University of Baghdad
College of Medicine

Title: Chronic liver disease (2)

Grade: Fifth year

Module: Pediatrics

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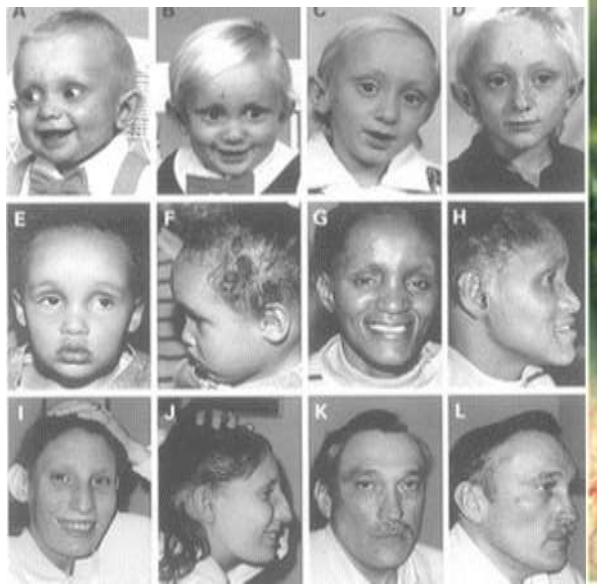
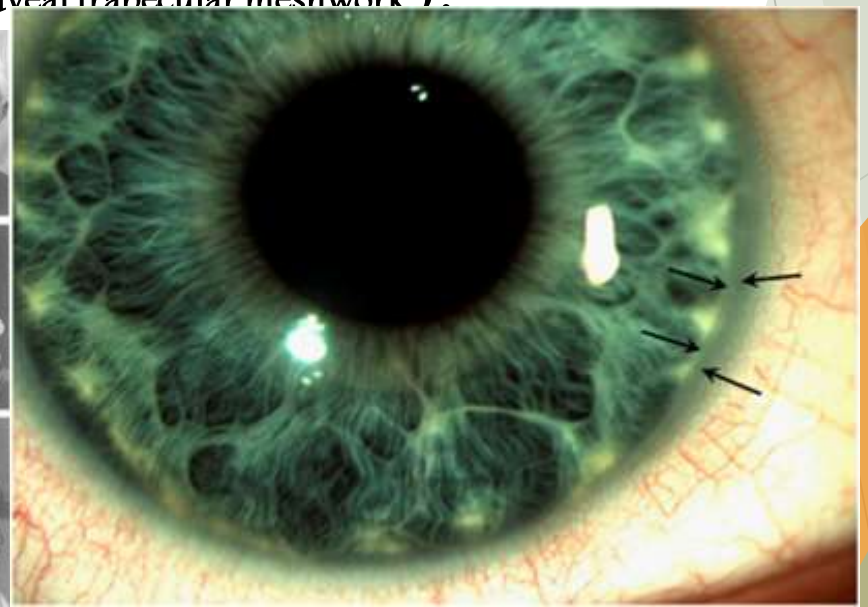
Alagille syndrome

This is a rare autosomal dominant condition with widely varying penetrance even within families. but in about half of cases, the mutation occurs as a new change

Clinical presentation is with characteristic triangular facies, skeletal abnormalities (including butterfly vertebrae), congenital heart disease (classically peripheral pulmonary stenosis), renal tubular disorders, bile duct paucity, and defects in the eye (posterior embryotoxon : is a corneal abnormality that is visible with slit-lamp biomicroscopy as a thin grey-white, arcuate ridge on the inner surface of the cornea, adjacent to the limbus. It is an anteriorly displaced Schwalbes line, the junction of Descemets membrane and the uveal trabecular meshwork).





Infants may be profoundly cholestatic with **severe pruritus** and faltering growth.

Diagnosis Identifying the gene mutations confirms the diagnosis.

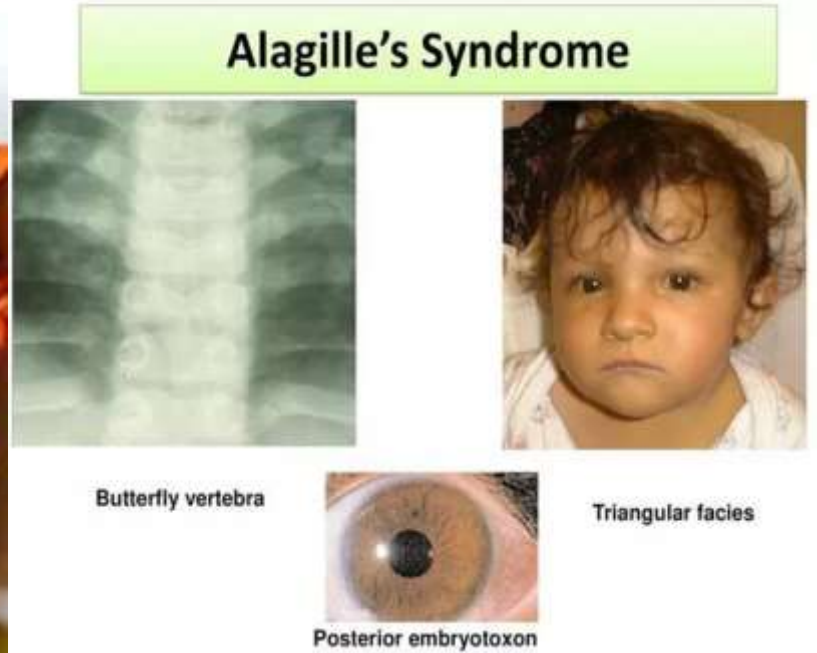
(the JAG1 gene in >88% or the NOTCH2 gene in about 2%

Treatment is to provide nutrition and fat-soluble vitamins.

Pruritus is profound and difficult to manage.

A small number will require liver transplant, but most survive into adult life.

Mortality is most likely secondary to the cardiac disease.



Progressive familial intrahepatic cholestasis

These autosomal recessive disorders all affect bile salt transport.
At present, specific gene defects have been identified for 3 subtypes of PFIC.
PFIC1 (the former Byler disease) and PFIC2 are characterized by low gamma-glutamyl peptidase (GGT) levels.
In PFIC3, patients have a similar clinical presentation, but laboratory results reveal an elevated serum GGT.
Rather than defective bile acid export, patients with PFIC3 have deficient hepatocellular phospholipid export. The lack of phospholipids produces unstable micelles that have a toxic effect on the bile ducts, leading to bile duct plugs and biliary obstruction.

Clinical presentation is with jaundice, intense pruritus, faltering growth, rickets, and in some cases diarrhoea and hearing loss.
Older children may present with gallstones.

The **diagnosis** is confirmed by identifying mutations in bile salt transport genes.

Treatment is with nutritional support and fat-soluble vitamins. Pruritus can be severe. Progression of fibrosis is usual with most requiring liver transplantation.

α1-Antitrypsin deficiency

It is inherited as an autosomal **recessive disorder** with an incidence of 1 in 2000 to 1 in 4000 in the UK.

There are many phenotypes of the protease inhibitor (Pi) which are coded on chromosome **14**, with liver disease primarily associated with the protein phenotype PiZZ.

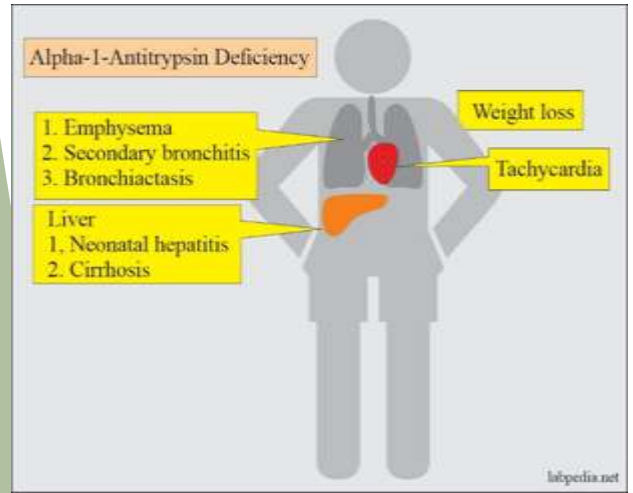
Abnormal folding of the protease α1-antitrypsin is associated with accumulation of the protein within the hepatocytes and hence liver disease in infancy and childhood.

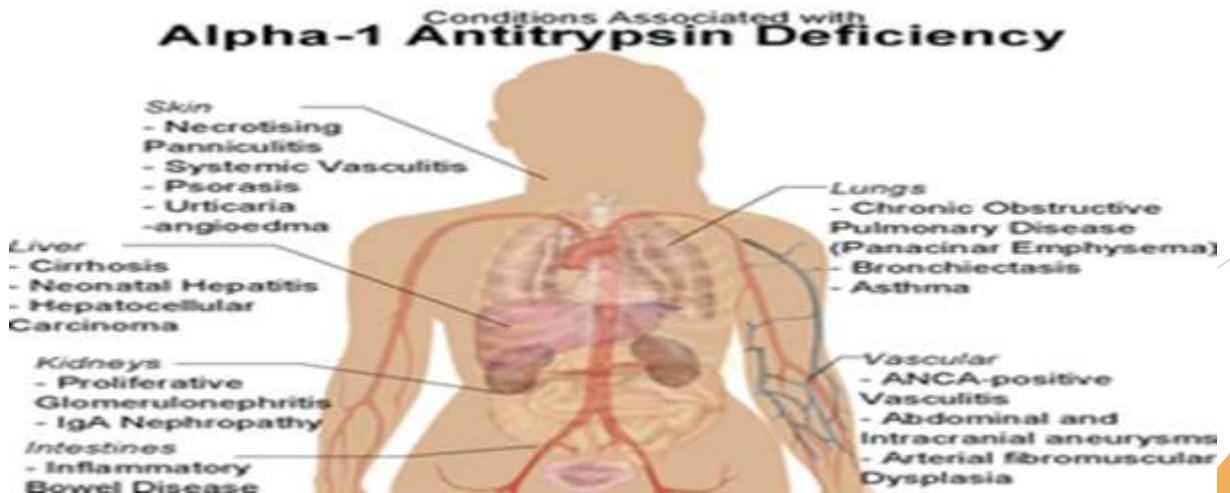
The lack of circulating α1-antitrypsin results in emphysema in adults.

The majority of children who present with α1-antitrysin deficiency will either have prolonged neonatal jaundice or, less commonly, bleeding due to vitamin K deficiency (hemorrhagic disease of the newborn).

Hepatomegaly is present. Splenomegaly develops with cirrhosis and portal hypertension.

The diagnosis is confirmed by estimating the level of α1- antitrypsin in the plasma and identifying the protein phenotype.
Approximately **50%** of children have a good prognosis, but the remainder will develop liver disease and may require transplantation.
Pulmonary disease is not significant in childhood, but is likely to develop in adult life.
Advice to avoid smoking (both active and passive) should be given.
The disorder can be diagnosed antenatally.





Autoimmune hepatitis and sclerosing cholangitis

Autoimmune hepatitis

The mean age of presentation is 7 years to 10 years.

It is more common in girls.

The prevalence of AIH is unknown (prevalences vary from 1 in 200,000 in the general population in the US to 20 in 100,000 in females over 14 years of age in Spain).

The etiology of AIH is unknown, although both genetic and environmental factors are involved in its expression.

Susceptibility to AIH is imparted by genes in the human leukocyte antigen (HLA) region on the short arm of chromosome 6, especially those encoding DRB1 alleles.

Variable age at onset (median of 10 years in type 1 and 7.4 years in type 2 AIH), with occasional presentation in infancy.

Clinical presentation

was variable, with the following predominant types emerging:

1• Acute presentation resembling that of viral hepatitis (in 50% of patients with type 1 and 65% of patients with type 2 AIH) with non-specific symptoms of malaise, nausea/ vomiting, anorexia, and abdominal pain, followed by jaundice, dark urine, and pale stools.

2• Fulminant hepatic failure (in 11%, five out of six of these patients having type 2); with grade II to IV hepatic encephalopathy developing 2 weeks to 2 months (median 1 month) after the onset of symptoms.

3• Insidious onset, characterized by progressive fatigue, relapsing jaundice, headache, anorexia, and weight loss, lasting from 6 months to 2 years (median 9 months) before diagnosis (25% of patients with type 2 and 38% of patients with type 1 AIH).

Diagnosis is based on:

Biochemistry

Elevated serum transaminase and positive autoantibodies (type 1 is positive for ANA and/or antismooth muscle (SMA) antibody, type 2 is positive for anti-LKM-1), a low serum complement (C4); and typical histology. These should include the following: elevated serum transaminase and IgG/ γ-globulin levels, and presence of ANA, SMA, or anti-LKM, anti-LC-1 autoimmune markers.

Immunoglobulins

The majority (80%) of the patients had increased levels of IgG, (IgG >20 g/L); but some of whom were positive for anti-LKM-1) had a normal serum IgG level for age, particularly patients who presented with acute hepatic failure – indicating that normal IgG values **do not exclude** the diagnosis of AIH.

Histology

Liver biopsy is necessary to establish the diagnosis.

The typical histological picture includes:

- A dense mononuclear and plasma cell infiltration of the portal areas, which expands into the liver lobule.
- Destruction of the hepatocytes at the periphery of the lobule, with erosion of the limiting plate ("interface hepatitis").
- Connective tissue collapse resulting from hepatocyte death and expanding from the portal area into the lobule ("bridging collapse").
- Hepatic regeneration with "rosette" formation.
- Cirrhosis.

Autoimmune hepatitis may occur in isolation or in association with inflammatory bowel disease, coeliac disease, or other autoimmune diseases.

Management and prognosis

Some 90% of children with autoimmune hepatitis will respond to prednisolone and azathioprine.

Standard treatment for AIH consists of prednisolone 2 mg/ kg/day (maximum 40-60 mg/day), which is gradually decreased over a period of 4-8 weeks in parallel to the decline of transaminase levels.

Once normal liver function tests are obtained, which may take several weeks or even a few months, the patient is maintained on the minimal dosage that is capable of sustaining normal transaminase levels – usually 5 mg/day.

If progressive normalization of the liver function tests is not obtained over this period of time, or if too high a dose of prednisolone is required to maintain normal transaminases,

azathioprine is added at a starting dose of 0.5 mg/kg/day, which in the absence of signs of toxicity is increased up to a maximum of 2.0 – 2.5 mg/kg/day until biochemical control is achieved.

Azathioprine is not recommended as first-line treatment because of its hepatotoxicity in severely jaundiced patients, but 85% of the patients will eventually require the addition of azathioprine.

Treatment should be continued for at least 3 years before considering its cessation, after which period stopping treatment can be attempted but only if liver function tests and IgG levels have been persistently normal.

Other immunosuppressive agents

Mycophenolate mofetil(dose of 20 mg/kg twice daily, together with prednisolone), side effects (headache, diarrhea, nausea, dizziness, hair loss, and neutropenia),

Ciclosporin (side effects: renal impairment, gingival hyperplasia, and hirsutism)

Tacrolimus is a more potent immunosuppressive agent than ciclosporin, but it also has significant toxicity.

Budesonide has a hepatic first-pass clearance of >90% of oral dose and fewer side effects than prednisone but cannot be used in the presence of cirrhosis, which affects at least two-thirds of AIH patients.

approximately 40% to 50% of the individuals with severe disease will die within 6 months to 5 years.

Sclerosing cholangitis

Sclerosing cholangitis is a chronic inflammatory disorder that may affect both the intrahepatic and extrahepatic bile ducts and may lead to fibrosis.

The diagnosis is based on typical bile duct lesions being visualized on **cholangiography**.

In childhood, sclerosing cholangitis may occur as an individual disease or may develop in association with a wide variety of disorders, including Langerhans cell histiocytosis, immunodeficiency, psoriasis, cystic fibrosis, and chronic inflammatory bowel disease.

An overlap syndrome between AIH and sclerosing cholangitis has been reported both in adults and children, most of the reported cases of overlap having been originally diagnosed as AIH.

AIH/sclerosing cholangitis overlap syndrome (ASC) has the same prevalence as AIH type 1 in childhood.

Treatment and prognosis

Children with ASC respond to the same immunosuppressive treatment described for AIH.

Liver test abnormalities resolve in most patients within a few months after treatment has been started.

However, although steroids and azathioprine are beneficial in abating the parenchymal inflammatory lesion,

they appear to be less effective in controlling the bile duct disease.

Ursodeoxycholic acid is usually added to the treatment of ASC, but whether it is helpful in arresting the progression of bile duct disease remains to be established.

It is prudent to use doses not higher than 15–20 mg/ kg/day. Fat-soluble vitamin supplements are required if cholestasis

develops. As in AIH, measurement of autoantibody titers and IgG levels is useful in monitoring disease activity and the response to treatment.

The medium- to long-term prognosis of ASC is worse than that of AIH because of progression of bile duct disease despite treatment in some 50% of patients, with 20% of them eventually requiring liver transplantation.

Wilson disease

Wilson disease is an autosomal recessive disorder with an incidence of 1 in 200 000.

Many mutations have now been identified.

The basic genetic defect is a combination of reduced synthesis of caeruloplasmin (the copper-binding protein) and defective excretion of copper in the bile, which leads to an accumulation of copper in the liver, brain, kidney, and cornea.

Wilson disease rarely presents in children under the age of 3 years.

In those presenting in childhood, a hepatic presentation is more likely.

They may present with almost any form of liver disease, including acute hepatitis, fulminant hepatitis, cirrhosis, and portal hypertension.

- Neuropsychiatric features are more common in those presenting from the second decade onwards and include deterioration in school performance, mood and behaviour change, and extrapyramidal signs such as incoordination, tremor, and dysarthria.
- Renal tubular dysfunction, with vitamin D-resistant rickets, and haemolytic anaemia also occur.
- Copper accumulation in the cornea (Kayser–Fleischer rings) is not seen before 7 years of age.

- A low serum caeruloplasmin and copper is characteristic, but not universal.
- Urinary copper excretion is increased and this further increases after administering the chelating agent penicillamine.
- However, the diagnosis is confirmed by the finding of elevated hepatic copper on liver biopsy or identification of the gene mutation.

Treatment is with penicillamine or trientine (20mg/kg).
Both promote urinary copper excretion, reducing hepatic and central nervous system copper.
Zinc (25-50 mg/3 times daily) is given to reduce copper absorption.
Pyridoxine is given to prevent peripheral neuropathy.
Zinc is used in asymptomatic children identified by screening families with an index case.
Neurological improvement may take up to 12 months of therapy. About 30% of children with Wilson disease will die from hepatic complications if untreated.
Liver transplantation is considered for children with acute liver failure or severe end-stage liver disease.

Fibropolycystic liver disease (Ciliopathies)

This is a range of inherited conditions affecting the development of the intrahepatic biliary tree.

Presentation is with liver cystic disease or fibrosis and renal disease.

Congenital hepatic fibrosis presents in children over 2 years old with hepatosplenomegaly, abdominal distension, and portal hypertension.

It differs from cirrhosis in that liver function tests are normal in the early stage.

Liver histology shows large bands of hepatic fibrosis containing abnormal bile ductules.

Complications include portal hypertension with varices and recurrent cholangitis.

Cystic renal disease may coexist and may cause hypertension or renal dysfunction.

Indications for liver transplant include severe recurrent cholangitis or deterioration of renal function requiring renal transplant, in which case a combined transplant would be offered.

Non-alcoholic fatty liver disease

Non-alcoholic fatty liver disease is the single most common cause of chronic liver disease in the high-income world.

It is a spectrum of disease, ranging from simple fatty deposition (steatosis) through to inflammation (steatohepatitis), fibrosis, cirrhosis, and end-stage liver failure.

In childhood, it may be associated with a metabolic syndrome or with obesity.

The prognosis in childhood is uncertain; few develop cirrhosis in childhood in contrast to 8% to 17% of adults.

They are usually asymptomatic, although some complain of vague right upper quadrant abdominal pain or lethargy.

The diagnosis is often suspected following the incidental finding of an echogenic liver on ultrasound or mildly elevated transaminases carried out for some other reason.

Liver biopsy demonstrates marked steatosis with or without inflammation or fibrosis.

The pathogenesis is not fully understood but may be linked to insulin resistance.

Treatment targets weight loss through diet and exercise, which may lead to liver function tests returning to normal.

Parenterally transmitted viral hepatitis

HEPATITIS B VIRUS

Hepatitis B virus (HBV) is a member of the Hepadnaviridae family which consists of a group of species-specific enveloped hepatotropic DNA viruses infecting various vertebral hosts, including mammals and birds.

The genome of HBV is a partially double-stranded, partially single-stranded circular DNA of 3200 nucleotides.

HBV infects human as well as great apes such as chimpanzees, orang-utans, and gibbons, though each primate species is infected by a distinct variant of HBV.

In humans, up to 10 different genotypes (A–J) have been described based on a genetic divergence of >8% over the entire genome.

Some genotypes have a wide geographical distribution but some are relatively restricted in its distribution.

Most infection in highly endemic areas is acquired through mother-to-child transmission.

Transmission may occur through placental tears, trauma during delivery, and contact of the infant mucous membranes with infected maternal fluids.

Intrauterine transmission may occur, but this does not appear to be a major route.

Mothers who are HBe Ag positive have the highest infectivity and without prophylaxis, a 70–90% risk of transmitting infection to their offspring.

Those who are anti-HBe positive have a lower risk of transmitting infection. However, if the offspring of these individuals are infected, they are at risk of developing fulminant hepatitis due to a mutant virus.

The virion of HBV, also known as the Dane particle, it consists of an outer coat of hepatitis B surface antigen (HBsAg) and an inner core of hepatitis B core antigen (HBc Ag).

As HBV is present in infected individuals in high concentrations in blood, serum and serous exudates, semen, vaginal fluid, and saliva,
horizontal transmission is also common through parenteral and sexual exposure routes.
Although HBV is also found in low concentrations in feces and breast milk, these are not associated with a significant risk of transmission..

Serological markers of HBV infection

HBsAg	Anti-HBs (>10 IU/L)	Anti-HBc	Anti-HBc IgM	HBeAg	Anti-HBe	HBV DNA*	Scenarios
+	-	+	++	+	-	+++	Acute HBV infection
-	-	+	+	-	-	+	Seroconversion window after acute HBV infection
-	+/-	+	-	-	+/-	-	Recovered hepatitis B with HBsAg clearance
-	+	-	-	-	-	-	Immunity due to vaccination
+	-	+	+/-	+	-	++++	HBeAg-positive chronic hepatitis B
+	-	+	+/-	-	+	++/+++	HBeAg-negative chronic hepatitis B
+	-	+	-	-	+	+	Chronic inactive hepatitis B
-	-	+	-	-	+/-	+	Occult hepatitis B

*HBV DNA levels: - undetectable <20 IU/mL; + <2000 IU/mL; ++ 2000–20,000 IU/mL; +++ >20,000 IU/mL; ++++ >200,000 IU/mL.

HBV is not a cytopathic virus. Immunopathology leads to liver damage, ranged from minimal inflammatory infiltrate to piecemeal necrosis, and from mild fibrosis to established Cirrhosis.
Chronic HBV infection is strongly associated with hepatocellular carcinoma (HCC).
Up to 80% of HCC worldwide is believed to be caused by HBV.

Chronic hepatitis B infection

CHB is defined as persistence of HBsAg for >6 months.

Ninety per cent of infected neonates and 25–50% of acutely infected children between the ages of 1 and 5 years will develop chronic infection.

The risk of developing chronic infection is less in adolescents and adults, <5% of symptomatic and 5–10% of asymptomatic infected teenagers and adults will develop CHB.

Children with CHB generally have a mild disease and are mostly asymptomatic with normal growth and physical examination.

Non-specific symptoms as fatigue and anorexia may occur and diagnosis is usually made by screening those known to be at risk.

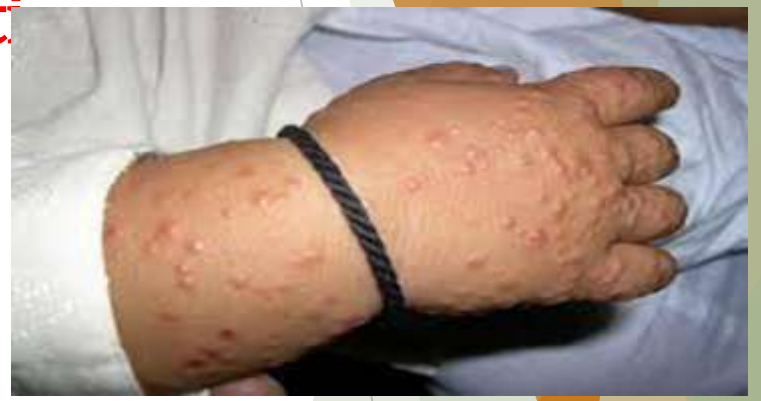
HBV infections can be associated with extrahepatic

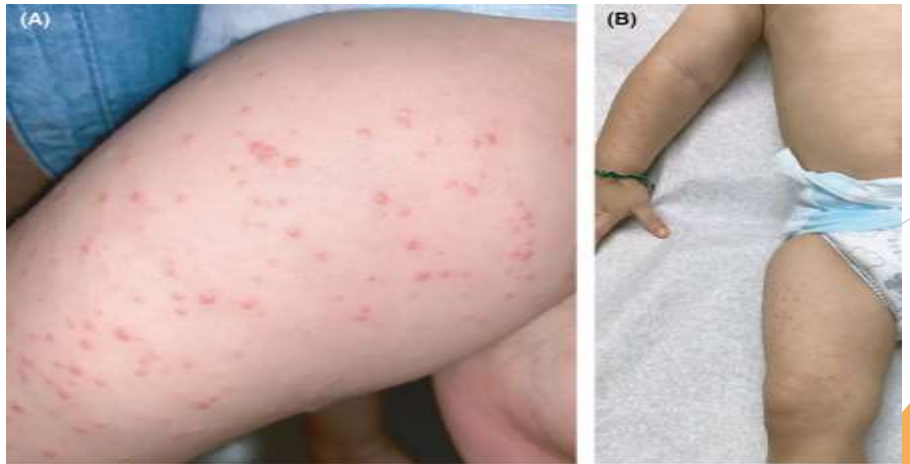
These manifestations include:

- Serum sickness like syndrome and reactive arthritis.
- Vasculitis (mainly polyarteritis nodosa).
- Membranous glomerulonephritis is the most common form of renal involvement in HBV infection.
- Papular acrodermatitis of childhood (**Gianotti–Crosti syndrome**).

Skin lesions are non-pruritic maculopapular and erythematous involving the face and extremities.

The rash may last 15–20 days and can either precede or follow the onset of jaundice in acute hepatitis B.





Management of hepatitis B virus infection

Management of children with CHB requires expert multidisciplinary input, support, counseling in addition to screening and immunization of other family members.

Routine review should include standard liver function tests (LFTs), α-fetoprotein (AFP), HBV serology, HBV DNA, and abdominal ultrasound scan for monitoring of disease progression, and/or HCC.

Interferon-α2b (IFN-α2b) has immunomodulatory and antiviral effects it has been used in children, with long-term viral response rates of 25%.

Interferon (IFN) use is limited by its subcutaneous administration, treatment duration of 24 wk, and side effects (flulike symptoms, marrow suppression, depression, retinal changes, autoimmune disorders).

IFN is further contraindicated in decompensated cirrhosis. One advantage of IFN, compared to other treatments, is that **viral resistance does not develop with its use.**

- **Lamivudine** is an oral synthetic nucleoside analog that inhibits the viral enzyme reverse transcriptase. In children **older than 2 yr of age**, its use for 52 wk resulted in Hbe Ag clearance in 34% of patients with an ALT >2 times normal; 88% remained in remission at 1 yr. It has a good safety profile.
- **Adefovir** (a purine analog that inhibits viral replication) is approved for use in children **older than 12 yr of age**, in whom a prospective 1-yr study showed 23% seroconversion.
- **Entecavir** (a nucleoside analog that inhibits replication) is currently approved for use in children **older than 2 yr of age**.
- **Tenofovir** (a nucleotide analog that inhibits viral replication) is also approved for use in children **older than 12 yr of age.**

Chronic Hepatitis C Infection

Hepatitis C virus (HCV) infection remains a major public health burden, with an estimated worldwide prevalence of 2.5% of the population.

In children and adolescents as in adults, HCV infection is suspected to be grossly underestimated. HCV infection across the pediatric age spectrum differs from infection acquired later in life in a variety of ways, including modes of transmission, rates of spontaneous clearance or progression of fibrosis, the potential duration of chronic infection when acquired at birth, and significantly, available treatment options.

Six distinct HCV genotypes have been identified. In Middle East, HCV genotype 1, genotype 4 represent the most common variants.

Historically, HCV was considered to be a transfusion-related disease in children and adolescents; however, with the advent of blood-bank screening practices, no new pediatric cases of transfusion-transmitted acute HCV infection have been detected in the United States since 1994.

Consequently, mother to infant transmission during the perinatal period has emerged as the most common mode of acquisition of infection in children, accounting for approximately 60% of cases.

Clinical Features

Many acute HCV infections are clinically asymptomatic but those who become icteric show a modest rise in aminotransferase levels.

Some patients have symptoms of acute hepatitis, such as anorexia, malaise, fatigue and abdominal pain.

In most instances, chronic HCV infection is **asymptomatic.**

Diagnosis

Serologic testing for anti-HCV antibodies is the appropriate screening test for HCV.

The next diagnostic step is the determination of quantitative HCV RNA and the genotype.

It is useful to perform an ultrasound examination including liver stiffness assessment for the baseline report.

As chronic hepatitis C usually is a histologically mild disease with low inflammatory activity in childhood, liver biopsy is not mandatory.

Treatment

The primary goal of HCV therapy is to cure the infection which is reflected by persistently negative HCV RNA in serum and normalized aminotransferases.

Sustained viral response (SVR) is defined as an undetectable HCV RNA level 24 weeks after cessation of treatment.

Non-genotype 1 patients are treated with peg-alpha-interferon in combination with ribavirin, for example, genotype 2 and 3 for 24 weeks.
With these regimens, considerable sustained viral response rates can be achieved ranging from more than 65% for genotype 1 to over 80 % for genotype 2 and 3 patients.

New direct-acting antivirals (DAA) against the HCV have been developed.
The first direct-acting antiviral drugs were approved for adolescents in 2017 is Sofosbuvir (Sovaldi).
Ledipasvir/sofosbuvir(Harvoni) is indicated for HCV genotypes 1, 4, 5, or 6. in adults and children **3 years** of age and older.

Sofosbuvir and velpatasvir (Epclusa) are antiviral medications is used to treat chronic hepatitis C in adults and children **3 years** of age and older, for genotypes 1, 2, 3, 4, 5 or 6 infection without cirrhosis or with compensated cirrhosis.

Glecaprevir/pibrentasvir (Mavyret) is used to treat adults and children **12 years** of age and older for genotypes 1, 2, 3, 4, 5 or 6 infection without cirrhosis or with compensated cirrhosis.


Thank
you