Indian Academy of Pediatrics (IAP)

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Viral Hepatitis

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Viral Hepatitis

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Acute Hepatitis

Definition

Acute hepatitis is a clinical syndrome characterized by acute onset of liver dysfunction (usually over a period 4 weeks) characterized by elevation of transaminases with variable synthetic dysfunction. On the other hand, chronic hepatitis refers to chronic elevation of transaminases, a specific time limit is not defined.

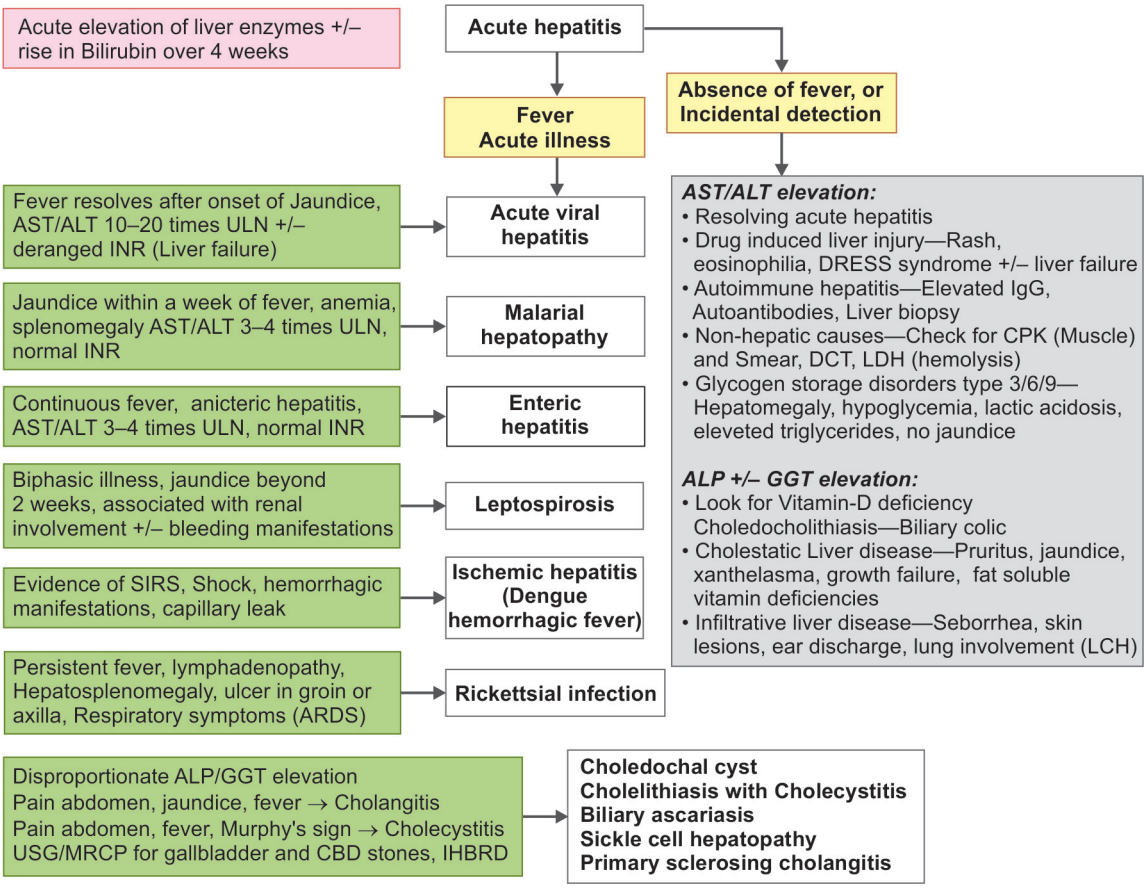
Causes

Acute hepatitis should be suspected when a child presents with a combination of features comprising of jaundice, nausea, vomiting, and pain over right upper quadrant of abdomen. The most common cause of acute hepatitis in Indian children is acute viral hepatitis A, rarely hepatitis E, B or nonhepatotropic viruses [dengue, parvo, *Cytomegalovirus* (CMV), Epstein–Barr virus (EBV), and herpes], drug-induced or autoimmune hepatitis, liver injury as a bystander hepatitis should also be considered in the setting of common tropical infections such as malaria, enteric fever, leptospirosis, and scrub typhus **(Flowchart 1)**. Occasionally, acute hepatitis can be a first manifestation of underlying chronic liver disease, which should be looked up clinically, and on laboratory tests and imaging **(Flowchart 2)**.

Clinical Features

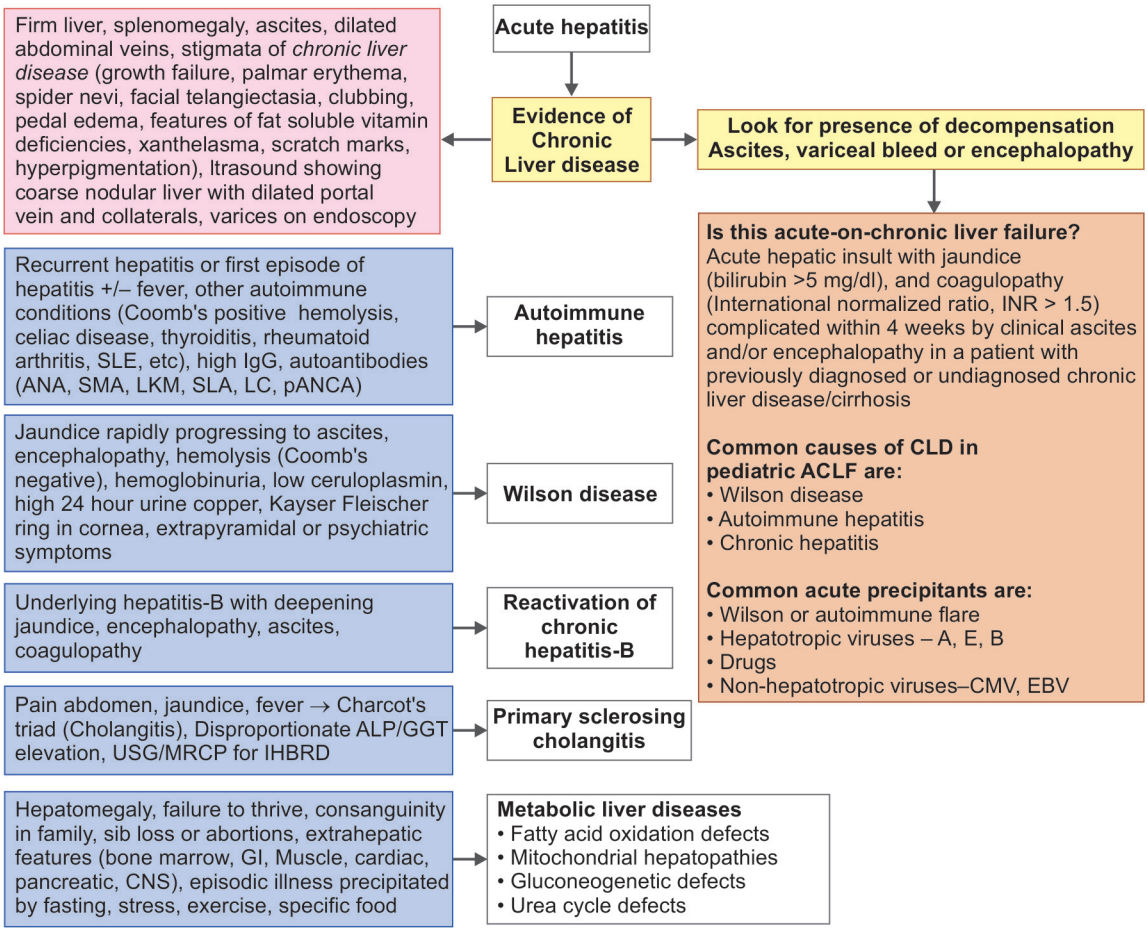
- ☑ Typical acute viral hepatitis A or E develops after an incubation period of 2–4 weeks and starts with prodromal illness (anorexia, nausea, vomiting, low-grade fever, pain right hypochondrium, and malaise) followed by jaundice.
- ☑ Risk of acute liver failure in hepatitis A and E is <0.1%, except in pregnant females where hepatitis E causes liver failure in around 20%.
- ☑ **Flowchart 3** presents the diagnostic algorithm in a child with suspected acute viral hepatitis.
- ☑ In all cases of acute viral hepatitis whether on outpatient follow-up or admitted as in-patient, danger signs or symptoms should be looked up carefully, and in case of liver failure appropriate management should be initiated.

Flowchart 1: Differential diagnosis of acute viral hepatitis.



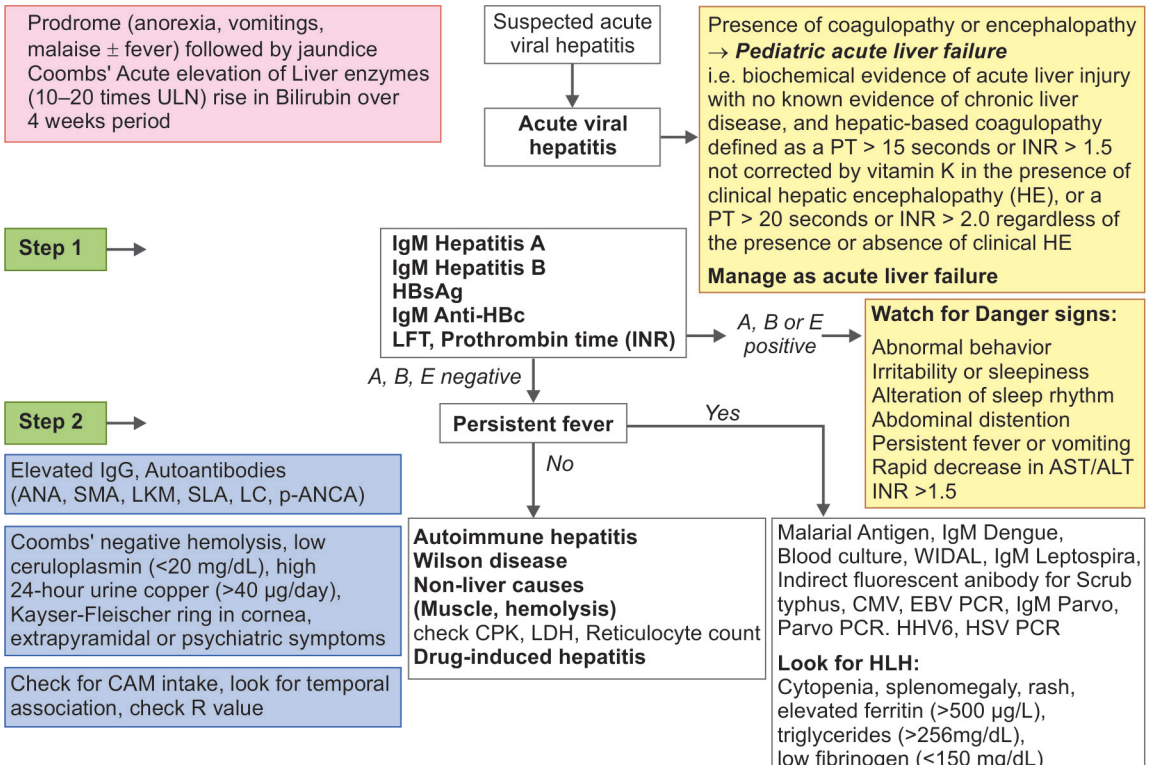
(AST: aspartate aminotransferase; ALP: alkaline phosphatase; ALT: alanine aminotransferase; CBD: common bile duct; CPK: creatine phosphokinase; DRESS: drug rash with eosinophilia and systemic symptoms; GGT: gamma-glutamyl transferase; IgG: immunoglobulin G; IHBRD: Intrahepatic biliary radicle dilatation; INR: international normalized ratio; LCH: Langerhans cell histiocytosis; LDH: lactic dehydrogenase; MRCP: magnetic resonance cholangiopancreatography; SIRS: systemic inflammatory response syndrome; ULN: upper limits of normal; USG: ultrasonography)

Flowchart 2: Differential diagnosis of chronic hepatitis.



(ACLF: acute-on-chronic liver failure; ALP: alkaline phosphatase; CLD: chronic liver disease; CMV: *Cytomegalovirus*; CNS: central nervous system; EBV: Epstein–Barr virus; GGT: gamma-glutamyl transferase; GI: gastrointestinal; IgG: immunoglobulin G; IHBRD: Intrahepatic biliary radicle dilatation; INR: international normalized ratio; LCH: Langerhans cell histiocytosis; LDH: lactic dehydrogenase; MRCP: magnetic resonance cholangiopancreatography; SIRS: systemic inflammatory response syndrome; USG: ultrasonography)

Flowchart 3: Algorithmic approach for management of acute hepatitis.



(AST: aspartate aminotransferase; ALT: alanine aminotransferase; CMV: *Cytomegalovirus*; CPK: creatine phosphokinase; EBV: Epstein–Barr virus; HBc: hepatitis B core; HBsAg: hepatitis B surface antigen; HHV-6: human herpesvirus 6; HLH: hemophagocytic lymphohistiocytosis; HSV: herpes simplex virus; IgM: immunoglobulin M; INR: international normalized ratio; LDH: lactic dehydrogenase; LFT: liver function test; PCR: polymerase chain reaction; PT: prothrombin time; ULN: upper limits of normal)

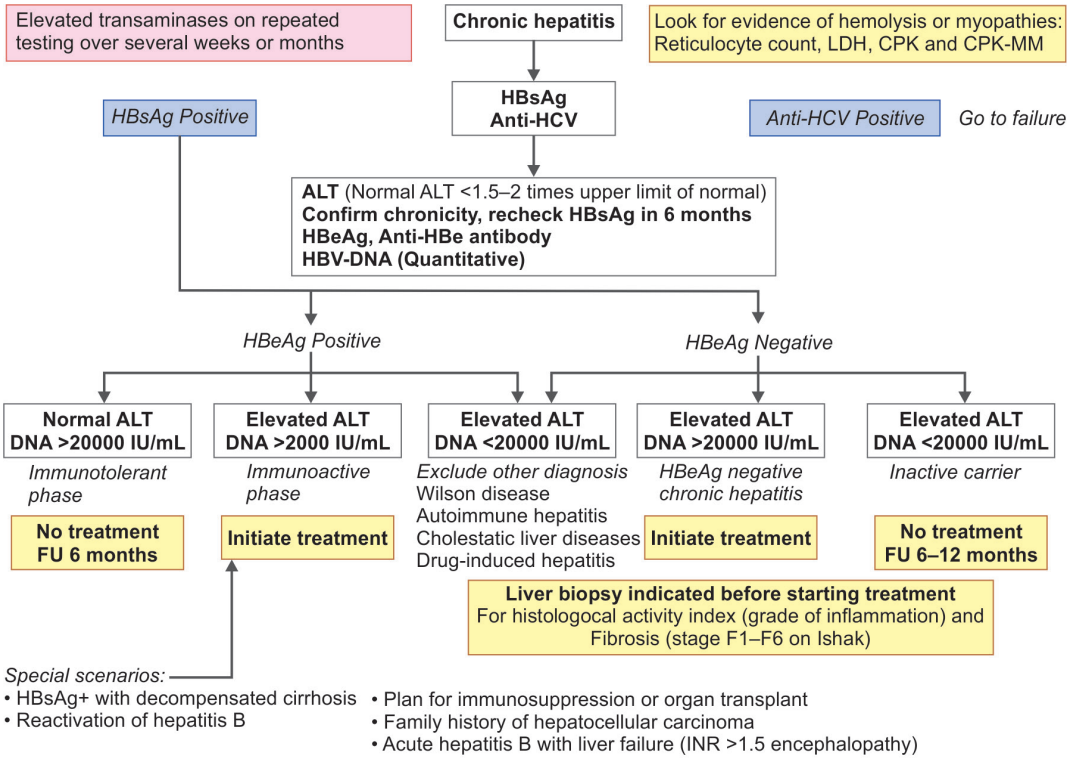
Introduction

- ☑ Around 2 billion people (one-third of world's population) is exposed to hepatitis B virus (HBV).
- ☑ Of these around 400 million (6% population) is chronically infected with the virus, three-fourths of the infected population live in Asia-Pacific.
- ☑ Globally, 57% of cirrhosis and 78% of hepatocellular carcinoma (HCC) are caused by hepatitis B.
- ☑ Maternal-to-child transmission is the most common mode of transmission in 50–70% of cases.
- ☑ Depending on the mode and age of acquisition of infection, the rate of chronic infection varies >90% for newborns with perinatal transmission, 25–30% for infants and children under-5-year age, and <5% for adolescents and adults.

Stages of Hepatitis B Infection and Management

- ☑ The various stages of hepatitis B infection in humans are described in **Flowchart 4 and Figure 1**.
- ☑ While considering a child or adolescent for treatment, it is imperative to characterize the patient into one of these categories as some phases (immunotolerant and inactive carrier) of chronic hepatitis B infection do not need any treatment.
- ☑ The treatment duration with antivirals is not finite, most of the guidelines suggest giving treatment for a period of 6–12 months following seroconversion.
- ☑ Hence, to avoid development of resistance to the current armamentarium of available drugs, choice of patient is important before starting treatment **(Flowchart 4 and Table 1)**.
- ☑ The American Association for Study of Liver Diseases (AASLD) guidelines say to treat children 2–17 years of age, with elevated alanine aminotransferase (ALT) and measurable deoxyribonucleic acid (DNA).
- ☑ The Asia-Pacific Association for Study of Liver (APASL) suggests treating children with ALT more than two times upper limit of normal, moderate inflammation or advanced fibrosis on liver biopsy, hepatitis B e antigen (HBeAg) negative with elevated ALT or significant fibrosis, presence of cirrhosis or reactivation of hepatitis B, or with family history of HCC.
- ☑ Similarly, the European Association of Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) recommends treating children with elevation of ALT for >6 months, DNA > 2,000 IU/mL, inflammation or fibrosis on liver biopsy, family history of HCC, or reactivation of hepatitis B in the setting of immunocompromised state.

Flowchart 4: Algorithmic approach for management of chronic hepatitis.



(ALT: alanine aminotransferase; CPK: creatine phosphokinase; DNA: deoxyribonucleic acid; HBeAg: hepatitis B e antigen; HBsAg: hepatitis B surface antigen; HBV: hepatitis B virus; HCV: hepatitis C virus; INR: international normalized ratio; LDH: lactic dehydrogenase)

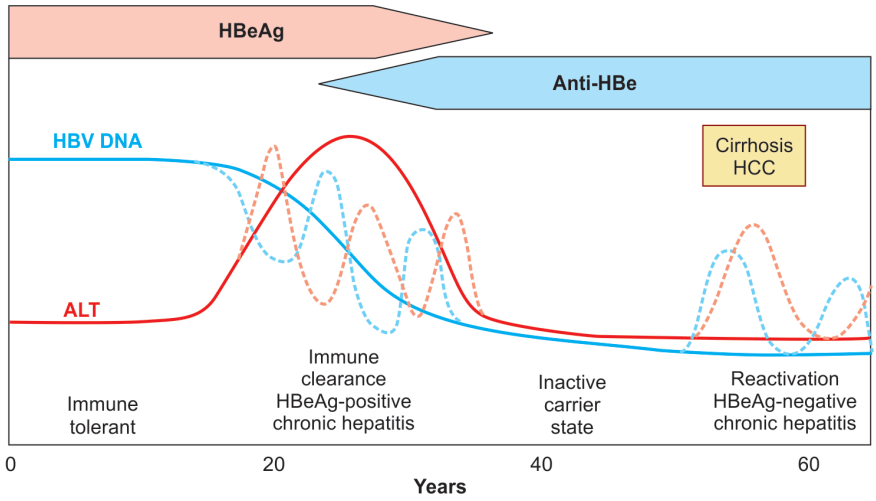


Fig. 1: Stages of hepatitis B infection.
(ALT: alanine aminotransferase; DNA: deoxyribonucleic acid; HBeAg: hepatitis B e antigen; HBV: hepatitis B virus; HCC: hepatocellular carcinoma)

Goal of Treatment

- ☑ Improve long-term survival and quality of life by reducing the risk of progressive liver disease, cirrhosis, and HCC.
- ☑ The ideal endpoint of treatment is sustained hepatitis B surface antigen (HBsAg) clearance, as it stops disease progression and reduces the risk of HCC, although this endpoint is rarely achieved (<5%).
- ☑ Closest and more achievable goal of treatment is seroconversion of HBeAg (HBeAg negative and anti-HBe antibody positive).
- ☑ Other goals may be normalization of ALT and suppression of HBV-DNA to undetectable limit.
- ☑ In adults, transient elastography (FibroScan) is routinely used to see progression or regression of fibrosis and being noninvasive is a feasible option for children.

TABLE 1: Drug used for management of chronic hepatitis B.

Drug	*Age-group*	*Dose*	*Duration*	*Advantages*	*Disadvantages*	*Side effects*
Interferon-alpha	≥12 months	5–10 MU/m^2 SC 3 times a week	6 months	Finite duration No resistance Durable off treatment response Immuno-modulatory + antiviral effects	Side effects Parenteral administration Not for decompensated cirrhosis	Flu like symptoms, anorexia Behavioral, lethargy, vomiting, alopecia, rash, neutropenia, arthralgia, thyroid dysfunction Dose reduction in one-fourth
Pegylated interferon-alpha 2 a/b	2–18 years	180 µg for a or 1.5 µg/kg for b, weekly	6–10 months	Same as above	Same as above	Same as above
Lamivudine	≥3 years	3 mg/kg/day	≥1 year	Few side effects Oral usage Inhibits viral replication	YMDD mutation risk increases with duration of treatment (38% and 67% at 2 and 4 years)	Mutation risk
Adefovir	≥12 years	10 mg/day	≥1 year	Same as above	Resistance increases with duration of treatment	High resistance rate
Entecavir	≥3 years	0.5 mg/day (1 mg/day for Lamivudine resistant)	≥1 year	Same as above + Negligible resistance	–	–
Telbuvidine	Not approved	600 mg/day for adults	≥1 year	Same as above + Renal sparing effect	Resistance increases with duration of treatment	High resistance rate
Tenofovir	12–18 years	300 mg/day	≥1 year	High response No resistance Fewer side effects	Effect on bone mineral density	Reduced bone mineral density
Combination or sequential treatment	Combining both interferon + oral nucleosides (-tides) – interferon being immunomodulator, decreases ccc-DNA & causes HBsAg loss, while nucleosides (-tides) inhibit viral replication, but no direct effect on ccc-DNA, thus adding interferon once viral load less boosts immunity against virus. Lamivudine or Entecavir or Tenofovir X 48 weeks, interferon added after 8 weeks and continued till end of treatment. Oral antivirals may be continued after stopping interferon.					

(DNA: deoxyribonucleic acid; HBsAg: hepatitis B surface antigen)

Chronic Hepatitis B

Testing of Newborn

- ☑ All newborns born to HBsAg positive mothers should receive hepatitis B immunoglobulin (0.5 mL) intramuscularly and first dose of hepatitis B vaccine within 12 hours of birth, followed by three more doses at 2, 4, and 6 months (or 6, 10, and 14 weeks).
- ☑ The newborns should be then tested for HBsAg and anti-HBs titer 3–12 months after the last dose of vaccine, and not before 9 months of age.

Family Screening for Hepatitis B

- ☑ All household contacts should be tested for HBsAg (for presence of current infection), total-anti-HBc antibody (for presence of resolved infection) and anti-HBs antibody (for presence of protective antibody).
- ☑ For anti-HBs antibody titers < 10 mIU/mL, three-dose vaccination (0, 1, and 6 months) should be initiated. In resource limited settings, at least HBsAg testing and vaccination should be done.

Hepatitis C

- ☑ Hepatitis C virus (HCV) is a single-stranded ribonucleic acid (RNA) virus of Flaviviridae family.
- ☑ HCV infection can be cured nowadays.
- ☑ The prevalence of chronic HCV infection is lower in children than adults, still an estimated 3.5–5 million children worldwide have chronic HCV infection.
- ☑ The rate of mother-to-child transmission (MTCT) of HCV infection is approximately 5%, although it is high among inadequately controlled human immunodeficiency virus (HIV) coinfection and women with higher HCV RNA levels (>6 log IU/mL).

Mode of Transmission

- ☑ MTCT—25–50% resolve spontaneously by 3–4 years of age.
- ☑ Intravenous (IV) drug abuse/tattooing.
- ☑ High-risk activities—intranasal cocaine and high-risk sexual activities.
- ☑ Blood transfusion—almost eliminated with effective screening procedures.
- ☑ Unsafe injection practices.
- ☑ Route of delivery does not influence vertical transmission rates.
- ☑ In HCV positive mothers, breastfeeding is not contraindicated unless the mother is also coinfected with HIV.

Investigations for Hepatitis C Virus Infection

- ☑ Screening/testing for HCV.
- ☑ Children born to HCV-positive mothers.
- ☑ Anti-HCV antibody screening of all children born to HCV-infected women recommended at or after 18 months of age.
- ☑ Testing with an HCV-RNA assay can be considered in the first year of life, even as early as 2 months of age.
- ☑ Children who are anti-HCV positive after 18 months of age should be tested with an HCV-RNA assay after 3 years of age to confirm chronic HCV infection.
- ☑ The siblings born of same mother should be tested for HCV infection.

Further Evaluation

- ☑ For those with confirmed infection with HCV RNA by polymerase chain reaction (PCR)
- ☑ Liver function test (LFT), prothrombin time (PT) [international normalized ratio (INR)], complete blood count (CBC), alpha-fetoprotein (AFP), and ultrasonography (USG) abdomen

Follow-up

- ☑ 6 months to annually with above tests
- ☑ To be checked for other coinfection—hepatitis B and HIV
- ☑ Liver biopsy is not routinely necessary before treatment. However, it may be needed if there is suspicion of advanced liver disease or when there are comorbid conditions which influence the treatment pathway.

Clinical Course

- ☑ Natural history of HCV infection is slow and indolent, usually with minimal symptoms or none at all.
- ☑ Development of advanced liver disease is infrequent until >30 years of infection. Children with nonalcoholic fatty liver disease, congenital heart disease with increased right heart pressure, thalassemia, and those receiving hepatotoxic medicines should be monitored carefully for disease progression.

Treatment (Tables 2 and 3)

- ☑ Direct-acting antiviral agents (DAAs) are the main stay of treatment for chronic HCV infection with simple, highly effective, and Food and Drug Administration (FDA) approved regimens.
- ☑ DAA is recommended for all children and adolescents with HCV infection aged ≥ 3 years as they will be benefitted regardless of disease severity.
- ☑ This is cost-effective and delaying treatment until early adulthood may increase lifetime risk of advanced liver disease.
- ☑ DAA agents are NS3/4A protease inhibitors, NS5A inhibitors, or NS5B polymerase inhibitors.

TABLE 2: Treatment-naïve or interferon-experienced children and adolescents without cirrhosis or with compensated cirrhosis.

Recommended	***Age group***	***Duration***
Pan-genotype: Combination of sofosbuvir/velpatasvir	≥3 years	12 weeks
Genotype 1, 4, 5, or 6: Combination of sofosbuvir/ledipasvir	≥3 years	12 weeks
Pan-genotype: Combination of glecaprevir/pibrentasvir	≥3 years	8 weeks

TABLE 3: Direct-acting antiviral agent (DAA)-experienced children and adolescents without cirrhosis or with compensated cirrhosis.

Recommended	***Age group***	***Duration***
Genotype 1: Combination of ledipasvir/sofosbuvir with prior exposed to an interferon (±ribavirin) plus a hepatitis C virus (HCV) protease inhibitor regimen	≥3 years	12 weeks (without cirrhosis) 24 weeks (with compensated cirrhosis)
Genotype 4, 5, or 6: Combination of ledipasvir/sofosbuvir for children and adolescents aged ≥ 3 years with prior exposure to an interferon (±ribavirin) plus an HCV protease inhibitor regimen without cirrhosis or with compensated cirrhosis	≥3 years	12 weeks
Genotype 1: Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) with prior exposure to an NS5A inhibitor but no NS3/4A protease inhibitor exposure, without cirrhosis or with compensated cirrhosis	≥12 years or weighing ≥45 kg	16 weeks

There DAA regimens with fixed dose combination of glecaprevir/pibrentasvir, but the molecules are yet to be available in India.

Further Reading

- ☑ HCV Guidance (2021). Recommendations for Testing, Managing, and Treating Hepatitis C. [online] Available from: https://www.hcvguidelines.org. [Last accessed February, 2022].
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- ☑ Yadav SR, Goldman DA, Murray KF. Hepatitis C: Current state of treatment in children. Pediatr Clin North Am. 2021;68(6):1321-31.