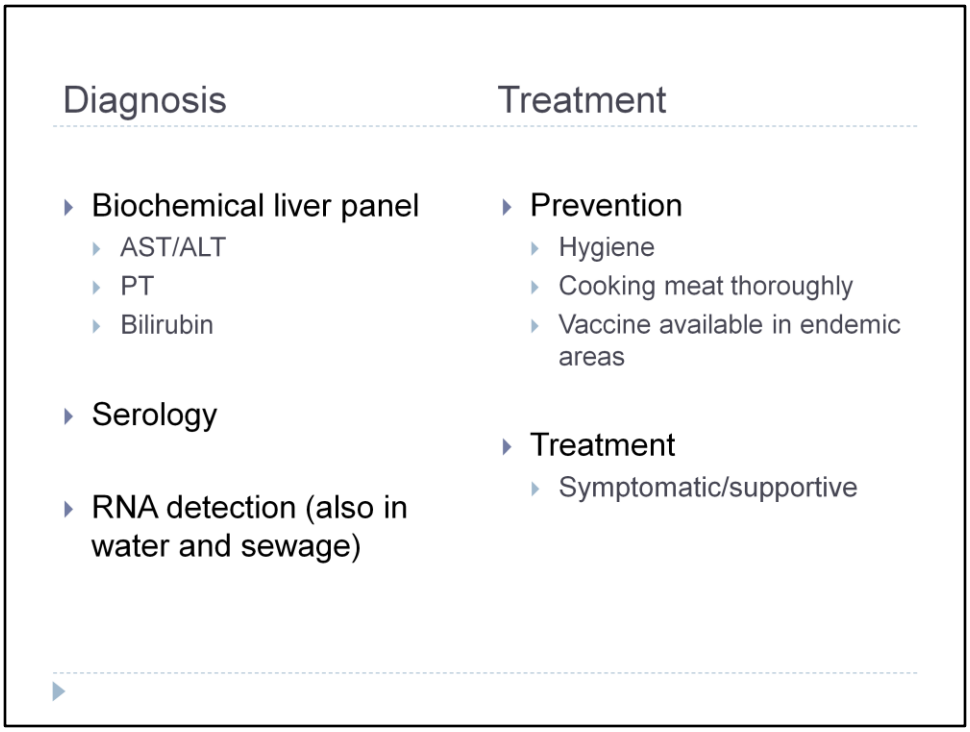
The discrepancy between the time of appearance of viral replication in the liver and histopathologic and biochemical evidence of hepatitis suggests that HEV is not cytopathic and that the pathogenesis of hepatitis E is immunologically mediated.



Immune responses to viral antigens occur very early during the course of acute infection. Both IgM anti-HEV and IgG anti-HEV can be detected, but both fall rapidly after acute infection, reaching low levels within 9–12 months.

The mortality of hepatitis E in pregnancy increases with each succeeding trimester and may reach 20%. In contrast, none of the other four recognized hepatitis viruses causes such severe hepatitis in pregnancy. The reason for the excessive mortality of hepatitis E in pregnancy is unknown.

HEV is an uncommon cause of fulminant hepatitis in nonpregnant individuals. Individuals with chronic liver disease of other etiologies are also at higher risk of severe, Life threatening hepatitis E. The hepatitis E mortality in such patients may be as high as 30%.



As with all types of viral hepatitis, serologic tests are necessary to establish a definite diagnosis. Specific tests for IgM and IgG antibodies to HEV have been developed and are commercially available. Current tests are capable of detecting IgM anti-HEV in up to 90% of acute infections if a serum sample is obtained 1 to 4 weeks after the onset of disease. IgM anti-HEV reaches peak titers during the first 4 weeks after the onset of hepatitis, and by 3 months after the onset of disease, IgM is no longer detectable in 50% or more of patients with hepatitis E. A rising titer of IgG antiHEV is also diagnostic. IgG antiHEV peaks in titer between 2 and 4 weeks after onset of hepatitis and diminishes relatively rapidly thereafter. It is not clear how long IgG antiHEV persists at detectable levels.

Broadly reactive RT-PCR primers that can detect most, if not all, mammalian HEV strains have recently been described. These are useful for detecting HEV in blood and feces during the acute phase of infection Thus, serologic and molecular approaches to diagnosis are complementary.

Access to a clean water supply and cooking meats to a temperature that inactivates HEV should, in theory, greatly decrease the incidence of HEV infections.

No specific treatment exists for acute hepatitis E. Both interferon alpha and ribavirin have been used successfully to treat chronic HEV infections.