Child India

July 2021

Monthly e-Newsletter of Indian Academy of Pediatrics

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CONTENT

Editor's Note

Dear friends,

Greeting from Child India – your monthly e newsletter. We hope you are enjoying browsing through the academic content of these releases.

July 28th is observed as World Hepatitis Day (WHD) to raise awareness of viral hepatitis that causes severe liver disease and hepatocellular cancer. This year's theme is "Hepatitis can't wait", conveying the urgency of efforts needed to eliminate hepatitis as a public health threat by 2030. With a person dying every 30 seconds from a hepatitis related illness – even in the current COVID-19 crisis – we can't wait to act on viral hepatitis.

July 28th is the birthday of Dr. Baruch Blumberg (1925–2011). Dr. Blumberg discovered the hepatitis B virus in 1967, and 2 years later he developed the first hepatitis B vaccine. These achievements culminated in Dr. Blumberg winning the Nobel Prize.

WHD is a day to celebrate the progress made in prevention, diagnosis and management of hepatitis to meet the current challenges.

There are five main strains of the hepatitis virus – A, B, C, D and E. Together, hepatitis B and C are the most common which result in 1.1 million deaths and 3 million new infections per year. 9,400,000 people are receiving treatment for chronic hepatitis C virus infection. It is estimated that only 10% of people who have chronic infection with hepatitis B virus are diagnosed, and 22% of them receive treatment. Only 42% of children, globally, have access to the birth dose of the hepatitis B vaccine. A lot more still needs doing.

This issue of Child India features articles by young pediatric gastroenterologists on the hepatitis caused by the different strains of the causative virus. We thank our guest contributor Dr Anil Kumar, HOD Microbiology, AIMS, Kochi for his contribution.

Jai IAP!

Dr Jeeson C Unni
Editor-in-Chief

President's Address

Dear colleagues,

The question we ask in this Hepatitis issue of Child India is whether elimination of viral hepatitis by 2030 is feasible.

Hepatitis B virus (HBV) and hepatitis C virus (HCV) combined are among the top four global infectious disease killers alongside tuberculosis, malaria and HIV. Although the number of people in the world dying from HIV, tuberculosis and malaria have all declined since 2008, global deaths from chronic HBV and HCV infection continue to rise,

Studies suggest that all regions of the world must substantially scale up rates of diagnosis, access to treatment and immunisation coverage to meet the global targets. Rates of hepatitis B and C diagnosis are very low, averaging 8% and 18%, respectively, globally. The diagnosis coverage worldwide should be increased from 9–20% in 2015 to 90% in 2030. In addition, treatment coverage should be improved from 7–8% in 2015 to 80% and HBV immunization coverage should increase to 90% in 2030. This entails substantial investments in health-care system strengthening and the full continuum of viral hepatitis services. An analysis published in 2019 found that a total of $58.7 billion is needed to eliminate viral hepatitis in 67 LMICs.

Countries are currently investing hundreds of billions of US dollars to mitigate the effect of COVID-19, which will, in part, eventually support strengthening of surveillance and the health-care systems that can be used for enhancement of viral hepatitis services.

However, at present it seems that the World Health Organization target of eliminating viral hepatitis by 2030 is difficult to achieve.

IAP will continue its work in this elimination drive with efforts from floor members and our dedicated pediatric gastroenterologist members.

Jai IAP!

Piyush Gupta
National President, IAP 2021

Secretary's Message

Dear All,

Greetings!

It is my immense pleasure to be writing on behalf of IAP NC-ECD committee towards the greatest action plan!

Nurturing care for early childhood development has been the dream project of our beloved president Dr Piyush Gupta and IAP in association with WHO, UNICEF, Government of India and Johnson & Johnson. This promotes the very important aspect of basic nutrition and overall development for children.

My sincere appreciations to the wonderful team lead by Dr Piyush Gupta, Dr Digant Shastri, Dr Sharmila Mukherjee, Dr Yogish Barek, Dr Remesh Kumar, Dr Bakul Parek and everybody involved in this initiative. We can most certainly feel the success it will lead to and my thanks to you all for the effort and enthusiasm shown.

It is an excitement to know about the launch of the first virtual national ToT on 25th July followed by 5 virtual zonal ToTs. I appeal the members to join your hands and gear up for this program.

Last but not the least, congratulations again to the entire team for bringing in new concepts and for taking the academics to great heights.

IAPians, Together let's build IAP.

Jai IAP!! Jai Hind!!

Sincere Regards,

Dr G V Basavaraja
Hon. Secretary General 2020 & 21

IAP National Executive Board virtual meeting held on 19th and 20th June 2021

Hepatitis Day 2021

Prof John Matthai
President,
Indian Society of Pediatric Gastroenterology, Hepatology & Nutrition

World hepatitis day is commemorated on July 28 every year to enhance the understanding about hepatitis around the globe. It aims to raise awareness by promoting discussion among the public and facilitate prevention and treatment of viral hepatitis. 28 July was chosen being the birthday of Nobel Laureate Dr Baruch Blumberg, who discovered hepatitis B virus as well as the diagnostic test and vaccine.

The theme this year is "Hepatitis can't wait" and highlights the urgent need of international efforts to eliminate the disease as a major public health threat by 2030. WHO seeks to reinforce the idea that a hepatitis-free future is achievable by the combined efforts of national leaders and policy makers with cooperation from the public. Key messages this year include

For the Public:

- People living with viral hepatitis can't wait for testing or life saving treatments
- Expectant mothers can't wait for hepatitis screening and treatment
- Newborn babies can't wait for birth dose vaccination
- People affected by hepatitis can't wait to end stigma and discrimination

For Policy makers & National leaders

- Funding hepatitis care can't wait
- Elimination of mother to child transmission can't wait
- Community organisations can't wait for greater investment
- Setting national hepatitis elimination targets can't wait.

Globally only 42 % of children have access to the birth dose of the hepatitis B vaccine.

India introduced HB vaccine in the Universal Immunization Program (UIP) on a pilot basis in 14 cities and 33 districts in 2002–2003, and subsequently to the entire country in 2011–2012. Data from the NFHS 4 survey (2015-16) showed that 45% of children aged 12–59 months were not vaccinated against hepatitis B. There is wide variation across different parts of the country and districts with very low coverage of HBV vaccine are clustered in the western, north-eastern regions and in some parts of central India. The two most important factors that have been correlated with better Hepatitis B vaccine coverage are maternal education and utilization of institutional facilities for obstetric care. In India, around 1 million children (out of 26 million) born every year are at risk of developing chronic HBV infection during their lifetime. It is important to note that most cases now occur from horizontal transmission, unlike in the past when vertical transmission predominated.

Universal screening for Hepatitis B and C are important. Important advances have been made in treatment of both these in recent years, with the latter now being considered curable. High cost and access to specialist care are limiting factors in ensuring universal treatment in developing countries.

Hepatitis A continues to be a public health problem in India. Sero prevalence against hepatitis A is almost 75% in children under 5 years and around 85% above 10 years of age. Since Hepatitis A vaccine is not covered under the UIP, it can be presumed that most of these children have had sub clinical infection. A recent study observed that almost half the total cases of acute viral hepatitis in a tertiary care hospital in Delhi was due to Hepatitis A. Among children admitted with acute liver failure, Hepatitis A was the cause in around 45%.

The world is still struggling to cope with the COVID pandemic, but that should not be a reason to forget the other diseases that impact lives globally. We have made rapid progress in management of Hepatitis in the last decade. World hepatitis day 2021 is a reminder that those gains should not be denied to those who need it.

Hepatitis A virus

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Hepatitis A virus (HAV) is a single-stranded RNA virus that belongs to the picorna virus family. HAV virus was first identified in 1973 in stools of human volunteers who were infected with hepatitis A virus (1). The virus is hepatotropic and is excreted in the faeces of those infected and is transmitted either through contaminated food or drinking water, or by close inter-personal contact. It is thermostable and acid-resistant.

Human HAV strains can be grouped into four different genotypes and all four genotypes (I,II,III and VII) do not appear to have any biological differences and all belong to a single serotype. Most of the human strains are genotype I, which has been further divided in sub-genotypes IA and IB and genotype III. Sub-genotype IIIA had been reported to be the major HAV genotype in India (2).

Epidemiology

HAV infection occurs worldwide. Approximately 1.5 million clinical cases of hepatitis A occur worldwide annually. The incidence rate is strongly related to socioeconomic indicators and access to safe drinking water. HAV is more prevalent in low socioeconomic areas where a lack of adequate sanitation and poor hygienic practices facilitate the spread of the infection.

HAV infection generally follows one of three epidemiologic patterns (3). In countries where sanitary conditions are poor, most children are infected at an early age. The second epidemiologic pattern is seen in industrialized countries, where the prevalence of HAV infection is low among children and young adults. The third epidemiologic pattern is observed in closed communities, such as some isolated communities in the South Pacific, in which HAV, infects the entire population as epidemics, which then becomes immune. Subsequently, only newborns remain susceptible until the virus is reintroduced into the community.

Infection with HAV is endemic in India as in several developing countries. Earlier studies showed a very high seroprevalence rate of nearly 100% in adolescents and adults and an early average age at infection (4). Studies conducted in the 2000s across India consistently found that more than 90% of adolescents and adults are immune. Majority of children acquire immunity during their preschool years (5).

In many parts of the world, with improvement in socio-economic conditions, early childhood exposure to the virus has decreased. Hence, there has been a gradual shift in the age of acquiring the infection from early childhood to adulthood. The peak age of seroprevalence is shifting from the 1st decade of life to the 2nd and 3rd decades. This shift in age of acquiring infection from childhood to older age groups is termed as epidemiological shift. The relative frequency of symptomatic hepatitis and asymptomatic infection is age dependent. Concomitantly, there is an increase in symptomatic HAV infection and heightened risk of hepatic failure as a consequence of this epidemiologic drift(6). Recently, a few studies from India have reported an increase in symptomatic cases of HAV among older populations, so as to substantiate epidemiological shift.

In a study from South Delhi, trends of acute sporadic viral hepatitis A over a period of 5 years showed upto three times increase in proportion of acute hepatitis due to HAV infections in adolescents and young adults. Kerala has particularly low HAV antibody seroprevalence rates with Mathews et al and Mall et al (7) have reported the lowest seroprevalence rates of 4.5% and 10.3% respectively in children below 5 years of age. This reduction in infection rate in Kerala in recent years has been associated with two epidemics in Kerala during 1998 and 2004. In an epidemic of hepatitis reported from central Kerala in 1998, majority (65%) were in the age range of 15-33 years. Another epidemic of hepatitis A in 2004 also, majority of affected patients were young adults (8). These events suggest that certain geographic regions of the country have features of intermediate HAV endemicity.

Clinical features

Acute hepatitis A virus (HAV) infection is usually a self-limited disease conferring lifelong immunity. Infection with HAV does not result in chronic infection. The incubation period averages 30 days (range 15 to 50 days). Prodromal symptoms including, fatigue, malaise, nausea, vomiting, anorexia, fever, and right upper quadrant pain which diappaears with the onset of jaundice.

Patients with HAV infection usually follows one of the five clinical patterns: 1) asymptomatic without jaundice 2) symptomatic with jaundice and self limited after approximately 8 weeks, 3) cholestatic, with jaundice lasting 10 weeks or more 4) relapsing, with two or more bouts of acute HAV infection occurring over a 6- to 10-week period, and 5) fulminant hepatic failure.

Symptomatic hepatitis occurs in approximately 30 percent of infected children younger than six years. Jaundice usually lasts for less than two weeks. In contrast, symptoms develop in most children (80%) 6 years or older. The rate of symptoms is high in adolescents and adults. Right upper quadrant tenderness and mild liver enlargement are found on physical examination in 85% of patients. Splenomegaly and cervical lymphadenopathy are each present in 15%. Less common findings include evanescent rash, arthritis, and, rarely leukocytoclastic vasculitis. Complete clinical recovery is achieved in 60% of affected persons within 2 months and in almost everyone by 6 months.

Cholestatic hepatitis : Patients with acute hepatitis A occasionally can have prolonged cholestasis. The clinical course is usually characterized by marked jaundice, pruritus, fever, weight loss, diarrhea, and malaise. Biochemical and serologic abnormalities show marked elevation of the serum bilirubin (often >10 mg/dL) and alkaline phosphatase, minimal elevation of serum aminotransferases. Peak bilirubin levels may be reached in the eighth week or later. The jaundice and pruritus may last for 12 weeks or more, but are followed by complete recovery.

Relapsing hepatitis : A relapsing form of hepatitis is observed in 3 to 20 percent of patients with HAV infection. The clinical course is usually preceded by an apparent full clinical recovery with near normalization of the serum aminotransferases, followed by biochemical and clinical relapse, which is often milder than the initial episode. The prognosis in the relapsing form of hepatitis A is excellent, as complete recovery occurs. The duration of clinical relapse is generally short, although biochemical relapses may last as long as 12 months. .

Fulminant hepatitis A: The main complication of HAV infection is fulminant hepatitis (FHF) or acute liver failure (ALF) which occurs in less than 1% of cases. Fulminant hepatic failure is a syndrome characterized by grossly impaired liver function in an acute setting and is defined as acute onset of hepatic encephalopathy and liver failure within 8 weeks of development of jaundice. O'Grady and colleagues (43) classified acute liver failure based on the interval between

jaundice and encephalopathy into hyperacute (onset within 1 week), acute (between 8 and 28 days), and subacute (between 29 days and 12 weeks).

In a report from India, where 276 patients with FHF were seen between 1994 and 1997, hepatitis A virus was the major etiologic agent among children accounting for 81.6% but only 10.6% of the cases among adults were caused by HAV. HAV had been responsible for only 3.5% of FHF cases in adults and 51.4% FHF among children in the same community from 1978 to 1981(10).

The hallmark of ALF is altered mental status or hepatic encephalopathy accompanied by jaundice and elevated serum aminotransferases and prothrombin time/INR in previously healthy individuals. Hepatic encephalopathy can present as slight alteration in mental status (stage I); confusion, drowsiness, and asterixis (stage II); stupor, incoherence, and agitation (stage III); or frank coma, unresponsiveness, and decerebration (stage IV). Laboratory tests show hypoglycemia, increased prothrombin time, serum ALT, and AST levels, metabolic acidosis, hypoglycemia, and increased blood urea nitrogen and serum creatinine. The arterial ammonia level may have prognostic implications.

Diagnosis

A diagnosis of acute hepatitis A requires the demonstration of IgM anti-HAV in serum. The test is positive from the onset of symptoms and continues to remain positive for approximately 4 months. IgG anti-HAV is also detectable at the onset of the disease but it remains persistent for life and is considered as a marker of previous HAV infection.

Management

Acute viral hepatitis A is usually self-limited and the treatment is supportive. Occasional patients require hospitalization. Patients who develop fulminant infection require aggressive supportive therapy, and should be transferred to a centre capable of performing liver transplantation.. Reported case fatality rates are 0.1 percent in infants and children, 0.4 percent between the ages of 15 and 39, and 1.1 percent in those over 40 years.

Management of acute liver failure : Patient with acute liver failure needs immediate hospitalization and admission to an intensive care unit. Nutrition, treatment of hypoglycemia, hydration, electrolyte imbalance, coagulopathy, and prevention of infection are mainstays of supportive care. Serial laboratory tests including blood gases and lactate, INR, liver chemistry, and factor V levels needs to be done every 6 to 8 hours depending on the patient's condition. Close monitoring of neurologic status and blood sugar level is essential. Hyperammonemia is considered a critical factor in the development of cerebral edema and herniation. Arterial ammonia levels over 200 µg/dL have been strongly correlated with cerebral herniation and death(53).

Cerebral edema is managed by head elevation to 300, avoiding unnecessary movement or stimuli, close monitoring of pupils and papilledema, cooling to lower patient's core temperature, mannitol, hyperventilation, and use of propofol for sedation. Because of its invasive nature in coagulopathic patients, intracranial pressure monitoring using intracranial probes is not being practiced in all units. Treatment is aimed at maintaining the central perfusion pressure at >50mmHg (the difference between the mean arterial pressure and the ICP), and the ICP at <20mmHg.

The prothrombin time/INR is one of the most sensitive liver function tests available in the setting of ALF and mirrors the prognosis and course of disease. However, the tendency to spontaneously bleed is low despite marked elevations in the prothrombin time/INR, therefore fresh frozen plasma (FFP) should be used only for active bleeding or when needed to perform invasive procedures and not prophylactically.

Liver transplantation:With the advent of orthotopic liver transplantation (OLT) as a treatment option in ALF, overall survival rates have further improved from 20% to 60%. For acute liver failure, living-related liver transplantation (LDLT) may reduce waiting time and provide better timing compared to deceased donor liver transplantation (DDLT). The 1-year survival rate following LDLT is approximately 75%. In auxiliary liver transplant, the recipient's liver is left in place and using a partial left or right lobe from the donor which acts as temporary support for the recipient's injured liver. Immunosuppression may be withdrawn following native liver recovery allowing the graft to atrophy naturally or it is surgically removed.

Liver transplantation has markedly changed the prognosis of HAV-related acute liver failure. However, HAV-related FH resolves spontaneously more frequently than FH of other origins, and the decision to transplant or not to transplant is thus particularly difficult. Auxiliary liver transplantation may be appropriate in this setting, pending possible regeneration of the native liver.

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Hepatitis B in Children

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Hepatitis B (HB) is a global public health problem of immense importance affecting and killing millions of people all over the world. It occurs worldwide and up to two billion people, more than 30 % of the world's population, have been infected. According to WHO, there are more than 400 million carriers of the HB virus in the world (approximately 5% of the world's population) , out of which almost 75% are in Asia and Western Pacific. There are 40 million carriers in India alone who are at a risk of developing cirrhosis and hepatocellular carcinoma. The incidence of new HB infections has dramatically decreased at present thanks to the implementation of HB vaccination in most countries. However, HB continues to be a major cause of morbidity and mortality in the world even now.

History of HB

Hepatitis B is a relatively new disease, unlike hepatitis A (HA) which is believed to be described first by Hippocrates in 44 BC.

- The first epidemic of HB was described in 1885 by Lürmann during an "icterus epidemic" which occurred after a small pox vaccination campaign. The vaccine had been made from human "lymph".
- In 1942, 50,000 American soldiers who were given yellow fever vaccine containing human serum developed hepatitis. In 1987, Seeff proved from the stored sera of these patients that this hepatitis epidemic was actually due to HB virus,
- The first post-transfusion hepatitis was described in 1943 by Beeson.
- In 1963, the American physician and geneticist Samuel Baruch Blumberg from Philadelphia discovered the HB surface antigen, from the serum of an Australian aborigine. Hence HBsAg was initially called 'Australia antigen'(AuAg). This epoch-making discovery made it possible to screen blood donors for HB and also subsequently develop a vaccine against HB. Blumberg was awarded the Nobel Prize in medicine/physiology for this great discovery in 1976.
- 1970- David S Dane (London) described the HB virus, which is called Dane virus.
- HBsAg screening of donor blood initiated in 1970s
- 1971- William S. Robinson (Stanford, California) detected HB viral DNA
- 1972- The Swedish virologist Lars Magnius discovered HBeAg which helped to distinguish the highly infectious from the less infectious HBV carriers
- 1978- cloning and sequencing of the HBV DNA by three pioneers in molecular biology - Pierre Tiollais (Paris) , William Rutter (San Francisco) and Kenneth Murray (Edinburgh). This paved the way to understand the viral life cycle, and allowed development of efficient vaccines and drugs
- 1980s - Interferon introduced for children with chronic HB
- 1982- the first commercial anti-HBc test was released as an enzyme immunoassay.
- The plasma derived vaccine became available in 1982 and the recombinant DNA vaccine in 1984.

- 1988 - Hiroaki Okamoto and colleagues described genotypes A-D
- From 1990–1994, various mutant strains were identified.
- 1992- WHO directed that all countries should integrate HB vaccination into their national immunization program by 1997.
- 1995- Lamivudine introduced for chronic HB by Jules Dienstag
- 2002- The acyclic nucleotide analog adefovir used for the therapy of lamivudine resistant HB.
- 2006- entecavir introduced
- 2008 onwards- tenofovir followed by several new drugs for chr HB
- 2011- WHO initiated World Hepatitis Day Campaign- on July 28th every year

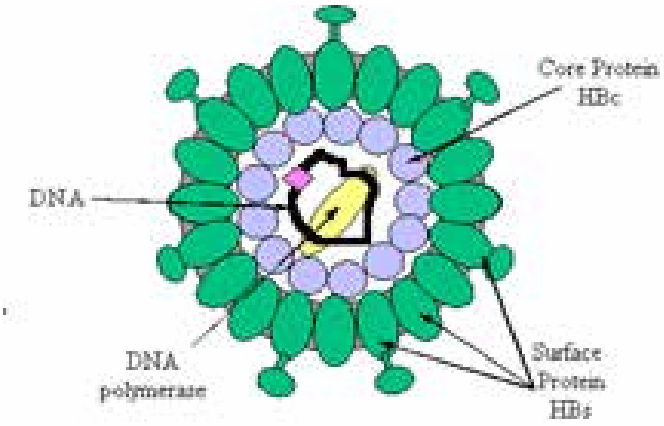
Virology

HBV is a small 42 nm DNA virus,3200 nucleotide bases in length, that belongs to the Hepadnaviridae family. Other members of this virus family are human HBV- like agents that infect the woodchuck, ground and tree squirrels, woolly monkey, crane, heron, Ross goose, and Peking duck.

The virion of hepatitis B (Dane particle) consists of surface and core. The core is formed in the hepatocyte nucleus and the surface particles in the cytoplasm. It contains the following: (Fig1)

- The genome of HBV
- DNA polymerase
- HBcAg
- HBeAg.

Fig 1: Structure of HB



HBV has a remarkable tropism for hepatocytes; replication in the infected hepatocytes produces a large excess of HBsAg, which can be found in the circulation as spherical or tubular forms.

Prevalence of HB

The overall prevalence of HBsAg is reported to be 3.5 percent; however, it varies depending upon the geographic area.

The global prevalence is divided into three zones depending upon the carrier rate:

- High zone (8%): 45% of global population
  - High endemicity
  - lifetime risk of infection > 60%
  - early childhood infections common
  - Mother-to-child transmission is the predominant mode of transmission
  - Southeast Asian countries, African countries and China are in this group.
- Intermediate zone (2%-7%): 43% of global population
  - Intermediate endemicity
  - lifetime risk of infection 20%-60%
  - infections occur in all age groups
  - horizontal transmission (child-to-child) is more common

- The Middle East, Central and South America, parts of Eastern Europe and India come under this zone

• Low zone (< 2%): 12% of global population

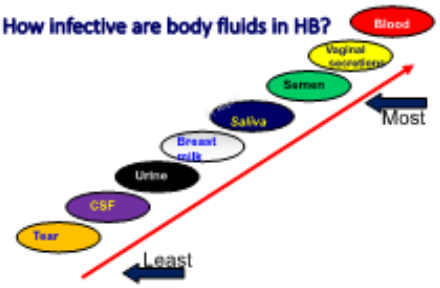
- Low endemicity
- lifetime risk of infection < 20%
- most infections occur in adult risk groups due to IV drug abuse and unprotected sexual intercourse
- Most developed countries(United States, Australia, and Western Europe) are in this zone

Transmission

Hepatitis B virus is transmitted from infected patients to those who are not immune (i.e., hepatitis B surface antibody [anti-HBs]-negative). The infective dose of VBH is extremely minute—just 0.00001 ml- but 1 ml blood contains 1 trillion viral particles. It has been shown that just ten or less virus particles are sufficient to initiate a readily detectable HBV infection if they are injected intravenously. Thus, if needles are not properly sterilized, the disease can be very easily transmitted.

The most infective body fluid is blood followed by vaginal secretions and semen , and the least infective is tear.(Fig 2)

Fig 2 Infectivity of body fluids



It is a common practice amongst residents and nurses to put back the needle into its sheath after giving an injection. If the needle pricks the finger during re-sheathing, he may develop HB ("needle-stick hepatitis").

As our dental colleagues are aware of the various routes of transmission of HB, they are taking sufficient precautions and hence dental procedures are also not major risk factors now.

Vertical Transmission (from the Mother to the Baby)

Transmission from the mother to baby may occur in utero, during delivery , or after birth. Most infections occur during delivery. The risk is as high as 90% if the mother is positive for both HBsAg and HBeAg and/or has a high HBV viral load, and if the baby is not given HB vaccine and hepatitis B immune globulin (HBIG) immediately after birth. The risk can be further reduced by giving anti-viral therapy to the mother.

HB virus has been found in the villous capillary endothelial cells and trophoblasts of the placenta. Transplacental transmission may rarely cause infection in the baby due to leakage, such as during a threatened abortion. Thus, a breach of the placental barrier may be responsible for intra-uterine infection. Preterm labor or spontaneous abortion may cause mixing of maternal and fetal blood, which may result in HB transmission.

There is no proof that HB transmission can be prevented by caesarean section. Thus, caesarean section should not be routinely recommended for HBsAg carriers for the purpose of reducing HB transmission.

Horizontal transmission (child-to-child)

This is very common in children in developing countries and is because of close physical contact between children with impetigo, eczemas, infected scabies, cuts or wounds. It can also spread to the mother from the child.

Role of barbers (Fig. 3)

In the last few decades many young men of Kerala were denied employment in Gulf countries as they were found to be HBsAg positive. Many of them did not have the usual risk factors for HB. Subsequently it was found that barbers may

have played a big role in this. A busy barber may shave more than 100 people daily, and it is quite possible that at least one of his clients is an HBsAg carrier. Till recently, barbers in some of the remote rural areas of Kerala were using only reusable razors instead of disposable razors. Hence, their razors may be contaminated with infected blood, resulting in infection of other clients.

Fig 3 Role of barbers in transmission of HB

Role of medical students in HB transmission (Fig 4)

A vigorous neurological examination by a 'virulent medical student' may result in the transmission of HB. The main culprits are usually the 3rd year UG students, who are thrilled to reach clinical wards. They are especially fascinated by the Babinski sign whose physiology they are thorough. Here you see 2 students simultaneously demonstrating Babinski sign using sharp nails in an HBsAg carrier. Their friend is enjoying the sight, while the patient is crying in agony as it is quite painful, and the nail may become contaminated with his blood. If the students try to demonstrate Babinski sign in another patient using the same nail, that patient stands a great risk of developing HB.

Testing for sensation by pins or needles may also transmit HB – hence, neurologists and dermatologists should be aware of this.

Fig 4. How medical students transmit HB

Clinical Presentation of HB

The incubation period of HB is relatively long (50-150 days) compared to HA (15-50 days), after which the patient may develop a prodrome consisting of nausea, vomiting, fever, anorexia, fatigue, arthralgia and malaise.

A. Asymptomatic or inapparent hepatitis

B. Symptomatic

- Anicteric hepatitis
- Icteric hepatitis
- Cholestatic hepatitis
- Fulminant hepatitis
- Chronic hepatitis
- Cirrhosis
- Hepatocellular carcinoma

Inapparent Hepatitis

The patient is asymptomatic and it is diagnosed only by the finding of elevated transaminases. They are not aware that they have been infected and such patients are more likely to become chronic carriers.

Anicteric Hepatitis

Here the patient has the clinical features of hepatitis, except jaundice. The clinical course is similar to icteric hepatitis but is of lesser duration.

Elevated transaminases and bilirubinuria help to suspect the diagnosis.

Icteric Hepatitis

The prodromal symptoms of HB are usually milder compared to HA. The duration of jaundice varies from 4–6 weeks. Clinical and biochemical recovery are usually complete within 6 months of onset. Some patients may develop severe intrahepatic cholestasis; but its incidence is less than that in HA.

Fulminant Hepatitis

The incidence of fulminant HB is about 1%, compared to HA (0.1%).

The risk of fulminant hepatitis is high in patients with acute HB and co-infection with hepatitis delta virus or hepatitis C virus. It is due to an exaggerated immune response of the host in which viral replication is inhibited along with massive lysis of infected hepatocytes.

Chronic hepatitis

Chronic hepatitis is characterized by the persistence of HBsAg for more than 6 months, with or without concurrent HBeAg. The age at the time of infection is the most important factor that determines progression to chronicity. About 90% of neonates born to mothers who are positive for both HBsAg and HBeAg develop CH while only 30% infected in childhood, and 5-10 % infected in adulthood develop CH.

Extrahepatic Manifestations of HB

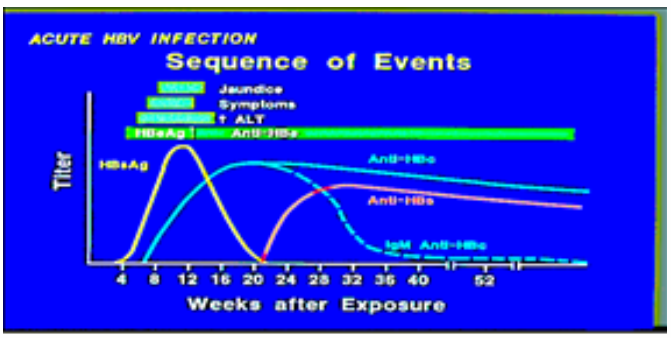
- Acute HB is sometimes heralded by a serum sickness - like syndrome consisting of fever, maculopapular rash and polyarthralgia
- Glomerulonephritis- membranous glomerulonephritis is the most common in children but membranoproliferative, mesangiocapillary or focal proliferative glomerulonephritis, minimal change disease and IgA nephropathy have also been reported
- Gianotti-Crosti syndrome (papular acrodermatitis)- this is strongly associated with HBs antigenemia in young children. It manifests as symmetrical, erythematous, maculopapular, non-pruritic eruptions over the face, buttocks, limbs and occasionally the trunk.
- Polyarteritis nodosa- about 10-30% of patients with PAN are found to be HBsAg positive
- Polymyalgia rheumatica
- Essential mixed cryoglobulinemia- incidence is less compared to HC

Diagnosis of acute HB infection (Fig 5)

It is difficult to differentiate HB from hepatitis caused by other hepatotrophic viral agents , and hence, laboratory confirmation of the diagnosis is essential. The most characteristic laboratory parameter is the marked elevation of transaminases (2000-3000) , which usually return to normal level in 12 weeks. Serum bilirubin rises for 10–14 days and then declines gradually over the next 4–6 weeks.

Following exposure to the virus, the first serological marker to appear is HBsAg by 4 weeks, even before the onset of symptoms and elevation of transaminases. It usually disappears by 5-6 months of the onset followed by the appearance of anti-HBs. Persistence of HBsAg for more than 6 months implies a carrier state.

Fig 5. Serological changes in HB



The second antigen to appear is HBeAg, soon after HBsAg. Its presence indicates active intrahepatic viral replication, and the presence in the blood of DNA polymerase, HBV DNA and virions,

reflecting high infectivity. It disappears before HBsAg, coinciding with the fall of transaminases. It is followed by the appearance of anti-HBe. As HBeAg is invariably present during acute hepatitis, its testing is indicated only in chronic infection and carriers.

HBcAg is not present in the blood, as it is enclosed within the HBsAg coat. But its antibody, IgM anti-HBc, appears in the blood, 1–2 weeks after the appearance of HBsAg. It is therefore the first antibody to appear, much before anti-HBe or anti-HBs. There is a brief period in which HBsAg is absent and anti-HBs has not yet appeared. This is called the window period, which can be diagnosed only by demonstrating IgM-anti HBc.

After 6 months, IgM anti-HBc is replaced by IgG anti-HBc which persists as long as viral replication within the liver cell continues. Thus, the presence of IgM anti-HBc indicates recent infection and IgG anti-HBc that of remote infection. Anti-HBc does not appear after HB vaccination. Hence, the presence of both anti-HBs and anti-HBc denotes immunity following infection while anti-HBs alone denotes immunity following vaccination.

The third marker of viral replication and infectivity is HBV-DNA, which appears along with HBsAg, peaks with the onset of symptoms, and then declines. PCR is very sensitive to detect HBV DNA. Monitoring of its serum level helps to assess the progress of patients with chronic hepatitis under antiviral treatment . HBV DNA is usually present along with HBeAg; however, there may be HB mutants that do not secrete HBeAg.

Resolution of HB is characterized by the disappearance of HBsAg and appearance of anti-HBs. However, HBV DNA may still be detected at this stage in both serum and liver by PCR. Rarely, there may be reactivation of resolved HB if the patient becomes immunosuppressed due to prolonged steroid therapy , anti-cancer therapy or following organ transplantation.

Treatment

Treatment for acute HB is mainly supportive and directed to ensuring adequate nutrition and hydration. Patients should be carefully monitored for the development of fulminant hepatitis. It is important to avoid unnecessary drugs especially indigenous ones as many of them are hepatotoxic. Tepid sponging is ideal to control fever. Indications for hospitalization include deep icterus, persistent vomiting, coagulopathy and encephalopathy.

The need for antiviral therapy in acute HB is still not clear. It may be given in sick children with coagulopathy (INR >1.5) or a protracted course (persistent symptoms or serum bilirubin >10 mg/dL for more than four weeks after presentation), and immunocompromised children. Children with associated HC or HD may also need anti-viral treatment. In fulminant HB anti-viral treatment helps to reduce the risk of reinfection following liver transplantation. Drugs like entecavir, tenofovir, lamivudine, adefovir and telbivudine have been tried as monotherapy. Treatment may be discontinued when it is confirmed that the child has cleared HBsAg.

PREVENTION OF HB INFECTION

Universal Immunization

The first country to implement mass vaccination against HBV was Taiwan. In 1992, WHO directed that all countries should integrate hepatitis B vaccination into their national immunization schedule by 1997. As many as 150 countries have already implemented this.

HB vaccine uses recombinant DNA technology to express hepatitis B surface antigen in yeast cells. It is a very effective vaccine as it induces protective antibody levels in more than 95% of infants, children and young adults. Protection lasts at least 20 years and is probably lifelong. Thus, WHO does not recommend booster vaccinations for persons who have completed the 3-dose vaccination schedule.

HB vaccine is adjuvanted with aluminium salts and should be stored at 2–80C. It should not be frozen. If frozen accidentally, it should be discarded.

How HB vaccine induces synthesis of antibodies

- HBsAg in the vaccine is recognized and internalized by antigen-presenting dendritic cells (DC) at the site of injection
- After processing the HBsAg , DCs migrate to the regional lymphoid tissues
- There they interact with clonally selected T and B lymphocytes at immunological synapses
- HBsAg-specific B lymphocytes and plasma cells are produced
- These cells secrete anti-HBs that are detected in the sera.

Vaccination schedule

HBsAg-positive mother

All women should be tested for HBsAg at the first prenatal visit itself.

The baby should be given the following as soon as possible and within 12 hours after birth:

- The first dose of HB vaccine IM
- HBIG 0.5 mL IM- to provide immediate protection against the virus. HBIG does not interfere with antibody response to hepatitis vaccine.

These should be given at different anatomic sites and regardless of birth weight or maternal antiviral therapy for high HB viral loads during pregnancy. These babies may be breastfed immediately after birth.

Subsequent doses are based upon the baby's birth weight:

 Birth weight ≥2 kg – The 2nd and 3rd doses should be given at 1 and 6 months of age, respectively.

 Birth weight < 2 kg – Require 3 additional doses (at 1 month , 2-3 months , and 6 months of age or at 2, 4 , and 6 months of age).

Baby's blood should be tested for HBsAg and anti-HBs at 9 to 12 months of age.

HBsAg-negative mother

- First dose – Within 24 hours of birth
- Second dose – At 1-2 months
- Third dose – At 6 months

Giving the first dose within 24 hours of birth helps to prevent perinatal infection in babies born to HBsAg-positive mothers who are not identified (due to error in testing or failure in reporting of test results) and infants at risk for HBV infection after the perinatal period.

HB vaccines should be given in the anterolateral thigh (in children < 3 years) or deltoid (in children ≥3 years). It should be given only by the IM route; if given by any another route or any other site other than deltoid or anterolateral thigh, it should not be counted as valid and should be repeated.

If HB vaccination schedule has been interrupted for some reason, it need not be restarted.

The remaining doses should be given as early as possible, adhering to the minimum interval of 4 weeks between the first and second doses; 8 weeks between the second and third doses; and 16 weeks between the first and third doses.

Contraindications to HB vaccine include hypersensitivity to yeast or to any vaccine component. Pregnancy is not a contraindication for vaccination.

Box1: Causes of HB Vaccine Failure

Age > 50 years
Gluteal injection of vaccine
Frozen vaccine
Associated HIV infection
Prolonged steroid therapy
Anticancer chemotherapy
HLA B8, DR-3, SCO1
HB mutants
10% of normal people

Adverse Effects of HB vaccine

These are usually mild and consist of fever, headache, myalgia etc. The incidence of anaphylaxis is very low -1 per 1.1 million doses. There was initially a scare of an association between the vaccine and Guillain-Barre syndrome and multiple sclerosis, which has, however, never been proved.

Post-vaccination serology

Immunocompetent children do not require serologic testing to assess antibody response to HB vaccine. However, it should be performed in infants born to:

- Mothers who are HBsAg-positive
- Mothers whose prenatal HBsAg results were not available at the time of delivery but who have other evidence suggestive of HB infection (presence of HBV DNA , positive hepatitis B e antigen, known to have chronic HB)
- Mothers whose HBsAg-status cannot be determined (babies abandoned after delivery)

Both HBsAg and anti-HBs should be done if the baby has received ≥3 doses of HB vaccine, usually at 9 - 12 months of age or 1 to 2 months after the last dose of HB vaccine if immunization is delayed . Serology should not be done before 9 months of age because HBIG may still be present in the baby's blood. Similarly, it should not be done sooner than 4 weeks after the last dose of HB vaccine because of the remote possibility of transient (<21 days) HBsAg-positivity related to the vaccine.

If a baby is found to be HBsAg positive at any time during post-vaccination testing, he should be evaluated for chronic liver disease.

In immunocompromised children (those on long term steroids or anti-cancer therapy etc.) the immune response to HB vaccine is reduced. As they have an ongoing risk of HBV exposure, anti-HBs may be done annually, and if <10 mIU/mL, a booster dose of HB vaccine may be given.

Breastfeeding

The breast milk of an HBsAg carrier mother does not consistently contain HB virus and so breastfeeding does not pose a substantial risk to the baby. However, if the mother has a cracked nipple, it is possible that the baby may be infected. Hence, baby may be breastfed only if he is given HBIG as well as the first dose of HB vaccine at birth. It is important that the baby completes the HB vaccine series.

HBsAg carrier mothers should not be allowed to donate breast milk.

Safe blood transfusion techniques

Blood transfusion was an important route for the transmission of HB prior to HBsAg screening of donor blood. Screening of donor blood for HBsAg was introduced in the 1970s which greatly reduced post-transfusion HB in the world. The risk was further reduced once anti-HBc was also introduced for screening in addition to HBsAg. This risk has now been reduced to 1 in 1 million by the addition of HBV DNA screening also by Mini-Pool Nucleic Acid Testing (MP-NAT) in countries like Singapore, Germany and US. However, this causes an exponential increase in the cost of blood transfusion which cannot be afforded by developing countries.

The immune status of the recipient of blood transfusion is another critical factor in transfusion related HB. Even if the recipient is immune to HB if his anti-HBs titre is low and the viral load of donor blood is very high, he may develop HB. Similarly, blood transfusion recipients on immunosuppressive therapy may also be susceptible to infection with a low viral dose in spite of the presence of anti-HBs.

In addition to the residual donor-related risk, the immune status of the recipient is another critical factor affecting transfusion transmission of HBV [9]. Recent data suggest that the neutralizing capacity of low anti-HBs may be insufficient and can be overcome by exposure to a high viral load.

Immunode□cient elderly patients and patients receiving immunosuppressive treatments may be susceptible to infection with a lower viral dose, even in the presence of anti-HBs.

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Medical personnel

Infected medical personnel can transmit infection to patients and this risk is highest if HBeAg is also positive and the HBV DNA level is more than 1.9 x 105 iu/mL. According to CDC Guidelines, HBV-infected medical personnel may be allowed to conduct exposure-prone procedures if their HB viral load is confirmed to be ≤1000 iu/mL or undetectable (spontaneously or while receiving antiviral therapy) on regular testing performed at least every six months. However, if a percutaneous exposure occurs during the procedure, the uninfected patient should be given post-exposure prophylaxis.

WHO response to HB

The target of WHO is to reduce new HB infections by 90% and to reduce deaths due to HB by 65% by 2030. In July 2020 WHO published additional guidance on "Prevention of mother-to-child transmission of hepatitis B virus: Guidelines on antiviral prophylaxis in pregnancy". In addition to the HB vaccination (including a first dose within 24 hours of birth), WHO now recommends that all HBsAg positive pregnant women with an HBV DNA equal to or greater 200,000 IU/ml should receive tenofovir prophylaxis from the 28th week of pregnancy until at least birth. If antenatal HBV DNA testing is not possible due to financial constraints, HBeAg testing may be done as an alternative to determine eligibility for tenofovir prophylaxis.

Testing for HB and treatment of eligible pregnant women can be integrated with the prevention of mother-to-child transmission of HIV and congenital syphilis with antenatal care service. This approach is often referred to as 'Triple elimination' – an initiative that promotes the elimination of mother-to-child transmission of three serious infections: HIV, HB and syphilis.

Since 2011, WHO has organized annual World Hepatitis Day campaigns to increase awareness and understanding of viral hepatitis. The date

of 28 July was chosen because it is the birthday of Nobel-prize winning scientist Dr Baruch Blumberg, who discovered HBsAg.

Key facts

- HB causes both acute and chronic liver disease in children and is an important cause of cirrhosis and hepatocellular carcinoma in the world
- India belongs to the intermediate zone of prevalence (2-7%)
- The most important routes of transmission of HB in children are vertical and horizontal
- Caesarean section does not prevent neonatal infection
- Hepatitis B can be prevented by vaccines that are safe, freely available, reasonably cheap and effective.
- July 28 is observed as the World Hepatitis Day

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Hepatitis C in Children

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INTRODUCTION

HCV viral infection is prevalent globally . While in the majority of children, HCV infection remains asymptomatic, it has the potential to progress to chronic hepatitis, cirrhosis and hepatocellular carcinoma.[1]

EPIDEMIOLOGY

The global prevalence of HCV is estimated at 2.5% with a viremic rate of 67% whereas in India it ranges from 1 to 1.9%.[2] In Punjab and Northeast India, a high anti-HCV positive rate due to the reuse of needles and syringes had been reported.[3]

Historically considered a transfusion-related disease in children, modern blood-bank screening practices have nearly eliminated the risk of transfusion-transmitted HCV infection. Currently, mother-to-child transmission (MTCT) during perinatal period is regarded as the most common mode of infection in children[4]. Outside of the perinatal period, intravenous drug use (IVDU) is a significant and common cause of HCV infection in adolescents and young adults, with a reported 364% increase in IVDU among this age group over the last decade [5]

VIRAL CHARACTERISTICS

Hepatitis C virus belonging to Flavi viridae family , is a 55 nm lipid enveloped RNA virus The two biomarkers of HCV, viz. anti-HCV antibody and HCV RNA, are helpful in establishing the diagnosis. There are six genotypes of HCV which may predict the response to therapy. In India, the principal genotypes are genotype 3 followed by genotype 1. In the hepatocyte, HCV remains as an intra cytoplasmic virus and does not integrate into host nucleus like HBV.

TRANSMISSION OF HCV

HCV spread by either vertical or horizontal route through blood, blood products and body fluids.

Mother–infant transmission of HCV occurs during pregnancy and delivery, with 31% of transmissions occurring in utero and 50% to 79% during the peripartum period. Risk multiplies with concomitant HIV infection, high maternal HCV viral load, and extended exposure to maternal blood (fetal pH monitoring, prolonged rupture of membranes, etc.).

Those children requiring repeated blood transfusions and adolescent IV drug abusers are also prone to HCV infection.

NATURAL HISTORY OF HCV INFECTION

HCV infection is detected incidentally in more than 90% of individuals who are asymptomatic.

Progression of chronic hepatitis C in children and adolescents may follow several different routes.[6]

- Spontaneous resolution of viremia (viral clearance)[7] in 25% to 40% of children with mother to child transmission , usually by age 2 and 6–12% up to 7 years of age. Spontaneous

viral clearance is considered a permanent state, essentially a "cure" of the HCV infection, with rare (<1%) relapses reported .

- Majority of children (80%) with chronic hepatitis C (CHC) do not undergo spontaneous resolution, but remain asymptomatic; 14% may present with chronic hepatitis, and 1–2% may progress to cirrhosis.[8]

CLINICAL SPECTRUM OF HCV INFECTION

The spectrum is akin to HBV infection. Progression to chronic liver disease takes more than two decades, problems do not manifest in the pediatric age group. However, as there is a 26-fold increase in the risk of liver-related death associated with CHC acquired in childhood, it is necessary to treat a subset of children.

Acute Hepatitis C (AHC)

Not common in children, may occur in adolescents using IV drugs with infected needles or following HCV infected blood transfusion.

Diagnosis: Anti-HCV positive and HCV RNA positive.

Treatment : Since spontaneous resolution is high, treatment only for those who continue to be HCV RNA positive 12 weeks after the exposure.

Chronic Hepatitis C (CHC)

The persistence of detectable serum HCV RNA >6 months with ongoing liver injury, the child is said to have chronic hepatitis C [9] (Isolated anti-HCV positivity is not significant)

Mild symptoms, such as fatigue and abdominal pain, hepatomegaly on examination . Extrahepatic manifestations very rare. All children more than 3 years of age with chronic hepatitis C should be treated. Obesity, congenital anemia requiring frequent blood transfusions, survivors of childhood cancer, HIV or HBV coinfection, and high-risk behaviours in adolescents such as IV drug usage and alcohol abuse increase the severity of CHC.

Diagnosis : HCV RNA positive, elevated serum transaminases.

Histologically, hepatocellular inflammation is mild, but severe inflammation is described in 3%, moderate fibrosis in 4%, and bridging fibrosis or cirrhosis in 2% to 12%.

DIAGNOSIS AND MANAGEMENT OF HCV INFECTION

History and Examination

- Presence and duration of jaundice.
- Pointers of CLD -oedema, altered sensorium, loss of weight or appetite, GI bleed,oliguria.
- Risk factors such as blood transfusions, IV drug abuse,surgery, needle pricks, tattoos, liver disease in the family and HCC to be asked for.
- A thorough clinical examination -for presence of icterus, clubbing, edema, nutritional status, palmar erythema, liver size and consistency, splenomegaly, free fluid and the presence of abdominal veins
- Other systemic examinations
- Extrahepatic manifestations such as arthralgia/arthritis, vasculitis, polyarteritis nodosa, thrombocytopenia, urticaria, and glomerulonephritis to be noted.

Investigations

- Complete blood count, LFT, prothrombin time, INR, serum creatinine, and blood sugar .
- Viral Serology- anti-HCV antibody estimation , HCV RNA, and genotype.
- Imaging- Ultrasound of abdomen when chronic HCV infection is suspected.
- Upper GI endoscopy – when chronic HCV infection suspected.

- Histopathology- in CHC, antiviral therapy can be started even without liver biopsy.
- FibroScan- Transient elastography is a good non invasive test to detect and grade liver fibrosis. It is painless, quick, highly reproducible, and easy to perform bedside and may replace liver biopsy in select situations.[10]

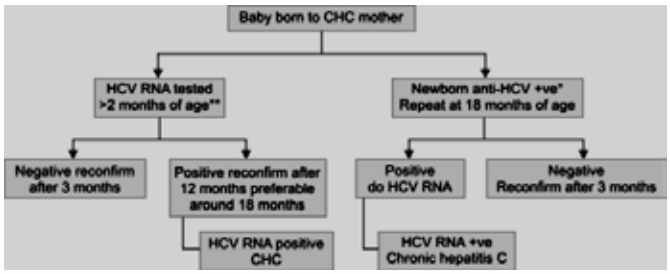
SCREENING, DIAGNOSIS, AND MONITORING IN CHILDREN

Children suspected of having an HCV exposure, including those born to HCV-positive mothers, should be screened for infection. The risk of HCV transmission to the neonate mainly depends on the maternal viral load and HIV positivity.

Since HCV antibody passively crosses the placenta persists in the infant till 18 months of age, this test should not be used as a screening test in the newborn or indiscriminately in infancy. HCV antibody should ideally be done after 18 months of age and, if positive, confirmed by HCV RNA.

An earlier diagnosis of HCV perinatal transmission may be required either because of parental anxiety or chances of being lost to follow up, a single test of HCV RNA may be done at the age of 2 months. Irrespective of whether the test result is negative or positive, HCV RNA should be repeated after the age of 1 year, preferably around 18 months to diagnose chronic hepatitis C.

Algorithm for testing HCV in newborns born to chronic hepatitis C mothers[1]



Infected children who are not receiving antiviral therapy should be evaluated annually for clinical and biochemical evidence of liver disease progression. With LFT, complete blood counts, HCV RNA levels and if cirrhosis is present , PT, INR. Annual abdominal ultrasound and semi annual alpha-fetoprotein (AFP) measurements to be done if a family history of early cirrhosis, HCC, or evidence of rapid disease progression.

Liver biopsy may be indicated in rare instances where the results may influence medical decision-making but is increasingly deferred and often unnecessary in the era of antiviral therapy.

THERAPY OF HCV INFECTION

Drugs approved for HCV infection, PEGylated IFN and ribavirin, have several side effects, variable response to therapy and require frequent monitoring.

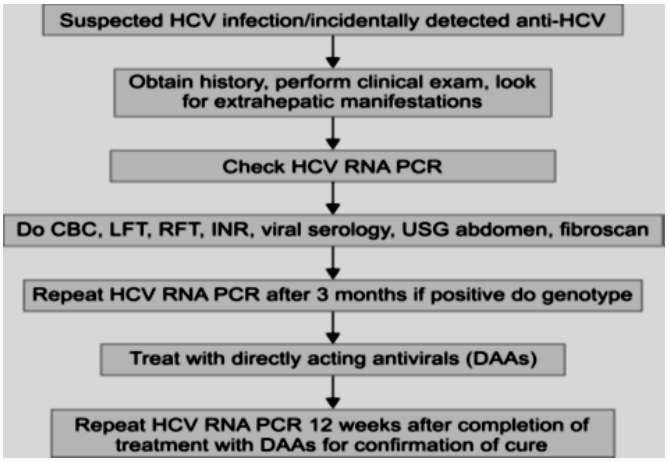
The currently available direct-acting antivirals (DAAs) have high efficacy and are well tolerated with a short duration of treatment. DAAs target specific non-structural proteins of HCV and act by disrupting viral replication and infection. They target the NS3/NS4A proteases, the NS5A proteins, and the NS5B RNA-dependent RNA polymerases.[12] A well-established and well-studied fixed drug combination is sofosbuvir (polymerase inhibitor) and ledipasvir (N5SA inhibitor)[11]

The doses for these fixed drug combinations in children are weight dependent and are as below:

- Weight less than 17 kg = 33.75 mg of sofosbuvir (S) and 150 mg ledipasvir (L).
- Weight between 17–35 kg = 45 mg of S and 200 mg of L.
- Weight more than 35 kg = 90 mg of S and 400 mg of L.
- The combination of sofosbuvir and ledipasvir has been approved for genotypes 1 and 4 for 12 weeks in treatment-naive patients and 24 weeks in treatment-experienced and cirrhosis patients.

- The end point of therapy is undetectable HCV RNA in blood by 12 weeks or 24 weeks.
- The combination therapy has shown >95% sustained viral response at 12 weeks (SVR 12) after the end of DAAs treatment
- Those with GT 2 and GT 3 should receive sofosbuvir and ribavirin.

. The algorithmic approach to HCV[1]



- Though several other pangenotypic DAAs such as velpatasvir and glecaprevir have been introduced for adults, they are not as yet approved for children.
- The goal of therapy in children is to cure HCV infection, thus preventing the possible progression to complications.
- Liver transplant is the definitive treatment for those with acute liver failure and decompensated chronic liver disease not responding to antivirals.

PREVENTION OF HCV INFECTION

As the virus spreads parenterally, screening of blood, avoiding unnecessary needle pricks, tattooing and sharing needles among intravenous drug users will decrease the spread of infection. The vaccines for hepatitis C virus are also in the pipeline. All children with liver disease should receive vaccines against hepatitis A and B.

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Hepatitis E

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Hepatitis E virus was first discovered in India. Two large epidemics of Hepatitis occurred in India- one in New Delhi in 1955-56, and the other in the Kashmir Valley in 1978-79, for which no etiology could be ascertained. They were initially labelled as Non- A and Non- B virus. On later retrospectively analyses of the preserved sera, these outbreaks were found to be due to Hepatitis E. The Global Burden of Disease Study 2017 has estimated that approximately 19.5 million cases of Acute Hepatitis E occur worldwide. In India the disease is endemic in the Northern and North eastern parts of the country.

Hepatitis E virus is a small (27-34nm diameter) particle with an icosahedral protein capsid enclosing a 7.2 kilobase long single stranded positive sense RNA genome. This genome has three open reading frames - ORF1, ORF2, and ORF 3. Each of these have a distinct function. ORF1 encodes for non-structural protein. ORF 2 is the most important one, as it encodes the capsid protein which carries neutralizing epitopes inducing antibody production in the host. This is the most important target for vaccine development. ORF 3 encodes for a protein involved in viral secretion. The Hepatitis E virus exists in 2 forms -i) naked virus particles in stools and ii) enveloped virions in blood circulation. The enveloped form helps the virus to escape destruction by antibodies.

The virus is divided into two genera: Orthohepevirus- which has almost all the mammalian HEV variants and Piscihepevirus which consists of only one species. Orthohepevirus A is divided into seven genotypes named GT 1 to 7 of which the first 4 are the most common. Genotypes 1 & 2 are seen only in humans while the rest occur in animals as well. Two types of epidemiological patterns are seen – one involving Genotypes GT1 and 2 and the other involving Genotypes 3 and 4. The differences between the two patterns are given in Table 1.

Clinical Features

The incubation period is 2-5 weeks.

Asymptomatic

Majority of the infected patients, irrespective of the genotype are asymptomatic or develop anicteric hepatitis.

Acute Hepatitis

Only < 20% develop Acute Icteric Hepatitis which follows the same pattern as all viral hepatitis – Prodromal Phase, Icteric Phase, cholestatic phase and recovery phase. The laboratory findings are also similar to other hepatitis with transaminitis followed by cholestatic phase and then recovery. In an occasional patient, the cholestatic phase can be prolonged, but this is usually self- limiting. Generally, recovery occurs within few weeks to months. However about 0.5-4% cases can progress to Acute Liver Failure which can lead to high mortality in the absence of a liver transplant. This is more commonly seen with Genotypes 1 and 2. During these periods of outbreaks- for reasons unknown- pregnant women, especially

Table 1: Difference between the two epidemiological patterns

	Genotype 1 & 2	Genotype 3 & 4
Endemicity	Low	High
Countries	Central America, Africa, South and Central Asia	North America, Europe, Australia, Japan, East Asia, South Africa
Reservoir	Humans	Animals
Transmission	Contaminated water sources	Animal contact, Blood transfusion
Occurrence	Frequent Outbreaks	Sporadic cases
Seasonal patterns	Yes	No
Age group	15-40 yrs (Children & elderly less affected)	Elderly
Clinical presentation	Acute Hepatitis, ALF	Acute Hepatitis , Chronic Hepatitis
Severity of Hepatitis	Mild to severe	Mild to moderate
Mortality & Morbidity	High	Intermediate
Pregnant Women & Fetal outcome	Higher risk of severe illness Increase risk of poor fetal outcome	No excessive risk
Non- Hepatic clinical manifestations	Generally uncommon except for pancreatitis	Neurological manifestations reported- Guillian-Barre syndrome etc.
Persistent infection	Not reported	Occurs in immunosuppressed persons
Specific Treatment	None	Ribavarin or pegylated interferon in case of chronic infection
Prevention	Safe drinking water, good sanitation, Good hygiene	Avoid contact with animals, Proper cooking of meat, Screening of donated blood

those in the second and third trimesters are susceptible to an increased risk of more severe infection, Acute Liver Failure and even death. The risk of mortality is 15-40% compared to 1% in the general population. Vertical transmission to the fetus can also occur resulting in hepatitis (icteric/ non-icteric), hypoglycemia and even neonatal death.

In developed countries, the virus occurs as a zoonotic disease and predominantly spreads due to close contacts with animals and consumption of undercooked meat. Hence, the occurrence of cases is sporadic. It affects extremes of age – infants and elderly, immunocompromised individuals, organ transplant recipients etc. The course of the disease is indistinguishable from any other hepatitis. However, in these immunocompromised patients there is a higher chance of chronic hepatitis.

Extra- hepatic manifestations: Involvement of other organs has been reported (Table 2) especially in low endemic areas probably reflecting better investigative facilities.

Table 2 : Extra hepatic manifestations*

Central Nervous system	• Acute transverse myelitis • Acute meningoencephalitis • Aseptic meningitis • Neuralgic amyotrophy • Pseudotumor cerebri • Bilateral pyramidal syndrome
Perpheral Nervous System	• Guillain-Barre´ syndrome • Cranial nerve palsies • Peripheral neuropathy
Kidney	• Membranous glomerulonephritis • Membranoproliferative glomerulonephritis • IgA nephropathy • Nephroangiosclerosis • Reduced glomerular filtration rate • Cryoglobulinemia
Pancreas	• Acute pancreatitis
Gall Bladder	• Cholecystitis
Hematological	• Thrombocytopenia • Hemolysis • Aplastic anemia • Pure red cell aplasia • Hemophagocytic syndrome
Heart	• Myocarditis
Miscellaneous	• Henoch-Schönlein purpura • Skin rash • Arthralgia • Thyroiditis • Myasthenia gravis • Monoclonal gammopathy of uncertain significance

**Table courtesy article:" Hepatitis E-Epidemiology Clinical course, Prevention and Treatment"- Amit Goel & Rakesh Aggarwal. Gastroenterl Clin N am 49(2020) 315-330.*

Chronic hepatitis E

Hepatitis E is generally known to be a self-limiting disease. However in immunosuppressed patients (like transplant recepients) it can become chronic. This is defined as presence of HEV RNA in stools of an infected person for more than six months and is usually seen with Genotypes 3 &4 in immunocompromised individuals. They can have features of persistent jaundice, subacute hepatic failure, fatigue, diarrhea, arthralgia, itching, nausea, abdominal pain and weight loss. They may also have persistent transaminitis which can lead to cirrhosis in 10% of cases. In liver transplant patients it can lead to graft failure necessitating a retransplant.

In patients with chronic liver disease superadded infection with Hepatitis E can lead to Acute on chronic liver failure especially with genotypes 1 and 4.

Diagnosis

Diagnosis is made by the detection of viral RNA in the serum or faeces of the patient or by checking the specific antibodies to ORF2. Anti HEV Ig M positivity indicates ongoing infection while presence of Anti HEV IgG indicates a past infection. On occasion both Ig M and Ig G may be positive which indicates an acute or recovering infection. According to EASL guidelines, in immunocompetent patients, it is recommended to check both Anti- HEV antibody and HEV-RNA . If both are positive the patent has Hepatitis E. In Immunocompromised patients HEV RNA is mandatory and antibody testing is optional.

Since most of the infections are asymptomatic, seroprevalence is a good way to determine the prevalence of the disease. The overall seroprevalence in resource poor countries is 70%. In children the seroprevalence rates are low but increase with age.

Treatment

Acute Hepatitis

Generally, in immunocompetent patients the condition is self-limiting and hence the treatment is supportive and symptomatic. Antipyretic and analgesics can be given as required. A small percentage of the patients can deteriorate and develop Acute Liver failure and hence they need to be carefully monitored. Patients who do develop Liver failure need to undergo Liver transplantation. In such patients the outcome is generally good.

Chronic Hepatitis

Patients on immunosuppressive medication such as solid organ transplant recipients, HIV patients, etc. have a higher risk of developing chronic hepatitis after an infection. Hence, in this group of patients the immunosuppressive medication needs to be reduced or stopped if possible, as this helps in viral clearance in 1/3rd of the cases. If this fails, it is advocated to give ribavirin monotherapy for six months which can lead to viral clearance in 2/3rd of the cases. Pegylated interferon alfa has been tried in a few studies when ribavirin was unsuccessful especially in liver transplant recipients. However, this may not suitable in other solid organ transplant patients (kidney, pancreas & small bowel), as it can lead to rejection. Other drugs that have been tested in vitro are sofosbuvir, mTOR inhibitors and calcineurin inhibitors but the results are not consistent.

Prevention

Since Hepatitis E is essentially spread by feco-oral route, it can be prevented by improving hygiene and providing clean drinking water. Complete virus particles are susceptible to high temperatures and become inactivated within 5 minutes of temperatures above 90 degrees C. This virus is also spread by consumption of undercooked pork or wild boar. To completely inactivate the virus in contaminated food, a temperature of 71 degrees C for 20 minutes is necessary. Other measures that need to be adopted are – screening of blood before transfusion and careful handling of pets.

Hepatitis E Vaccine

The only approved vaccine for Hepatitis E is HEV 239 (Hecolin) is a recombinant vaccine developed in China which contains 30 mcg of the purified antigen. It has been in use in China since 2011 but has not been approved for use in other countries. HEV has only one identified serotype which offers cross protection against all four HEV genotypes and hence the efficacy of the vaccine was said to be around 90% in immunocompetent patients. The vaccination schedule is 3 doses of vaccine at 0,1and 6 months, administered Intramuscularly. It is safe in pregnant women.

Passive Immunoprophylaxis

Passive immunoglobulin does not prevent the infection but mitigates the symptoms of hepatitis

Suggested Reading

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Laboratory Diagnosis of Viral Hepatitis

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Viral hepatitis is a major health care challenge worldwide. It has received recent attention because of the increased burden of the disease. It is defined as the inflammation caused by hepatotropic viruses, namely Hepatitis Virus A-E. Other causes of viral hepatitis include Adenovirus, Cytomegalovirus (CMV), Epstein-Barr virus (EBV), Herpes simplex virus (HSV), Yellow fever Virus (YFV). Majority of them cause acute self-limiting illness although some have the potential to become chronic. Chronic hepatitis can lead to severe complications like cirrhosis and hepatocellular carcinoma. According to WHO, 325 million people or 4% of world's population live with viral hepatitis and the disease cause 1.34 million deaths per year. Hepatitis B and C are responsible for 96% of mortality due to hepatitis. All hepatotropic viruses are RNA viruses except Hepatitis B which has partially double stranded DNA virus. The main mode of transmission of hepatitis A and E is via faeco-oral route, while hepatitis B, C, D are primarily blood borne. Other modes of transmission like sexual , vertical , blood transfusion and intravenous drug use are also common. The patient presents with fever, anorexia, malaise, nausea, vomiting, right upper quadrant fullness or pain, jaundice, dark urine and pale stool. Some times in acute illness the patient may be asymptomatic. Chronic disease can lead to fulminant liver failure.

Indian scenario

Viral hepatitis, mainly caused by hepatitis viruses A through E, still remains a major public health problem in India. India has "intermediate to high endemicity" for Hepatitis B infection . Hepatitis B surface Antigen (HBsAg) positivity ranges from 1.1% to 12.2%, with an average prevalence of 3-4% in general population. Anti-Hepatitis C virus (HCV) antibody prevalence in the general population is estimated to be between 0.09-15% In a recent study conducted in Northern part of India, 5.2% prevalence of HCV infection was noted. In India , HAV is accounts for 10-30% of acute hepatitis and 5-15% of acute liver failure cases HEV is responsible for 10-40% of acute hepatitis and 15-45% of acute liver failure in India.

Laboratory testing

Whole blood /serum (3-5ml) or water and sewage samples for RT-PCR (if outbreaks of Hep B or E is suspected) are usually collected for detection of hepatitis infection. It is important to avoid haemolysis of samples as it may interfere with the ability of test to accurately detect the markers. The serum should be removed from clotted blood within 4 hours of collection and stored at 4-8°C for 7 days or at -20°C to -70°C for longer durations so as to avoid degradation of the viral nucleic acid.

Diagnostic approaches

HEPATITIS A

Hepatitis A IgM is generally detectable 5-10 days before onset of symptoms and can persist for up to 6 months. Therefore, the presence of Hepatitis A IgM indicates acute infection. Hepatitis A IgG becomes the predominant antibody during convalescence and remains detectable indefinitely, hence the patients with serum anti-HAV total (IgG and IgM) or specific IgG (but negative for anti-HAV IgM) denotes immunity to the infection either due to infection or vaccination.

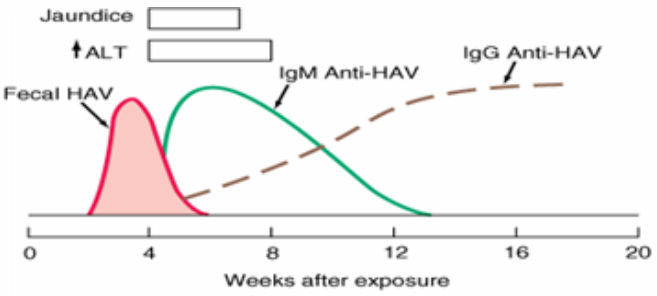


Fig :1 Serological markers of Hepatitis A

Detection of HAV-Specific Antibodies

IgM anti-HAV - It is the primary marker of acute infection comprised mainly of antibodies against capsid proteins. The various methods of detection include radioimmunoassay, immunochemical staining, enzyme-linked immunosorbent assay, immunoblotting and dot blot immunogold filtration. The current commercially available IgM assays can detect antibody for a short period of time in persons who were recently administered hepatitis A vaccine.

Total anti-HAV (both IgG and IgM antibodies) - Presence of total anti-HAV and the absence of IgM anti-HAV can be used to differentiate between past and current infections.

Molecular methods for detection are PCR, DNA sequencing, and sequence analysis. Amplification of viral RNA by RT-PCR is currently the most sensitive and widely used method for detection of HAV RNA. Nucleic sequencing should be performed on VP1-P2B genomic region.

Immune-electron microscopy (IEM)

It is done for the detection of virus or viral components in faecal samples during the late incubation period and the pre-icteric phase but is not used routinely.

Cell culture propagation- Cell culture propagation can be done in primary and secondary African green monkey kidney cells and foetal rhesus monkey kidney cells. HAV replicates in cell culture without cytopathic signs of infection and without apparent host cell damage hence immunological assays are required to detect HAV antigen.

HEPATITIS B

The definitive diagnosis of Hepatitis B depends on the serological demonstration of viral markers.

The various serological markers for diagnosis of Hepatitis B are

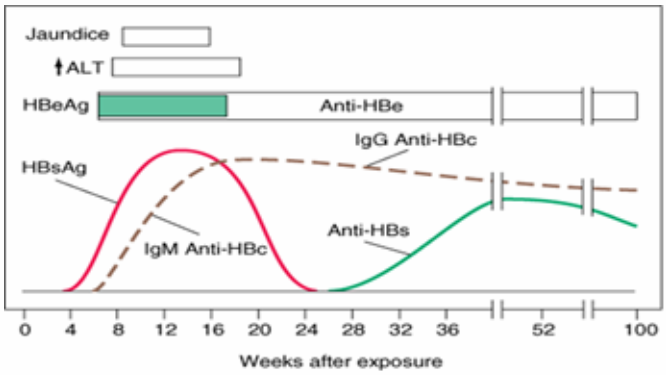


Fig 2:
Serological markers in the various stages of Hep B

1) HBsAg (Hepatitis B surface Antigen)
2) Anti-HBs (Hepatitis B surface Antibody)
3) Anti-HBc (Hepatitis B core Antibody)
4) HBeAg (Hepatitis B precore Antigen)
5) Anti-HBe. (Hepatitis B precure Antibody)
6) HBV DNA

HBsAg is the first serological marker to appear after infection The antigen is detectable even before the elevation of liver enzymes and the onset of clinical illness. Normally it disappears after 2 months of onset of jaundice. The positive test implies that the patient is infectious.

Anti-HBs antibody appears when HBsAg is no longer detectable and is a protective antibody. It indicates immunity to HBV either through past infection or through vaccination. The protective level of anti-HBs antibodies is ≥ 10 mIU/ml.

Anti-HBc IgM is the earliest antibody marker following infection and appears in the serum a week or two after the appearance of HBsAg. The IgM anti-HBc is seen in acute infections but after six months is replaced by IgG. The anti-HBc IgG antibody persists for life and is therefore a useful indicator of prior infection with HBV. IgG anti-HBc is a reliable marker for previous HBV infection as it even persists when anti-HBs titres decline to undetectable levels many years following recovery from HBV infection.

HBeAg appears in the blood concurrently with HBsAg, or soon afterwards and generally disappears within several weeks in acute, resolving cases. It is an indicator of active intrahepatic viral replication therefore if detected implies that the person is highly infectious. Presence of this antigen is also used as a parameter for selection of patients for treatment. It disappears and is followed by the appearance of anti-HBe. However, HBeAg absence does not preclude active viral replication.

Anti-HBe in blood denotes low infectivity. It has prognostic implication as appearance of anti-HBe in acute hepatitis B implies a high likelihood that HBV infection will resolve spontaneously.

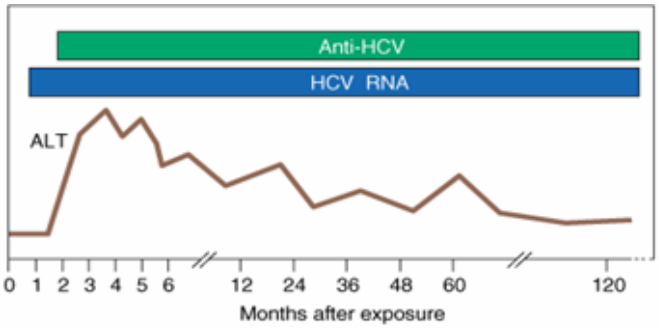
HBV DNA (Quantitative): Hepatitis B DNA can be detected by PCR. It is also an indicator of viral replication and infectivity. It is also used for monitoring therapy to assess response to treatment (every 3 months for years when the patient is on oral agents and every 1 month for 6-12 months if the patient is on PEG/IFN). It may also be used to diagnose occult HBV infection.

Genotyping and Resistance Testing: is indicated for detection of mutations that confer resistance to antiviral agents and for epidemiological purpose in case of outbreak investigation. It has categorized patient isolates into 8 different HBV genotypes (A to H). The methods used for genotyping are sequencing and hybridization techniques.

Interpretation of Serologic Tests in Hepatitis B

HBsAg	Anti-HBs	Anti-HBc	HBeAg	Anti-HBe	DNA	Liver enzymes	Interpretation
+	-	-	-	-	+	Normal	Early Acute infection
+	-	+ IgM	+	-	+	Elevated	Acute hepatitis, high infectivity
+	-	+ IgG	+	-	+	Elevated	Chronic hepatitis, high infectivity
+	-	+ IgG	-	+	+	Elevated	Chronic hepatitis, low infectivity
+	-	+ IgG	+	-	+	Normal	Immunotolerant chronic HBV infection (super carriers)
+	-	-	-	+/-	+	Normal	Chronic inactive HBV infection (simple carriers)
-	+	IgG	-	+/-	-	Normal	Recovery
-	+	-	-	-	-	Normal	Post vaccination
-	-	IgG (+/-)	-	-	+	Normal	Occult hepatitis B infection

HEPATITIS C



Anti-HCV antibody detection is the usually employed test for screening of Hepatitis C infection. The standard method of diagnosis is antibody detection by Chemiluminescence immunoassay (CLIA) or ELISA. Currently the fourth-generation immunoassay, which incorporates proteins from the core, NS3, and NS5 regions, detect anti-HCV antibodies during acute infection with increased sensitivity and specificity. The antibodies are detected in 6-8 weeks of infection i.e., during the initial phase of elevated aminotransferases activity. Children should not be tested for anti-HCV antibodies before 12 months of age as anti-HCV from the mother may last until this age. The diagnosis depends on determination of ALT levels and presence of HCV RNA in baby's blood after 2nd month of life.

Recombinant Immuno Blot Assay (RIBA) was used earlier as a supplemental assay for testing samples that are reactive for anti-HCV by ELISA or CLIA to aid in distinguishing specific from non-specific reactivity i.e., to help resolve false-positive results.

Now anti-HCV Signal-to-Cut-off Ratio (S/CO) is used as a supplemental test. RIBA is no longer considered necessary confirming reactive anti-HCV results. Confirmation of indeterminate anti-HCV results is by detection of HCV RNA, or by determination of anti-HCV Signal-to-Cut-off Ratio (S/CO) according to CDC guidelines. Tests are not yet available to distinguish acute from chronic HCV infections as anti- HCV IgM is present in high percentage in both acute and chronic HCV infected patients.

HCV Core antigen (ARCHITECT i2000SR) can be detected in blood long before the appearance of antibody and is highly conserved among all genotypes and quasispecies. It is a cost effective, sensitive and specific assay that is easy to perform and can reduce the serological window period by an average of 35.8 days. HCV Ag is a marker of HCV replication and used as an alternative to RNA for detection and diagnosis. The diagnostic sensitivity, specificity, and positive and negative predictive values of the HCV core antigen assay compared to the HCV RNA test were 77.35%, 100%, 100%, and 89.38%, respectively.4 HCV core antigen levels showed a good correlation with those from HCV RNA quantification (r =0.872). 4 However, samples with a viral load of less than 4000 IU/mL were negative in the HCV core antigen assay. 4 Therefore a negative HCV core antigen test should be confirmed using HCV RNA PCR. It is used to diagnose infection in the early window period, active infection, to assess chronic infection and to monitor treatment response. HCV Ag testing is recommended by 2017 WHO Global Hepatitis report and 2018 European Association for the study of Liver (EASL) as an alternative option.

HCV-RNA is the most sensitive indicator of HCV infection as it determines the viral load. It is detected by PCR or transcription mediated amplification (TMA). It can be used for treatment monitoring and in some circumstances for confirmation of positive or indeterminate serology. HCV RNA is detectable in 2 to 14 days after an exposure i.e., even before acute elevation of aminotransferases activity and before the appearance of anti-HCV. HCV-RNA remains detectable indefinitely in patients with chronic hepatitis C. HCV RNA is reported as international units (IUs) per millilitre or as copies/ml. Quantitative HCV RNA can be used for treatment monitoring also.

HCV genotyping has important implications such as determining the duration of anti-viral treatment especially if interferon-based regimens are considered. Genotyping has categorized HCV into 11 genotypes with 24 subtypes.

INTERPRETATION OF HCV RNA TEST (CDC GUIDELINES)

TEST OUTCOME	INTERPRETATION	FURTHER ACTIONS
HCV antibody nonreactive	No HCV antibody detected	Sample can be reported as nonreactive for HCV antibody. No further action required. If recent exposure in person tested is suspected, test for HCV RNA.
HCV antibody reactive	Presumptive HCV infection	A repeatedly reactive result is consistent with current HCV infection, or past HCV infection that has resolved, or biologic false positivity for HCV antibody. Test for HCV RNA to identify current infection.
HCV antibody reactive, HCV RNA detected	Current HCV infection	Provide person tested with appropriate counselling and link person tested to care and treatment.
HCV antibody reactive, HCV RNA not detected	No current HCV infection	No further action required in most cases. If distinction between true positivity and biologic false positivity for HCV antibody is desired, and if sample is repeatedly reactive in the initial test, test with another HCV antibody assay. In certain situations, follow up with HCV RNA testing and appropriate counselling.

HEPATITIS D

The diagnosis of HDV infection based on detection of antibody to HDV antigen (anti-HDV) by EIA or RIA. The appearance of anti-HDV is variable and persist only for a short time after the resolution of acute hepatitis D leaving no marker of previous infection. The detection of IgM anti-HDV does not distinguish acute from chronic HDV infection as IgM anti-HDV also persists in chronic infection and high titres are often found in patients with severe liver inflammation.

In co-infection, IgM against HDAg and HBc Ag are elevated. In superinfection, HBV infection is already established and IgG anti-HBc and IgM anti-HDV would be detected initially but as the patient progress to chronic state both IgM and IgG would persist for months or longer.

HEPATITIS E

The incubation period of hepatitis E is 21-60 days. Both anti-HEV IgM and anti-HEV IgG are available for diagnosis of Hepatitis E. It can be detected, but both fall rapidly after acute infection, reaching low levels within 9-12 months. HEV can also be demonstrated by immunoelectron microscopy (IEM) in the faeces of patients in the incubation period or acute phase of illness.

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Non Hepatotropic viruses affecting the Hepatobiliary system - a comprehensive review

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Introduction

Hepatitis or inflammation of the liver results from various etiologies:

Infections: viral, bacterial, fungal, and parasitic agents.

Others: autoimmune hepatitis, metabolic diseases, ischemic injury drug induced liver injury.

It is more commonly caused by Hepatotropic viruses A,B,C,D,E. But there are other viral agents that can affect the liver as part of systemic involvement and they are commonly called as Non hepatotropic viruses. Clinical manifestations include hepatitis, cholestatic disease and even acute liver failure. There are a number of cases of acute liver failure of unknown etiology where the patient deteriorates rapidly with standard management. Clinical Metagenomic next generation sequence (mNGS) testing shows promising results and most likely will be included in the workup of hepatitis to identify these lesser-known viruses.

Objective: To give the reader a compilation of information on hepatotropic viruses and its effect on the liver and the biliary system and how it is important to identify the virus especially in today's era of organ transplantation and immunosuppression.

Methods: A PubMed and UpToDate search with keywords of non- hepatotropic viruses, hepatitis, CMV, Epstein Barr viruses, COVID 19. References also taken from the textbook of Diseases of the liver and biliary system in children by Deidre Kelly,4th Edition and other references mentioned at the end of the article.

Herpes viruses

The herpesviruses are a family of icosahedral double- stranded DNA viruses. We will be discussing 8 of the viruses which causes infections in humans. They persist in the host after primary infection either in the neurons or T, B lymphocytes and mononuclear cells and this latent virus reactivates when the host is immunosuppressed (1)(2).

Herpes simplex virus 1and 2(HSV1&2)

(HSV) viremia: involves the esophagus, lungs, and liver. HSV hepatitis occurs primarily in neonates, pregnant patients, and immunocompromised patients, rarely in immunocompetent adults. (3), (4) as a part of the systemic infection or during reactivation. In children, severe PEM and post measles state predispose the child to disseminated HSV infection (5). Oral ulcers and skin lesions may or may not be present.

Liver biopsy: "patchy, nonzonal coagulative necrosis with minimal to absent inflammatory response. Fatty change can be present (5). Two

types of intranuclear inclusions Cowdry Type A and Type B can be found in hepatocytes at the edge of the necrotic foci. (3), (4).

Diagnosis is confirmed by the detection of HSV DNA sequences by PCR, which is more sensitive. HSV hepatitis is one of "the infectious disease emergencies" associated with worsening course if not treated early. Early institution of antiviral therapy (IV Acyclovir) improves outcome (6).

Varicella Zoster Virus (VZV)

Disseminated infection with vesicular rash is very rare in children but can cause encephalitis, pneumonitis, myocarditis, and hepatitis, especially in the immunocompromised patients, neonates, and adults (5). Rash with hepatitis which can progress to severe fulminant hepatic failure especially in transplant patients and immunocompromised patients. The transaminitis is in several thousands. In children, chicken pox may be followed by Reye's syndrome characterized with vomiting transaminitis, diffuse steatosis, hepatic encephalopathy with aspirin usage. Primary varicella infection in organ transplantation can be of rapid onset and mostly fatal. Visceral involvement, cane be immediate or delayed after many months post transplantation (7,8).

Liver biopsy resembles HSV. Immunohistochemistry is done to confirm the presence of a herpes virus but PCR is necessary to distinguish the two viruses. (2) VZV IgG is a useful marker for the determination of susceptibility to VZV. (1) Hospitals should follow CDC guidelines in case of nosocomial infection to prevent transmission of VZV infection (9). Therapy: High dose acyclovir (30 mg/kg body weight I.V. daily in 3 divided doses for 7-10 days) or liver transplantation in fulminant cases with organ failure (10, 11).

Cytomegalovirus (CMV)

Congenital cytomegalovirus (CMV) infection presents as neonatal hepatitis or neonatal cholestasis, but due to poor IgM production in neonates and maternal transfer of antibodies serology can be inconclusive (12).

Several studies have found the presence of CMV DNA in the serum and liver tissue of neonates with liver dysfunction or cholestasis (12,13).

Liver biopsy: resembles extrahepatic biliary atresia (EHBA), with portal expansion, bile ductular proliferation, and bile stasis. Post mortem biopsies had shown hepatocyte necrosis, lobular disarray with pseudo rosettes, giant cell transformation with ductular metaplasia of hepatocytes. Cytomegalic inclusion bodies or owl's eyes is associated with CMV hepatitis (14). Immunohistochemistry is useful when they are not seen (13).

In infants with cholestasis, studies have shown CMV DNA been isolated in liver tissue when biopsy was done with EHBA as a diagnosis and a small population of biliary atresia infants had urine PCR positive for CMV (15,16,17).

This possible association between EHBA and CMV at times cause delay in the diagnosis when a child presenting with cholestasis is found to have clinical evidence of CMV infection (15,16). Sometime the CMV infection acts as a "red herring". Even if there is evidence of CMV infection the workup of cholestasis should continue to rule out other causes especially causes requiring early surgery. (2)

CMV-specific IgM is positive during primary infection and reactivation. Quantitative PCR is used to monitor viral load during follow up. For congenital CMV within the first 3 weeks of life best sample is urine or oral swab (1).

CMV in immunocompromised: most common infection in post-transplant setting with the highest risk seen in the first 3 months when the immunosuppression is at the highest (18). CMV occurs in various forms in post-transplant setting either as a primary infection presenting as right

upper quadrant pain with jaundice or disease due to reactivation (19).

Treatment of CMV disease: IV Ganciclovir 3–5 mg/kg body weight twice daily for severe CMV infection for at least 2-3 weeks and followed by oral Valganciclovir 900 mg twice daily.

Oral Valganciclovir can be given for less severe CMV hepatitis. (20). These drugs are nephrotoxic hence routine urinary tests to be done serially (21).

Epstein Barr virus

Infectious mononucleosis (IMN), Burkitt's lymphoma, nasopharyngeal carcinoma, Hodgkin's disease, peripheral T-cell lymphoma, and post-transplant lymphoproliferative disease are all different forms of EBV infection (22).

Majority children can get EBV infection with nonspecific symptoms which is managed conservatively and this early infection can cause about 90% seropositivity in adulthood.

Primary EBV infection is self-limiting and managed conservatively. EBV stays dormant in the B cells (23). When there is decreased activity of the Cytotoxic T cells as a result of immunosuppression seen in post liver transplant immunosuppression, EBV reactivation occurs and can cause proliferation of the EBV infected B cells which is seen in 10% of patients.

Uncontrolled proliferation and clonal transformation these cells can result in post-transplant lymphoproliferative disorders (PTLD) with an incidence of 4.7% in children and 1% in adult LT recipients (24,25,26).

Liver involvement: Elevated liver enzymes two to three times the upper limit of normal, and elevated lactic dehydrogenase levels is seen in up to 90% of cases of IMN. Mild elevation of the alkaline phosphatase and bilirubin is seen in more than 50% of the cases. The EBV infection is more severe in the 3rd decade of life when compared to younger age groups and they present with icterus and right upper quadrant pain. Jaundice which is predominantly due to associated hemolytic anemia and virus induced cholestasis. Other presentations include post-transfusion hepatitis, granulomatous hepatitis and fatal fulminant hepatitis with the latter reported in both immunocompetent and immunocompromised individuals (8)

Diagnosis: EBV-specific IgG and IgM antibodies against the viral capsid antigens (VCA) are positive in adults during infection but negative in 50% of children.

PCR detection and quantitation of EBV DNA in blood samples is preferred in transplant units (1).

The Blood counts shows leukocytosis with lymphocytosis and monocytosis with mild thrombocytopenia.

Ultrasound abdomen: fatty liver appearance or thickening of GB wall.

Liver biopsy though not indicated may show: mononuclear cell infiltration of the portal system and sinusoids with hepatic necrosis or fatty infiltration.

The differential diagnosis: A-E viral hepatitis, CMV hepatitis, drug induced liver injury.

Treatment: Supportive care only as there is no specific drug which is effective (8).

HHV6A/HHV6B

Almost majority of adults, about 95% has seropositivity to this virus due to childhood infections (27)

HHV-6 infection occurs in immunocompromised state, post-transplant due to reactivation of the dormant virus in the mononuclear cells (28). Occurs as an asymptomatic infection with low viral load (29). Clinically, HHV-6 infection patient

develops fever, skin rash and raised liver enzymes (30,31).

Diagnosis: Virus□specific PCR

Reactivation of the HHV6 associated with significant graft failure rates, mortality, hepatitis C progression and CMV disease (32).

Treatment: LT patients can be treated successfully with Ganciclovir, Cidofovir and Foscarnet.

Human Herpes virus 8 (HHV 8)

HHV 8 is associated with almost 50% of cases of Castleman syndrome which is a rare disease of Lymph nodes and also rarely HHV 8 associated Lymphoproliferative disease.

Quantitative HHV8 DNA PCR to measure the viral load aids in the diagnosis (1)

Multicentric Castle man is difficult to treat but with corticosteroids, chemotherapy and immunotherapy gives some benefit.

The following table to summarize. extracted from Table 13.8 (1)

Herpesviridae family	**Context of liver involvement**
Herpes simplex Virus (HSV) 1	Neonatal disseminated infection+ hepatic dysfunction and fulminant hepatitis; Immunosuppressed patients
Herpes simplex virus (HSV) 2	Neonatal disseminated infection + hepatic dysfunction and fulminant hepatitis; Immunosuppressed patients
Varicella Zoster Virus (VZV)	During systemic infection (both immunocompetent and immunosuppressed)
Cytomegalovirus (CMV)	Primary infection (IMN like syndrome) Congenital infection; Immunosuppressed patients; Infection of transplanted liver from CMV positive donor
Human Herpesvirus 6A and 6B (HHV 6A & HHV 6B)	Immunosuppressed patients
Human herpes virus (HHV 7)	Immunosuppressed patients
Epstein Barr Virus (EBV)	Primary infection (infectious mononucleosis/glandular fever); EBV driven lymphoproliferative disorder and EBV associated malignancy in immunosuppressed patients
HHV 8/ Kaposi's sarcoma associated Herpes virus (KSHV)	Multicentric Castleman disease

Common childhood viral infections which may be associated with hepatitis.

See table 2 below.

Extracted from Common childhood viral infections (Table 13.9, 1)

Virus	Systemic illness	Liver involvement
Measles	Part of measles	Transaminitis, rarely cholestasis
Rubella	Congenital rubella syndrome	Hepatitis, Hepatomegaly, jaundice or massive hepatic necrosis
Parvovirus B19	Part of erythema infectiosum with aplastic crisis in immunocompromised patient	Acute Hepatitis Fulminant Liver failure
Adenovirus	Immunocompromised patient	Acute hepatitis Fulminant liver failure
Enteroviruses (polio, cocksackie, Echo)	In neonates part of sepsis	Hepatitis with or without coagulopathy Fulminant liver failure
Para echoviruses	Neonates	Hepatitis

Adenovirus is used as a vector for gene therapy, Zolgensma for Spinal Muscular therapy.

One of the side effects is hepatitis detected by elevated transaminases and it has the potential to cause liver failure. Management is conservative as per protocol and serial monitoring to see the trend of the transaminases.

Laboratory diagnosis: Serological assays for measles, rubella, and parvovirus B19 are available but diagnosis is by detection of viral nucleic acid.

Treatment: Mostly supportive. Cidofovir may be of value in immunosuppressed children with adenovirus infection.

Prevention by vaccination with MMR vaccine (1)

Viruses causing haemorrhagic fever

Viral haemorrhagic fever presents with multiorgan failure and severe hepatocellular necrosis and caused by a group of viruses: Dengue virus, yellow fever virus, Lassa virus, Crimean Congo haemorrhagic fever virus, Ebola and Marburg viruses. (1) It is not feasible to talk about all the viruses hence will take an example of the dengue virus in this article.

Dengue

As we all know there four serotypes of dengue virus, and infection with one serotype gives protection against further infection of the same serotype. But there is antibody mediated immune complex formation when the patient is infected a second type with a different serotype (33)

Patients with dengue haemorrhagic fever suffer from bleeding phenomena and circulatory failure. Dengue shock is caused by severe plasma leakage and manifests as cyanosis, hypotension, and encephalopathy (33.) The severity of hepatic involvement parallels the severity of the dengue infection. Serotypes 3 and 4 are associated with more severe liver disease (33) Acute liver failure may develop at a median of 7.5 days after the onset of fever (34)

The prognosis varies; children may have higher mortality than adults (35, 36, 37)

The histology is characterized by necrosis, mild microvesicular steatosis (37). As with arboviruses hepatitis there is little inflammation (38, 39). There is diffuse parenchymal calcifications in the liver once the infection resolves (40).

Laboratory diagnosis: Depending on the stage of the illness appropriate serology tests with specific viral RNA test (1)

Corona viruses

SARS associated coronavirus (SARS-CoV) responsible for the epidemic in the southern Chinese province of Guangdong in November 2002. There is isolated elevation of liver enzymes or as part of multiorgan involvement (15).

SARS associated coronavirus (SARS-CoV)-2 The 2019 corona virus disease (COVID-19) is caused by a new strain of corona virus named as SARS-CoV-2 with 80% similarity to the earlier corona virus (42). SARS-CoV-2 uses angiotensin converting enzyme (ACE2) receptor to enter the cells and is present abundantly in the alveolar cells (43). Extrapulmonary tissues like the stratified epithelial cells of oral and oesophageal mucosa, enterocytes of small intestine and colon, liver, myocardial cells, vascular endothelium and smooth muscle cells also contain (ACE2) expression (44).

Hepatic involvement in 14–53% of patients with severe COVID-19 (45).

ACE2 receptor is expressed mostly in cholangiocytes (59.7%) and vascular endothelial cells, but no expression in sinusoidal endothelial cells. Only 2% Hepatocytes are involved (44). Hepatic disease is possible due to the direct viral cytopathic effect and increased cytokine storm in severe disease

A cocktail of drugs is used in the treatment of COVID 19 and can cause liver injury. A recent

randomized controlled trial (RCT) failed to show clinical benefit of Remdesivir in COVID-19. Drug induced liver injury is seen in 10–13% of patients (46)

Newer diagnostics on the block

The indeterminate ALF is characterized by liver damage of unknown aetiology. It can be any due to any virus even ones whom we have not discovered yet who causes liver injury. By doing multiple PCR test targeting specific microorganisms will be a costly affair and time consuming. Clinical Metagenomic sequencing can integrate many of the likely pathogens together. Early diagnosis of HSV hepatitis can be lifesaving with early treatment of acyclovir.

Clinical Metagenomic next generation sequencing mNGS testing is likely to become part of a routine diagnostic workup for acute infectious diseases such as hepatitis [47, 48, 49, 50]. It needs more standardisation across centres and very soon it will be a part of diagnostic workup of infectious causes of Hepatitis (51).

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Vaccines to Prevent Viral Hepatitis

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Hepatitis vaccines have two purposes: to prevent the morbidity and occasional mortality associated with acute hepatitis virus infection and to reduce the occurrence of chronic liver disease and hepatocellular carcinoma. For the former aim, the principal targets for prevention are hepatitis A and B, whereas for the latter, the principal targets are hepatitis B and C. Although multiple factors have prevented the development of vaccines for hepatitis C, both hepatitis A and hepatitis B can be prevented by immunization.

Some queries regarding HepB and HepA vaccines

Who should be tested for anti-HBs after vaccination?

Serologic testing for immunity is not necessary or recommended after routine vaccination of infants, children, or adults. Testing for anti-HBs after vaccination is recommended for the following groups whose subsequent clinical management depends on knowledge of their immune status:

- Infants born to HBsAg-positive women and infants born to women whose HBsAg status remains unknown (for example, infants surrendered shortly after birth); postvaccination serologic testing should consist of testing for anti-HBs and HBsAg
- Healthcare professionals and public safety workers at risk for blood or body fluid exposure
- Hemodialysis patients (and other persons who might require outpatient hemodialysis), HIV-infected persons, and other immunocompromised persons (such as hematopoietic stem-cell transplant recipients or persons receiving chemotherapy), to determine the need for revaccination and the type of follow-up testing, and
- Sex partners of HBsAg-positive persons, to determine if they have not achieved immunity and will need revaccination and to continue to use other methods of protection against HBV infection.

Testing should be performed 1–2 months after administration of the final dose of the vaccine series using a method that allows determination of a protective concentration of anti-HBs (10 mIU/mL or higher).

Patient who is positive for anti-HBc (hepatitis B core antibody) but negative for all other hepatitis B serologic markers. Should he receive hepatitis B vaccine?

Some isolated positive anti-HBc results are false positives (it is the most common false positive HBV marker). If that can be established, the individual can and likely should be vaccinated, assuming there is an indication or desire to be protected. If the positive anti-HBc is believed to be a true positive, the individual would not require vaccination since they have already (presumably) had HBV infection. Isolated positive anti-HBc could indicate low-level chronic infection. In an infant isolated anti-HBc could indicate passive transfer of antibody from a mother who is HBsAg positive. People found to be anti-HBc positive should be tested for HBsAg. HBsAg testing may be performed on the same specimen collected for anti-HBc testing. If the HBsAg test result is positive, the person is infected and should receive appropriate management.

If lab reports anti-HBs results as adequate or inadequate, rather than providing a quantitative result. Is this acceptable?

Reporting of adequate and inadequate is acceptable only if the lab is using mIUs as the measurement for anti-HBs and the cutoff is below 10 mIU for reporting inadequate anti-HBs and 10 mIU or higher for reporting adequate anti-HBs. Check with the lab to be certain this is being done.

Hepatitis B panel for a new hospital employee. She had no documentation of having been vaccinated. Her results showed HBsAg nonreactive, anti-HBc reactive, IgM anti-HBc nonreactive, and anti-HBs borderline. How does one interpret these results. Should she be immunized?

Most likely this person has a resolved hepatitis B infection and is immune. However, it would be preferable to test her again for all these serologic markers, and also quantify the anti-HBs result. If the results are still positive for anti-HBc, and anti-HBs is less than the immune level of 10 mIU/mL, give her one dose of hepatitis B vaccine and test again in 1–2 months. If the anti-HBs is positive (10 mIU/mL or higher), she is immune. No further action is needed other than to document the results. If the anti-HBs is still negative, complete the vaccine series and test again 1–2 months after the last dose of vaccine.

How is Hepatitis B vaccines administered?

Routine vaccination:

- Minimum age: birth
- Administer monovalent HepB vaccine to all newborns within 24 hours of birth.
- Monovalent HepB vaccine should be used for doses administered before age 6 weeks.
- Administration of a total of 4 doses of HepB vaccine is permissible when a combination vaccine containing HepB is administered after the birth dose.
- The ideal minimum interval between dose 1 and dose 2 is 4 weeks, and between dose 2 and 3 is 8 weeks. Ideally, the final (3rd or 4th) dose in the HepB vaccine series should be administered no earlier than age 24 weeks and at least 16 weeks after the first dose, whichever is later.
- Hep B vaccine may be given in any of the following schedules: Birth, 1, & 6 months, Birth, 6 and 14 weeks; 6, 10 and 14 weeks; Birth, 6,10 and 14 weeks. All schedules elicit similar seroprotection rates.
- There is no recommendation for booster doses.

Catch-up vaccination:

- Administer the 3-dose series to those not previously vaccinated.

In catch up vaccination use 0, 1, and 6 months schedule.

Birth dose (monovalent HepB vaccine only)

- Mother is HBsAg-negative: 1 dose within 24 hours of birth for all medically stable infants ≥2,000 grams. Infants <2,000 grams: Administer 1 dose at chronological age 1 month or hospital discharge (whichever is earlier and even if weight is still <2,000 grams).
- Mother is HBsAg-positive:

o Administer HepB vaccine and hepatitis B immune globulin (HBIG) (in separate limbs) within 12 hours of birth, regardless of birth weight. For infants <2,000 grams, administer 3 additional doses of vaccine (total of 4 doses) beginning at age 1 month.

o Test for HBsAg and anti-HBs at age 9–12 months. If HepB series is delayed, test 1–2 months after final dose.

- Mother's HBsAg status is unknown:

o Administer HepB vaccine within 12 hours of birth, regardless of birth weight.

o For infants <2,000 grams, administer HBIG in addition to HepB vaccine (in separate limbs) within 12 hours of birth. Administer 3 additional doses of vaccine (total of 4 doses) beginning at age 1 month.

- Determine mother's HBsAg status as soon as possible. If mother is HBsAg-positive, administer HBIG to infants ≥2,000 grams as soon as possible, but no later than 7 days of age.

Adult dose vaccine: 20 mcg dose (1.0 ml suspension) is recommended for adults aged 20 years and above.

HepB vaccine while undergoing hemodialysis, will the vaccine be effective? Will the dose need to be repeated?

Neither the ACVIP nor the manufacturers address the timing of vaccination and dialysis. Persons with end-stage renal disease including predialysis, hemodialysis, peritoneal dialysis, and home dialysis should be tested for hepatitis B surface antibody (anti-HBs) 1–2 months after vaccination, and annually. If the anti-HBs level is below 10mIU/mL, they should be revaccinated.

How often do hemodialysis patients who have received HepB vaccination have to be tested for anti-HBs and HBsAg?

Recommendations for immune compromised people, such as hemodialysis patients, are different than those for immune-competent people. Hemodialysis patients who do not respond to an initial vaccine series should be revaccinated with two to four additional doses of HepB (depending on the brand). Hemodialysis patients are considered immune as long as they have adequate anti-HBs (at least 10 mIU/mL). For hemodialysis patients who have responded with adequate anti-HBs (postvaccination testing should be done 1 to 2 months after the vaccine series) to HepB vaccination, no HBsAg testing is needed but anti-HBs should be done annually. If anti-HBs declines below 10 mIU/mL, a booster dose of HepB should be given and annual anti-HBs testing should be continued. Retesting immediately after the booster dose is not necessary.

What is the maximum number of hepatitis B vaccine doses a dialysis patient can receive?

There is no maximum number of HepB booster doses a dialysis patient can receive. Serology should be performed once a year and a booster dose given if serology is negative (less than 10 mIU/mL). Serology is not recommended more frequently than once a year, so boosters wouldn't be given more than once a year

Some nephrologists give a high dose (40 mcg) of hepatitis B vaccine (2 adult doses) to all patients with renal failure with glomerular filtration rates (GFRs) of less than 30 ml/min even if the patient is not on dialysis. Is this practice advisable?

When using HepB to vaccinate hemodialysis or other immunocompromised people, a higher dose is recommended, so to the extent these patients are immunocompromised. Regardless, this practice is appropriate for several reasons, including that these patients may be starting hemodialysis soon, and because use of the higher dose is not harmful. This is somewhat of a gray area but the clinician can use his/her clinical judgment.

At what anatomic site should hepatitis B vaccine be administered to adults? What needle size should be used?

For adults, administer HepB intramuscularly (IM) in the deltoid muscle. A 22- to 25-gauge, 1–1½ -inch needle should be used. The gluteus muscle should not be used as a site for administering HepB. For optimal protection, it is crucial that the vaccine be administered IM, not subcutaneously.

What should be done if a healthcare personnel's postvaccination anti-HBs test is negative (less than 10 mIU/mL) 1–2 months after the last dose of vaccine?

There are two options for healthcare personnel who test negative after completing their first HepB series. The first option is to give one dose of HepB, then retest for anti-HBs. If the result is positive, the person should be considered immune. If negative, the person should receive the remaining doses in the series, and then retest for anti-HBs. If the result is positive, the person

should be considered immune. If negative, the person should be tested for HBsAg and total anti-HBc to determine their HBV infection status. People who test negative for HBsAg and total anti-HBc should be considered vaccine non-responders and susceptible to HBV infection. They should be counseled about precautions to prevent HBV infection and the need to obtain hepatitis B immune globulin (HBIG) prophylaxis for any known or likely exposure to HBsAg-positive blood. Those found to be HBsAg negative but total anti-HBc positive were infected in the past and require no vaccination or treatment. If the HBsAg and total anti-HBc tests are positive, the person should receive appropriate counseling for preventing transmission to others as well as referral for ongoing care to a specialist experienced in the medical management of chronic HBV infection. They should not be excluded from work.

The second option is to repeat the 3-dose series and test for anti-HBs 1–2 months after the final dose of the repeat series. The same sequence followed thereafter.

The choice of option 1 and option 2 should be based on epidemiologic considerations and likelihood that the patient is HBsAg positive, since there is a delay in option 1 in determining HBsAg status.

If an employee receives both HBIG and hepatitis B vaccine after a needlestick from a patient who is HBsAg positive, how long should one wait to check the employee's response to the vaccine?

Anti-HBs testing for HCP who receive both hepatitis B immune globulin (HBIG) and hepatitis B vaccine can be conducted as soon as 6 months after receipt of the HBIG.

Is anti-HBs of 10 mIU/mL or higher sufficient as a correlate of vaccine-induced protection in a unvaccinated or incompletely vaccinated HCP?

Testing unvaccinated or incompletely vaccinated HCP (including those without written documentation of vaccination) is not necessary and is potentially misleading because anti-HBs of 10 mIU/mL or higher as a correlate of vaccine-induced protection has only been determined for persons who have completed a HepB vaccination series. The result would only mean that the person is immune at the time the person was tested but does not assure that the person has long-term immunity. Persons who cannot provide written documentation of a complete HepB vaccination series should complete the series, then be tested for anti-HBs 1 to 2 months after the final dose.

If a person has been sexually assaulted, should he/she be offered HBIG and hepatitis B vaccine?

Sexually transmitted infections, including hepatitis B, can be transmitted by sexual assault. Unless the victim has a documented history of completed HepB vaccination, a series of HepB alone should be administered with the first dose as soon as possible after the assault. Administration of hepatitis B immune globulin (HBIG) is not necessary.

Hepatitis A vaccine

Routine vaccination:

- Minimum age: 12 months
- Inactivated HepA vaccine: Start the 2-dose HepA vaccine series for children aged 12 months onwards; the 2 doses should be administered 6 to 18 months apart.
- Live attenuated H2-strain Hepatitis A vaccine: Single dose starting at 12 months of age

Catch-up vaccination:

- Either of the two vaccines can be used in 'catch-up' schedule beyond 2 years of age
- Administer 2 doses of inactivated vaccine at least 6 months apart to unvaccinated persons
- Only single dose of live attenuated H2-strain vaccine

1-18 yrs	720 El.U.*	0.5 ml	2	0, 6-12 mos.
19 yrs and older	1440 El.U.*	1.0 ml	2	0, 6-12 mos.

For hepatitis A vaccination, the minimum interval between the 2-dose series is at least 6 months. Is this the same as 24 weeks?

No. The minimum interval between dose #1 and #2 of HepA vaccine is 6 calendar months, not 24 weeks.

Child who was given her second dose of hepatitis A vaccine 4 months after the first dose. Does it need to be repeated, and if so, when?

The second dose was given more than 4 days before the minimum interval of 6 calendar months, so it is considered invalid and should be repeated. The repeat dose should be administered the proper minimum interval (6 months) after the invalid dose. If this repeat dose is inadvertently given less than 6 months after the invalid dose, it does not need to be repeated again as long as the interval between the initial HepA vaccine and the most recent dose is at least 6 calendar months.

What are the recommendations for postexposure prophylaxis (PEP) for hepatitis A?

Healthy people who have completed the HepA vaccination series at any time do not need additional PEP if they are exposed to HAV. People who have recently been exposed to HAV and who have not received HepA vaccine previously should receive PEP as soon as possible, within 2 weeks of exposure.

People age 12 months and older exposed to HAV within the past 14 days and who have not previously completed the HepA vaccine series should receive a single dose of HepA vaccine as soon as possible. In addition to vaccine, immune globulin (IG; 0.1 mL/kg) may be administered to people who are immunocompromised or have chronic liver disease, are older than age 40 years depending on the providers' risk assessment. For long-term immunity, the HepA vaccine series should be completed with a second dose at least 6 months after the first dose. However, the second dose is not necessary for PEP. A second dose should not be administered sooner than 6 calendar months after the first dose, regardless of HAV exposure risk.

People with HIV infection develop protective levels of antibody more slowly and are less likely to develop protective antibody levels after vaccination with HepA, especially if their CD4+ count is low at the time of vaccination. Protection following vaccination of a person with HIV may wane over time. Vaccine should be administered if the exposed individual is not fully vaccinated; however, clinicians to consider administering IG PEP to an individual with HIV after a high-risk exposure (such as a household or sexual contact) even if the individual has been fully vaccinated.

It is important to avoid live attenuated H2-strain vaccine in people who are immunocompromised.

Infants younger than age 12 months and persons for whom vaccine is contraindicated should receive IG (0.1 mL/kg) instead of HepA vaccine as soon as possible and within 2 weeks of exposure. MMR and varicella vaccines should not be administered sooner than 6 months after IG administration in order to avoid possible IG interference with the effectiveness of MMR and varicella vaccines.

Can HepA vaccine be given to immunocompromised child?

Yes. All people age 1 year or older living with HIV infection should be vaccinated against hepatitis A if they have not been vaccinated, regardless of their CD4+ count.

If any immunocompromised person has a risk factor that places them at increased risk of hepatitis A (e.g., international travel, drug use), they should be vaccinated with HepA vaccine.

Patient on interferon for hepatitis C. Is it okay to vaccinate against hepatitis A while on interferon?

Yes. HepA vaccine should be given to all susceptible patients with chronic liver disease. HepA vaccine is very immunogenic.

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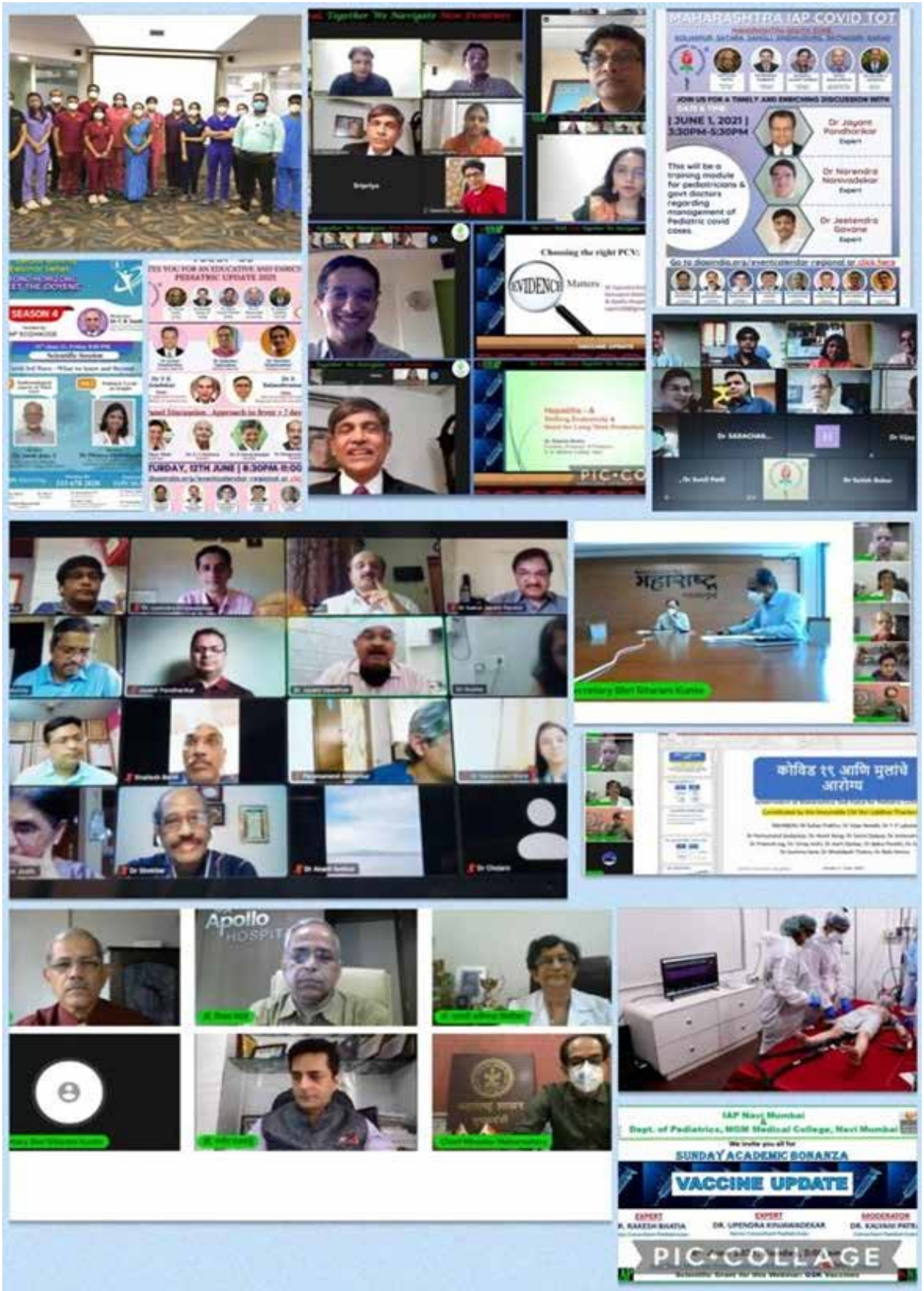

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26th June 8 PM
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Consultant Psychiatrist & President, IMA Thalassery
Dr Uanathi Subramoniam
Nodal Officer, District Mental Health Programme, Kannur
Mr Rajesh, ADNO, SPC, Kannur
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Release of Research Methodology Manual for Beginners on June 8th, Tuesday, 7.30 pm
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Dr TP Jayaraman President, IAP TVM
Release of Manual by
Prof. Piyush Gupta President, CIAP
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Third Wave?
Prediction or Speculation?
T Jacob John, FNA
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