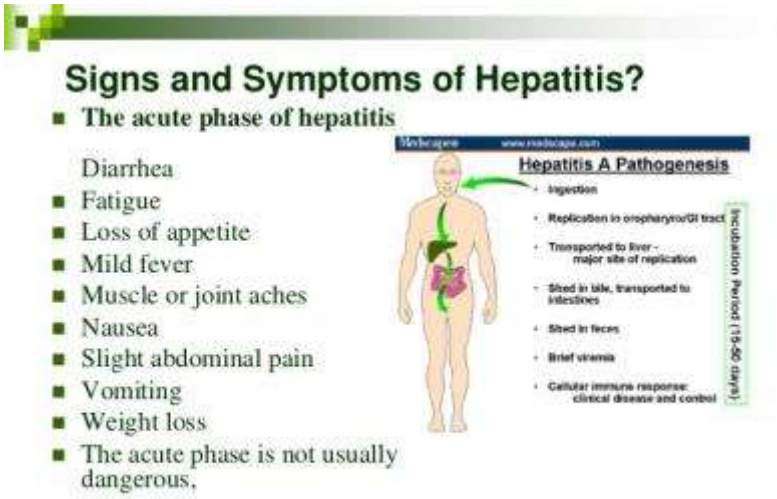
Hepatitis

Prevention, Treatment
Prognosis & Epidemiology

Prevention

Vaccines

Hepatitis A



Hepatitis A vaccine

- The CDC recommends the hepatitis A vaccine for all children beginning at age one, as well as for those who have not been previously immunized and are at high risk for contracting the disease.
- For children 12 months of age or older, the vaccination is given as a shot into the muscle in two doses 6–18 months apart and should be started before the age 24 months.
- The dosing is slightly different for adults depending on the type of the vaccine.
- If the vaccine is for hepatitis A only, two doses are given 6–18 months apart depending on the manufacturer.
- If the vaccine is combined hepatitis A and hepatitis B, up to 4 doses may be required.

Hepatitis B

Hepatitis B vaccine

- The CDC recommends the routine vaccination of all children under the age of 19 with the hepatitis B vaccine.
- They also recommend it for those who desire it or are at high risk.
- Routine vaccination for hepatitis B starts with the first dose administered as a shot into the muscle before the newborn is discharged from the hospital.
- An additional two doses should be administered before the child is 18 months.

- For babies born to a mother with hepatitis B surface antigen positivity, the first dose is unique – in addition to the vaccine, the **hepatitis immune globulin** should also be administered, both within 12 hours of birth.
- These newborns should also be regularly tested for infection for at least the first year of life.
- There is also a combination formulation that includes both hepatitis A and B vaccines.

Other

- There are currently no vaccines available for hepatitis C or E.
- In 2015, a group in China published an article regarding the development of a vaccine for hepatitis E.
- As of March 2016, the United States government was in the process of recruiting participants for the phase IV trial of the hepatitis E vaccine.

Behavioral changes

Hepatitis A

- Because hepatitis A is transmitted primarily through the oral-fecal route, the mainstay of prevention aside from vaccination is good hygiene, access to clean water and proper handling of sewage.

Hepatitis B and C

- As hepatitis B and C are transmitted through blood and multiple bodily fluids, prevention is aimed at
  - ***Screening blood prior to transfusion,***
  - ***Abstaining from the use of injection drugs,***
  - ***Safe needle and sharps practices in healthcare settings, and***
  - ***Safe sex practices.***

Hepatitis D

- The hepatitis D virus requires that a person first be infected with hepatitis B virus, so prevention efforts should focus on limiting the spread of hepatitis B.
- In people who have chronic hepatitis B infection and are at risk for superinfection with the hepatitis D virus, the preventive strategies are the same as for hepatitis B.

Hepatitis E

- Hepatitis E is spread primarily through the oral-fecal route but may also be spread by blood and from mother to fetus.
- The mainstay of hepatitis E prevention is similar to that for hepatitis A (namely, good hygiene and clean water practices).

Alcoholic hepatitis

As excessive alcohol consumption can lead to hepatitis and cirrhosis, the following are maximal recommendations for alcohol consumption:

- Women – ≤ 3 drinks on any given day and ≤ 7 drinks per week
- Men – ≤ 4 drinks on any given day and ≤ 14 drinks per week

Prevention and Control of HEPATITIS

Hepatitis	Primary prevention	Secondary prevention	Tertiary prevention
A	a) Health Promotion: - Health education of people, - environmental sanitation - Food hygiene - Use of boiled water - Hand washing before taking food and after toilet - Personal hygiene - Avoid contamination of food & water by covering food and protection from flies. b) Specific protection: Hepatitis A vaccine (inactivated) Parenteral administration 2 dose regimen, 6-18 months apart Children: Hep A + Recombinant Hep B c) Vaccination 0,1,6 months of food handlers	a) Early Diagnosis: - Demonstration of HAV antigens in blood, stools b) Prompt Treatment: Immunoglobulins	a) Disability limitation Self limited diseases b) Rehabilitation:

Prevention and Control of HEPATITIS

Hepatitis	Primary prevention	Secondary prevention	Tertiary prevention
B & C	a) Health Promotion: - Health education - Awareness about disease and complications. - Screening of blood before transfusion - Use of individual razor blades - Use of barrier methods of contraception - Sterilization of needles and syringes - Avoid multiple sex partners - Avoid contact of body fluids b) Specific protection: Hepatitis B vaccination a) plasma derived vaccine b) RDNA-Yeast derived vaccine Administration in Adults: 1st Dose→ at elected date 2nd Dose→ 1 month later 3rd Dose→ 6 months after 1st dose Administration in Children: Can be given in combinations or either as monovalent. Combinations (with DPT or / and Hib but its dose is given at birth and there should be time of 4 weeks b/w 2 doses [total = 4 doses]	a) Early Diagnosis: Screening through detection of HbSAg in blood b) Prompt Treatment: Hep-B: Immunoglobulin's given within 24 hours of getting infected. Symptomatic: - • Interferons • Lamirudine • Adefovir Hep-C: Begin interferon usually in combination with ribavirin **Administration in high risk person ells** **Perinatal transmission:** Children of carrier or case mothers should be administered HBV vaccine & HBIG within 12 hours of birth, followed by second dose of Hep B vaccine at 1-2 months & a third dose at 6 months **Hepatitis- C:No vaccine is available so far**	a) Disability limitation b) Rehabilitation: Hep B & C Surgical liver transplant

Successes

Hepatitis A

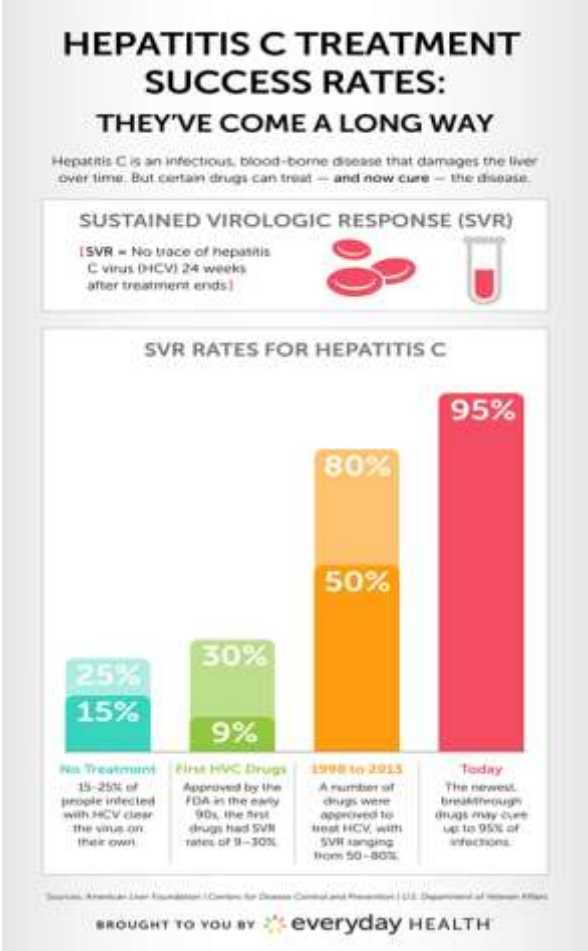
- In the United States, universal immunization has led to a **two-thirds decrease** in hospital admissions and medical expenses due to hepatitis A.

Hepatitis B

- In the United States new cases of hepatitis B decreased 75% from 1990–2004.
- The group that saw the greatest decrease was children and adolescents, likely reflecting the implementation of the 1999 guidelines.

Hepatitis C

- Hepatitis C infections each year had been declining since the 1980s, but began to increase again in 2006.
- The data are unclear as to whether the decline can be attributed to needle exchange programmes.



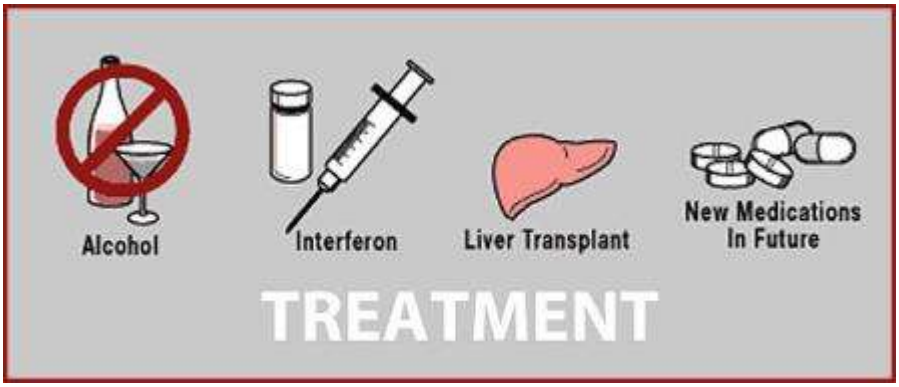
Alcoholic hepatitis

- Because people with alcoholic hepatitis may have no symptoms, it can be difficult to diagnose and the number of people with the disease is probably higher than many estimates.
- Programs such as Alcoholics Anonymous have been successful in decreasing death due to cirrhosis, but it is difficult to evaluate their success in decreasing the incidence of alcoholic hepatitis.

Treatment

The treatment of hepatitis varies according to the type, whether it is acute or chronic, and the severity of the disease.

- **Activity** - Many people with hepatitis prefer bed rest, though it is not necessary to avoid all physical activity while recovering.
- **Diet** -A high-calorie diet is recommended.
- Many people develop nausea and cannot tolerate food later in the day, so the bulk of intake may be concentrated in the earlier part of the day.
- In the acute phase of the disease, intravenous feeding may be needed if patients cannot tolerate food and have poor oral intake subsequent to nausea and vomiting.
- **Drugs** - People with hepatitis should avoid taking drugs metabolized by the liver.
- Glucocorticoids are not recommended as a treatment option for acute viral hepatitis and may even cause harm, such as development of chronic hepatitis.
- **Precautions** - Universal precautions should be observed.
- Isolation is usually not needed, except in cases of hepatitis A and E who have fecal incontinence, and in cases of hepatitis B and C who have uncontrolled bleeding.



Hepatitis A

- Hepatitis A usually does not progress to a chronic state, and rarely requires hospitalization.
- Treatment is **supportive** and includes such measures as providing intravenous (IV) hydration and maintaining adequate nutrition.
- Rarely, people with the hepatitis A virus can rapidly develop liver failure, *fulminant hepatic failure*, especially the elderly and those who had a pre-existing liver disease, especially hepatitis C.
- Mortality risk factors include greater age and chronic hepatitis C.
- In these cases, more aggressive supportive therapy and liver transplant may be necessary.

Hepatitis B

Acute

- In healthy patients, 95–99% recovers with no long-lasting effects, and antiviral treatment is not warranted.
- Age and comorbid conditions can result in a more prolonged and severe illness.

- Certain patients warrant hospitalization, especially those who present with clinical signs of ascites, peripheral edema, and hepatic encephalopathy, and laboratory signs of hypoglycemia, prolonged prothrombin time, low serum albumin, and very high serum bilirubin.
- In these rare, more severe acute cases, patients have been successfully treated with antiviral therapy similar to that used in cases of chronic hepatitis B, with nucleoside analogues such as Entecavir or Tenofovir.
- As there is a dearth of clinical trial data and the drugs used to treat are prone to developing resistance, experts recommend reserving treatment for severe acute cases, not mild to moderate.

Chronic

Chronic hepatitis B management aims to control viral replication, which is correlated with progression of disease.

Seven drugs are approved in the United States:

- Injectable interferon alpha was the first therapy approved for chronic hepatitis B.
- It has several side effects, most of which are reversible with removal of therapy, but it has been supplanted by newer treatments for this indication.
- These include long-acting interferon bound to polyethylene glycol (pegylated interferon) and the oral nucleoside analogues.
- Pegylated interferon (PEG IFN) is dosed just once a week as a subcutaneous injection and is both more convenient and effective than standard interferon.
- Although it does not develop resistance as do many of the oral antivirals, it is poorly tolerated and requires close monitoring.
- PEG IFN is not effective in patients with high levels of viral activity and cannot be used in immunosuppressed patients or those with cirrhosis.
- Lamivudine was the first approved oral nucleoside analogue.
- While effective and potent, lamivudine has been replaced by newer, more potent treatments in the Western world and is no longer recommended as first-line treatment.
- However, it is still used in areas where newer agents either have not been approved or are too costly.
- Generally, the course of treatment is a minimum of one year with a minimum of six additional months of "consolidation therapy."
- Based on viral response, longer therapy may be required, and certain patients require indefinite long-term therapy.[19] Due to a less robust response in Asian patients, consolidation therapy is recommended to be extended to at least a year.
- All patients should be monitored for viral reactivation, which if identified, requires restarting treatment.
- Lamivudine is generally safe and well tolerated.
- Many patients develop resistance, which is correlated with longer treatment duration.
- If this occurs, an additional antiviral is added.
- Lamivudine as a single treatment is contraindicated in patients co-infected with HIV, as resistance develops rapidly, but it can be used as part of a multidrug regimen.
- Adefovir dipivoxil, a nucleotide analogue, has been used to supplement lamivudine in patients who develop resistance, but is no longer recommended as first-line therapy.

- Entecavir is safe, well tolerated, less prone to developing resistance, and the most potent of the existing hepatitis B antivirals; it is thus a first-line treatment choice.
- It is not recommended for lamivudine-resistant patients or as monotherapy in patients who are HIV positive.
- Telbivudine is effective but not recommended as first-line treatment; as compared to Entecavir, it is both less potent and more resistance prone.
- Tenofovir is a nucleotide analogue and an antiretroviral drug that is also used to treat HIV infection.
- It is preferred to Adefovir both in lamivudine-resistant patients and as initial treatment since it is both more potent and less likely to develop resistance.
- **First-line treatments currently used include PEG IFN, Entecavir, and Tenofovir**, subject to patient and physician preference.
- Treatment initiation is guided by recommendations issued by The American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) and is based on detectable viral levels, HBeAg positive or negative status, ALT levels, and in certain cases, family history of HCC and liver biopsy.[1]
- In patients with compensated cirrhosis, treatment is recommended regardless of HBeAg status or ALT level, but recommendations differ regarding HBV DNA levels; AASLD recommends treating at DNA levels detectable above $2x10^3$ IU/mL; EASL and WHO recommend treating when HBV DNA levels are detectable at any level.
- In patients with decompensated cirrhosis, treatment and evaluation for liver transplantation are recommended in all cases if HBV DNA is detectable.
- Currently, multidrug treatment is not recommended in treatment of chronic HBV as it is no more effective in the long term than individual treatment with Entecavir or Tenofovir.

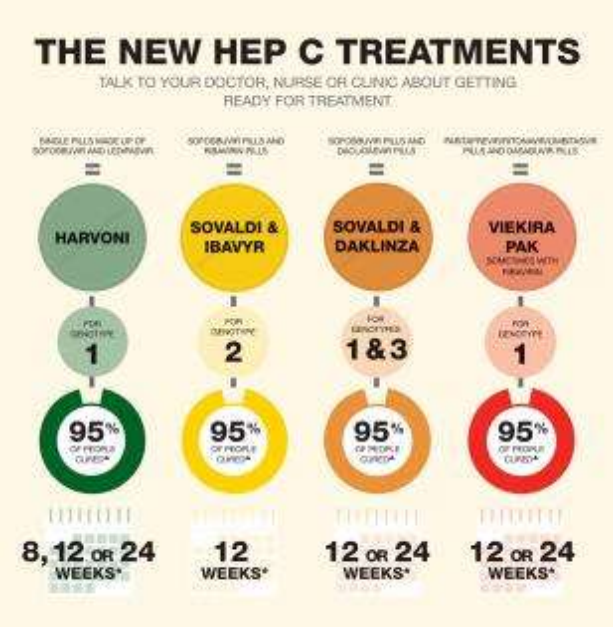
Hepatitis C

- The American Association for the Study of Liver Diseases and the Infectious Diseases Society of America (AASLD-IDSA) recommend antiviral treatment for all patients with chronic hepatitis C infection except for those with additional chronic medical conditions that limit their life expectancy.
- Once it is acquired, persistence of the hepatitis C virus is the rule, resulting in chronic hepatitis C.
- The goal of treatment is prevention of hepatocellular carcinoma (HCC).
- The best way to reduce the long-term risk of HCC is to achieve sustained virological response (SVR).
- SVR is defined as an undetectable viral load at 12 weeks after treatment completion and indicates a cure.
- Currently available treatments include indirect and direct acting antiviral drugs.
- The indirect acting antivirals include Pegylated interferon (PEG IFN) and ribavirin (RBV), which in combination have historically been the basis of therapy for HCV.
- Duration of and response to these treatments varies based on genotype.
- These agents are poorly tolerated but are still used in some resource-poor areas.

- In high-resource countries, they have been supplanted by direct acting antiviral agents, which first appeared in 2011; these agents target proteins responsible for viral replication and

Include the following three classes:

- NS3/4A protease inhibitors, including telaprevir, boceprevir, simeprevir, and others
- NS5A inhibitors, including ledipasvir, daclatasvir, and others
- NS5B polymerase inhibitors, including sofosbuvir, dasabuvir, and others
-



- These drugs are used in various combinations, sometimes combined with ribavirin, based on the patient's genotype, delineated as genotypes 1–6.
- Genotype 1 (GT1), which is the most prevalent genotype in the United States and around the world, can now be cured with a direct acting antiviral regimen.
- First-line therapy for GT1 is a combination of **sofosbuvir** and ledipasvir (SOF/LDV) for 12 weeks for most patients, including those with advanced fibrosis or cirrhosis.
- Certain patients with early disease need only 8 weeks of treatment while those with advanced fibrosis or cirrhosis who have not responded to prior treatment require 24 weeks.
- Cost remains a major factor limiting access to these drugs, particularly in low-resource nations; the cost of the 12-week GT1 regimen (SOF/LDV) has been estimated at US$94,500.

Hepatitis D

- Hepatitis D is difficult to treat, and effective treatments are lacking.
- Interferon alpha has proven effective at inhibiting viral activity but only on a temporary basis.

Hepatitis E

- Similar to hepatitis A, treatment of hepatitis E is supportive and includes rest and ensuring adequate nutrition and hydration.
- Hospitalization may be required for particularly severe cases or for pregnant women.

Alcoholic hepatitis

- First-line treatment of alcoholic hepatitis is treatment of alcoholism.
- For those who abstain completely from alcohol, reversal of liver disease and a longer life are possible; patients at every disease stage have been shown to benefit by prevention of additional liver injury.
- In addition to referral to **psychotherapy and other treatment programs**, treatment should include nutritional and psychosocial evaluation and treatment.
- Patients should also be treated appropriately for related signs and symptoms, such as ascites, hepatic encephalopathy, and infection.
- Severe alcoholic hepatitis has a poor prognosis and is notoriously difficult to treat.[32][60][105]
- Without any treatment, 20-50% of patients may die within a month, but evidence shows treatment may extend life beyond one month (i.e., reduce short-term mortality).[32][105][106]
- Available treatment options include pentoxifylline (PTX), which is a nonspecific TNF inhibitor, corticosteroids, such as prednisone or prednisolone (CS),
- corticosteroids with *N*-acetylcysteine (CS with NAC), and
- corticosteroids with pentoxifylline (CS with PTX).
- Data suggest that CS alone or CS with NAC are most effective at reducing short-term mortality.
- Unfortunately, corticosteroids are contraindicated in some patients, such as those who have active gastrointestinal bleeding, infection, kidney failure, or pancreatitis.
- In these cases PTX may be considered on a case by case basis in lieu of CS; some evidence shows PTX is better than no treatment at all and may be comparable to CS while other data show no evidence of benefit over placebo.
- Unfortunately, there are currently no drug treatments that decrease these patients' risk of dying in the longer term, at 3–12 months and beyond.
- Weak evidence suggests milk thistle extracts may improve survival in alcoholic liver disease and improve certain liver tests (serum bilirubin and GGT) without causing side effects, but a firm recommendation cannot be made for or against milk thistle without further study.

Prognosis

Acute hepatitis

- Nearly all patients with hepatitis A infections recover completely without complications if they were healthy prior to the infection.
- Similarly, acute hepatitis B infections have a favorable course towards complete recovery in 95–99% of patients.
- However, certain factors may portend a **poorer outcome**, such as co-morbid medical conditions or initial presenting symptoms of ascites, edema, or encephalopathy.
- Overall, the mortality rate for acute hepatitis is low: ~0.1% in total for cases of hepatitis A and B, but rates can be higher in certain populations (super infection with both hepatitis B and D, pregnant women, etc.).
- In contrast to hepatitis A & B, **hepatitis C** carries a much higher risk of progressing to chronic hepatitis, approaching 85–90%.

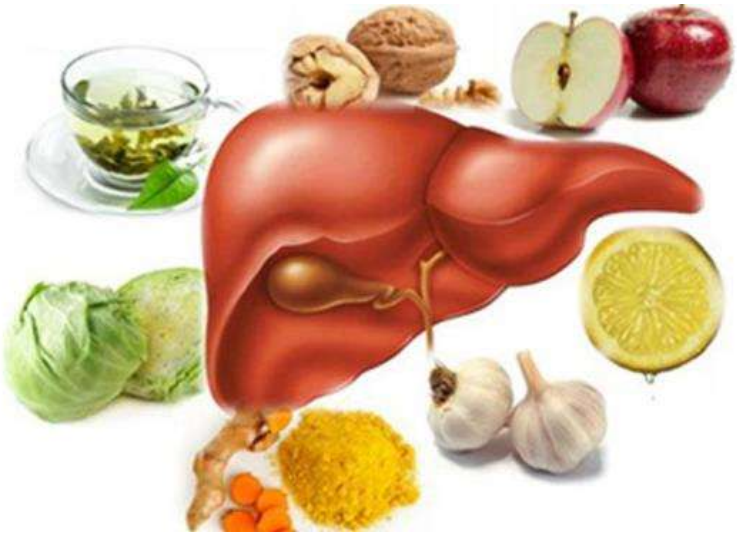
- Cirrhosis has been reported to develop in 20–50% of patients with chronic hepatitis C.
- Other rare complications of acute hepatitis include
    - Pancreatitis,
    - Aplastic anemia,
    - Peripheral neuropathy, and
    - Myocarditis.

Fulminant hepatitis

- Despite the relatively benign course of most viral cases of hepatitis, fulminant hepatitis represents a **rare but feared complication**.
- Fulminant hepatitis most commonly occurs in hepatitis B, D, and E.
- About 1–2% of cases of hepatitis E can lead to fulminant hepatitis, but pregnant women are particularly susceptible, occurring in up to 20% of cases.
- Mortality rates in cases of fulminant hepatitis rise over 80%, but those patients that do survive often make a complete recovery.
- Liver transplantation can be life-saving in patients with fulminant liver failure.
- Hepatitis D infections can transform benign cases of hepatitis B into severe, progressive hepatitis, a phenomenon known as superinfection.

Chronic hepatitis

- Acute hepatitis B infections become less likely to progress to chronic forms as the age of the patient increases, with rates of progression approaching 90% in vertically transmitted cases of infants compared to 1% risk in young adults.
- Overall, the 5-year survival rate for chronic hepatitis B ranges from 97% in mild cases to 55% in severe cases with cirrhosis.
- Most patients who acquire hepatitis D at the same time as hepatitis B (co-infection) recover without developing a chronic infection; however, in people with hepatitis B who later acquire hepatitis D (superinfection), chronic infection is much more common at 80-90%, and liver disease progression is accelerated.
- Chronic hepatitis C progresses towards cirrhosis, with estimates of cirrhosis prevalence of 16% at 20 years after infection.
- While the major causes of mortality in hepatitis C is **end stage liver disease**, **hepatocellular carcinoma** is an important additional long term complication and cause of death in chronic hepatitis.
- Rates of mortality increase with progression of the underlying liver disease.
- Series of patients with compensated cirrhosis due to HCV have shown 3,5, and 10-year survival rates of 96, 91, and 79% respectively.
- The 5-year survival rate drops to 50% upon if the cirrhosis becomes decompensated.



Epidemiology

Viral hepatitis

Hepatitis A

- Hepatitis A is found throughout the world and manifests as large outbreaks and epidemics associated with fecal contamination of water and food sources.
- Hepatitis A viral infection is predominant in children ages 5–14 with rare infection of infants.
- Infected children have little to no apparent clinical illness, in contrast to adults in whom greater than 80% are symptomatic if infected.
- Infection rates are highest in low resource countries with inadequate public sanitation and large concentrated populations.
- In such regions, as much as 90% of children younger than 10 years old have been infected and are immune, corresponding both to lower rates of clinically symptomatic disease and outbreaks.
- The availability of a childhood vaccine has significantly reduced infections in the United States, with incidence declining by more than 95% as of 2013.
- Paradoxically, the highest rates of new infection now occur in young adults and adults who present with worse clinical illness.
- ***Specific populations at greatest risk include:***
    - Travelers to endemic regions,
    - Men who have sex with men,
    - Those with occupational exposure to non-human primates,
    - Individuals with clotting disorders who have received clotting factors,
    - Individuals with a history of chronic liver disease where co-infection with hepatitis a can lead to fulminant hepatitis, and
    - Intravenous drug users (rare).

Hepatitis B

- Hepatitis B is the most common cause of viral hepatitis in the world with more than 240 million chronic carriers of the virus, 1 million of whom are in the United States.
- In approximately two-thirds of patients who develop acute hepatitis B infection, no identifiable exposure is evident.
- Of those acutely infected, 25% become **lifetime carriers of the virus.**

- ***Risk of infection is highest among***
  - Intravenous drug users,
  - Individuals with high-risk sexual behaviors,
  - Healthcare workers,
  - Individuals with a history of multiple transfusions,
  - Organ transplant patients,
  - Dialysis patients and newborns infected during the birthing process.
- Close to 780,000 deaths in the world are attributed to hepatitis B.
- The most endemic regions are in sub-Saharan Africa and East Asia, where as many as **10% of adults are chronic carriers.**
- Carrier rates in developed nations are significantly lower, encompassing less than 1% of the population.
- In endemic regions, transmission is thought to be associated with exposure during birth and close contact between young infants.

Hepatitis C

- Chronic hepatitis C is a major cause of liver cirrhosis and hepatocellular carcinoma.
- It is a common medical reason for liver transplantation due to its severe complications.
- It is estimated that 130–180 million people in the world are affected by this disease representing a little more than 3% of the world population.
- In the developing regions of Africa, Asia and South America, prevalence can be as high as 10% of the population.
- In Egypt, rates of hepatitis C infection as high as 20% have been documented and are associated with iatrogenic **contamination related to schistosomiasis treatment in the 1950s–1980s.**
- Currently in the United States, approximately 3.5 million adults are estimated to be infected.
- Hepatitis C is particularly prevalent among people born between 1945–1965, a group of about 800,000 people, with prevalence as high as 3.2% versus 1.6% in the general U.S. population.
- Most chronic carriers of hepatitis C are unaware of their infection status.
- The most common mode of transmission of hepatitis C virus is exposure to blood products via blood transfusions (prior to 1992) and intravenous drug injection.
- A history of intravenous drug injection is the most important risk factor for chronic hepatitis C.
- Other susceptible populations include individuals with high-risk sexual behavior, infants of infected mothers, and healthcare workers.

Hepatitis D

- The hepatitis D virus causes chronic and fulminant hepatitis in the context of co-infection with the hepatitis B virus.
- It is primarily transmitted via non-sexual contact and via needles.
- Susceptibility to hepatitis D differs by geographic region.
- In the United States and Northern Europe, populations at risk are intravenous drug users and individuals who receive multiple transfusions.
- In the Mediterranean, hepatitis D is predominant among hepatitis B virus co-infected individuals.

Hepatitis E

- Similar to Hepatitis A, hepatitis E manifests as large outbreaks and epidemics associated with fecal contamination of water sources.
- It accounts for more than 55,000 deaths annually with approximately 20 million people worldwide thought to be infected with the virus.
- It affects predominantly young adults, causing acute hepatitis.
- In infected pregnant women, Hepatitis E infection can lead to fulminant hepatitis with third trimester mortality rates as high as 30%.
- Individuals with weakened immune systems, such as organ transplant recipients, are also susceptible.
- Infection is rare in the United States but rates are high in the developing world (Africa, Asia, Central America, and Middle East).
- Many genotypes exist and are differentially distributed around the world.
- There is some evidence of hepatitis E infection of animals, serving as a reservoir for human infection.

Alcoholic hepatitis

- Alcoholic hepatitis (AH) in its severe form has one-month mortality as high as 50%.
- Most people who develop AH are men but women are at higher risk of developing AH and its complications likely secondary to high body fat and differences in alcohol metabolism.
- Other contributing factors include younger age <60, binge pattern drinking, poor nutritional status, obesity and hepatitis C co-infection.
- It is estimated that as much as 20% of people with AH are also infected with hepatitis C.
- In this population, the presence of hepatitis C virus leads to more severe disease with faster progression to cirrhosis, hepatocellular carcinoma and increased mortality.
- Obesity increases the likelihood of progression to cirrhosis in individuals with alcoholic hepatitis.
- It is estimated that a high proportion of individuals (70%) who have AH will progress to cirrhosis.