UNIVERSITATEA DE STAT DE MEDICINĂ ȘI FARMACIE
"NICOLAE TESTEMIȚANU" DIN REPUBLICA MOLDOVA

Chronic hepatitis in children. Hepatic cirrhosis in children

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Presentation topics

- Definition
- Epidemiology
- Etiological classification
- Clinical presentation
- Approach to a child with CLD
- Management
- Upcoming research

Hepatitis

- **Hepatitis** is a term for inflammatory diseases of the liver, grossly subdivided into infectious and noninfectious, which are characterized by a wide variety of clinical and histologic manifestations, ranging from mild and self-limited to severe and progressive forms leading to liver failure, cirrhosis, or hepatocellular carcinoma.

- ***Acute/Chronic hepatitis*** means ongoing inflammation of the liver persisting for **less/more than six months** that is detectable by biochemical and histologic means

Chronic hepatitis classification

The **first classification (1968)** of CH distinguished

- cirrhotic and non-cirrhotic stages
- classified the disease according to the histological degree of disease activity
  - chronic persistent
  - chronic aggressive varieties

The discovery of viral and other etiologies for CH substantiate a development of a **new classification (1994)**,

- which included primary classification according to **etiology**,
- determination of disease **severity**, and **stage of progression**

Causes (etiology) of hepatitis

- Infectious
  - Viral hepatitis – most common
  - Nonviral hepatitis
- Noninfectious
  - Autoimmune hepatitis
  - Drug-induced liver injury
  - Metabolic-genetic hepatitis
- Cryptogenic hepatitis

Causes (etiology) of hepatitis

- Infectious
  - Viral hepatitis – most common

- **Hepatotropic viruses**
  - A
  - B
  - C
  - D
  - E
  - G

- **Non-hepatotropic viruses**
  - HSV
  - CMV
  - EBV
  - HIV
  - Rubella
  - Adenoviruses
  - Enteroviruses

Causes (etiology) of hepatitis

- Infectious
  - Viral hepatitis – most common
  - Nonviral hepatitis

- **Non-viral hepatitis**
  - Leptospirosis
  - TB
  - Histoplasmosis
  - Amebiasis

Causes (etiology) of hepatitis

- Noninfectious
  - Autoimmune hepatitis

- **Autoimmune hepatitis**
  - systemic lupus erythematosus
  - juvenile idiopathic arthritis
  - hepatitis with gigantic cells
  - infant autoimmune hemolytic anemia

Causes (etiology) of hepatitis

- Noninfectious
  - Autoimmune hepatitis
  - Drug-induced liver injury

- **Drug-induced hepatitis**
  - Nonsteroidal anti-inflammatory drugs (acetaminophen, ibuprofen, diclofenac)
  - Antibiotics (Erythromycin, Tetracyclines, Amoxicillin-clavulanate)
  - Antituberculosis drug (isoniazid , rifampicin, pyrazinamide)

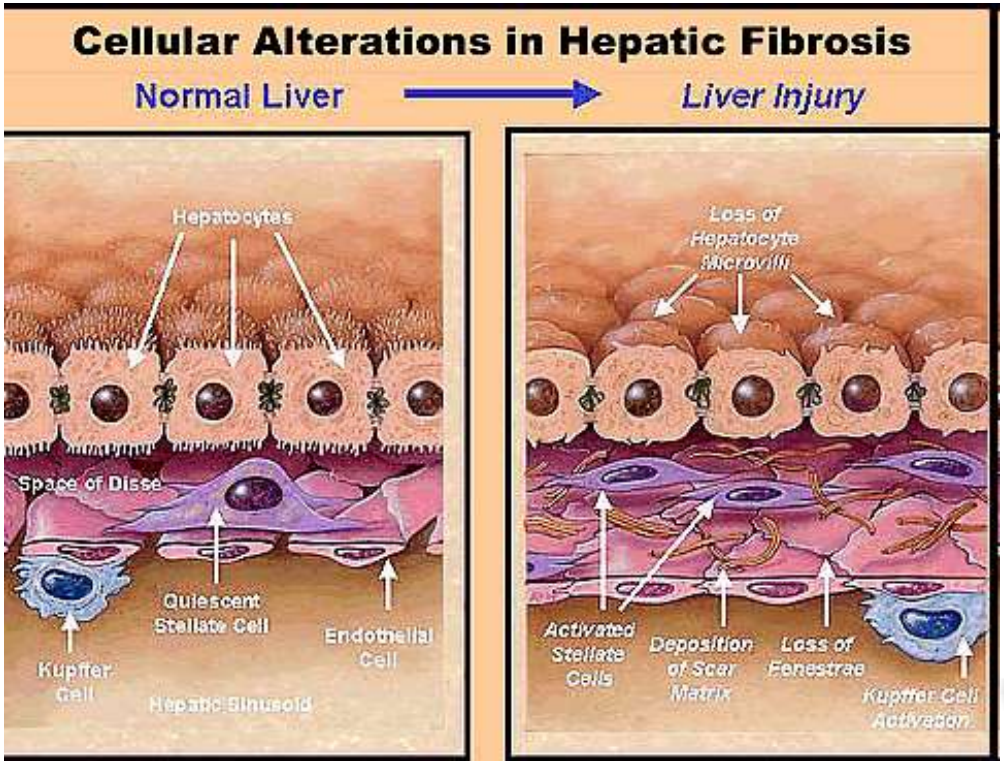
Causes (etiology) of hepatitis

- Noninfectious
  - Autoimmune hepatitis
  - Drug-induced hepatitis
  - Metabolic-genetic (rare diseases) hepatitis

- **Metabolic-genetic hepatitis**
  - Wilson disease
  - cystic fibrosis
  - α1-antitrypsin deficiency
  - haemochromatosis
  - glycogen storage disease type IV

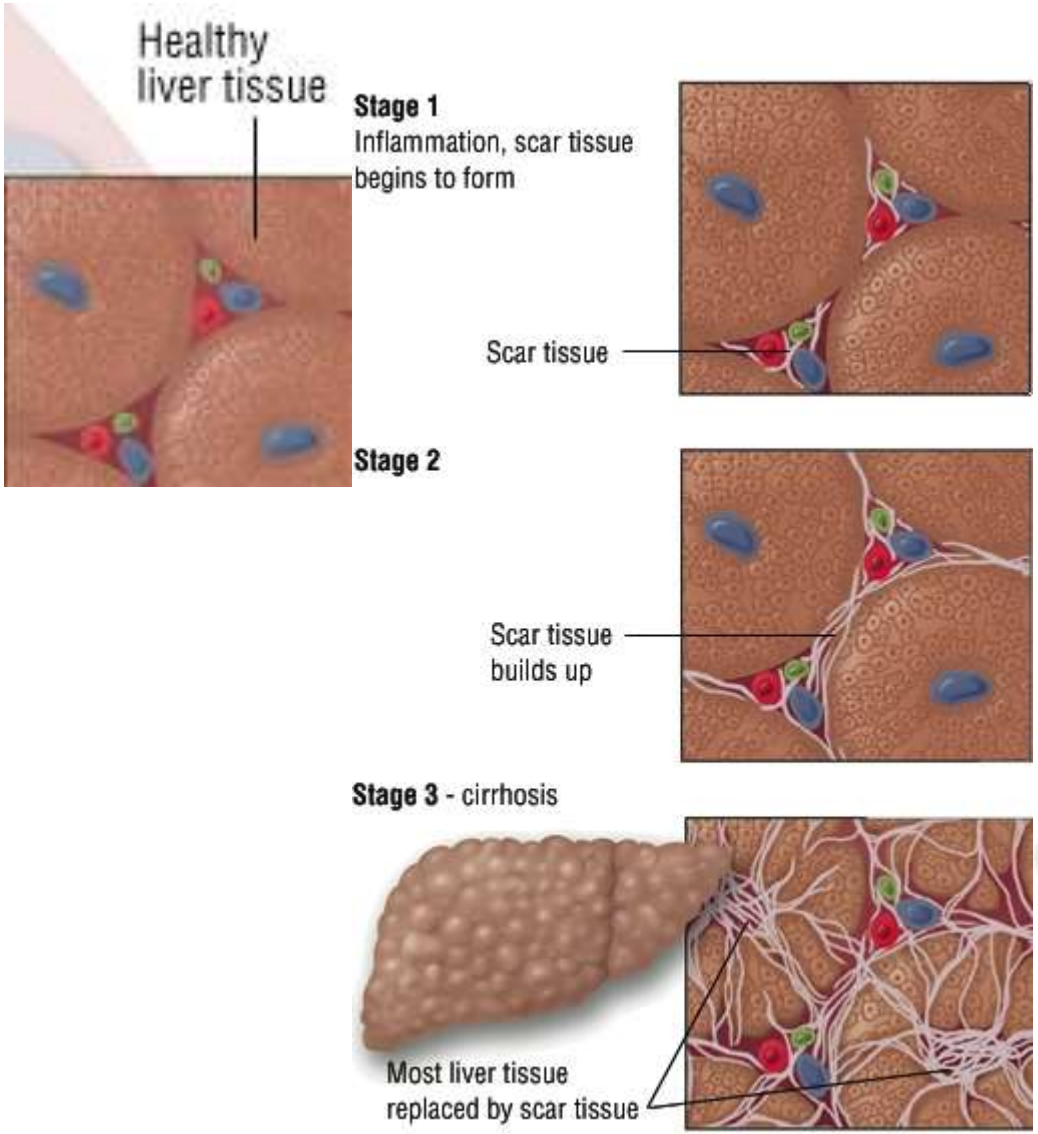
Grade (stage of progression) of chronic hepatitis

Histological assessment of necroinflammatory activity



- Portal inflammation
  - Periportal necrosis
  - Piecemeal necrosis or interface hepatitis
- Bridging necrosis

Severity of chronic hepatitis



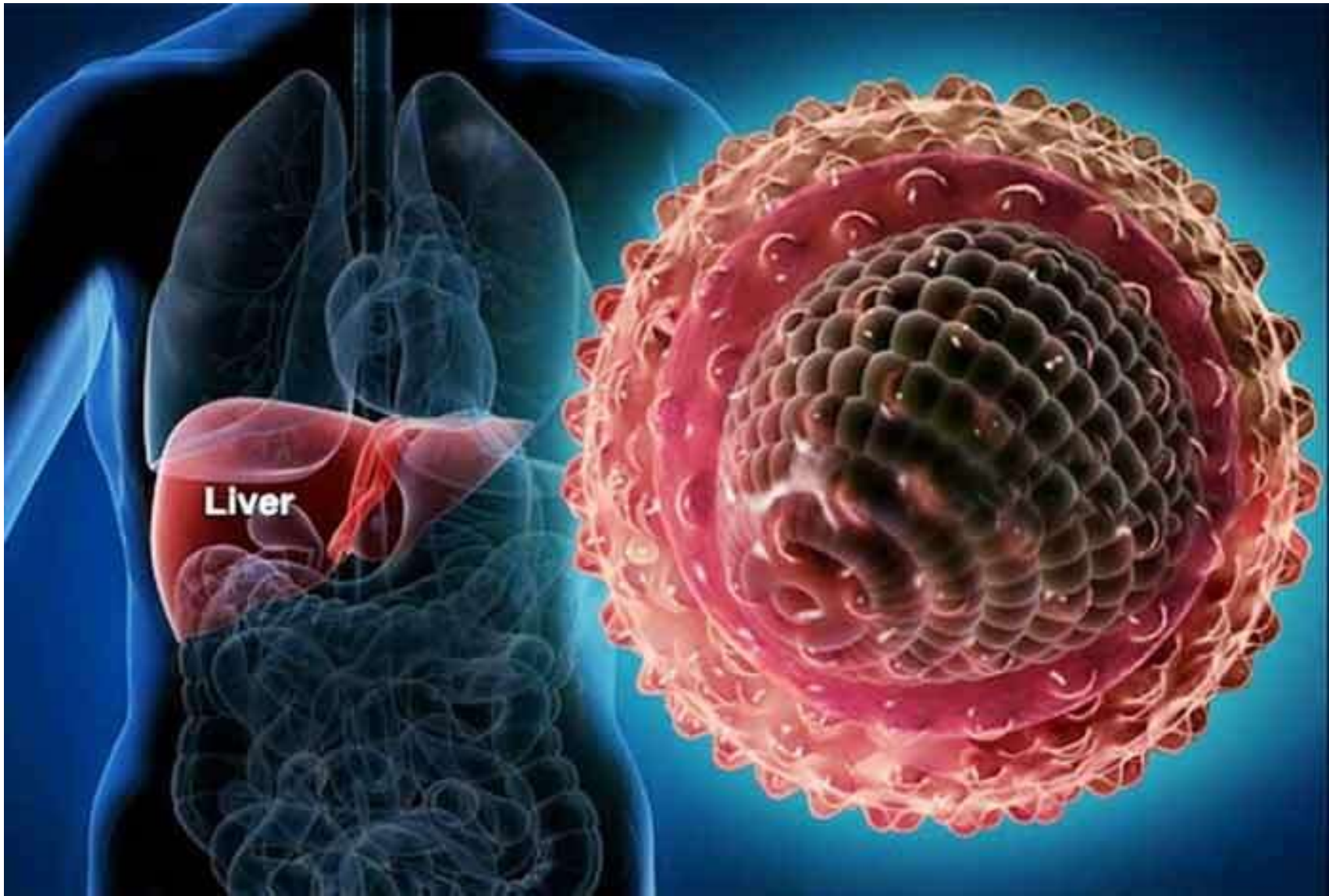
- Level of progression of the disease based on the degree of fibrosis or cirrhosis

KNODELL score

0. NO fibrosis
1. Fibrous portal expansion
2. Bridging fibrosis (portal-portal or portal-central linkage)

3-4. Cirrhosis

Viral hepatitis



Burden of viral hepatitis

The problem of viral hepatitis remains the urgent

- 325 million people were living with viral hepatitis worldwide in 2017, of these
  - 4 million were children living with hepatitis C
  - 48 million were children living with hepatitis B

- Both viruses can lead to chronic liver disease, liver cancer and deaths

CDC Yellow Book 2020: Health Information for International Travel. New York: Oxford University Press; 2017

Viral hepatitis

- Why are the hepatitis viruses considered together?
- Hepatotropic viruses have little in common from a virology standpoint other than that they infect the same organ.
- In general, the symptoms result from the body's immune response, not infection itself.
- The key differences are:
  - Transmission route
  - Incubation period
  - Clinical manifestations
  - Availability of a vaccine
  - Treatment
  - Outcomes

Viruses	Type	Incubation period (days)	Transmission	Chronic infection	Fulminant disease
HAV	**Vaccine Preventable**				
HBV					
HCV	RNA	14-160	Parenteral, sexual, perinatal	Yes	Rare
HDV	RNA	21-42	Parenteral, sexual, perinatal	Yes	Yes
HEV	DNA	21-63	Faeco-oral	No	Yes

Clinical Spectrum of viral hepatitis

- **Subclinical Infection** – serologic and biochemical evidence of infection but asymptomatic
- **Clinical Infection** – signs and symptoms of hepatitis
  - Acute fulminant – massive necrosis
  - Acute self-limited – complete recovery
  - Chronic carrier – usually non-progressive
  - Chronic active – progressive damage +/- symptoms
    - Cirrhosis and liver failure
    - Hepatocellular carcinoma

Clinical presentation in CVH

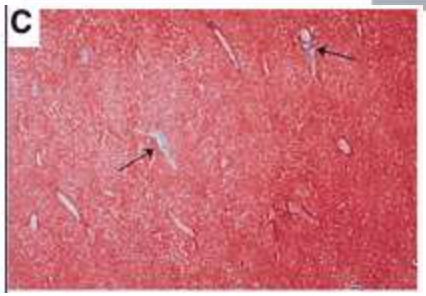
Chronic signs (rare in children)

- Malaise
- Anorexia
- Weight loss
- Easy bruising
- Hepatolienal syndrome
- Hepatomegaly
- Jaundice
- Vascular “stars”
- Red palms (“hepatic palms”)
- Epistaxis
- Petechial rash
- Insidious onset, presence of IV/IM procedures in life history
- Liver – dense, usually painful, smooth surface
- CNS abnormalities: depression, anxiety, anger, irritability, insomnia

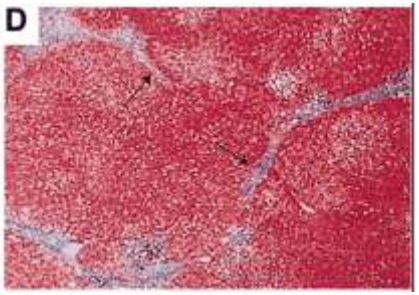
Biochemical Profiles in CVH

1. **Cytopathic injury**
   - Increased AST/ALT
   - Rapidly falling AST/ALT predict poor outcome
2. **Cholestasis**
   - Elevated conjugated billirubin
   - Elevated ALP, 5’ nucleotidase, Urobilinogen, GGT
3. **Altered Synthetic functions**
   - Hypoalbuminaemia
   - Prolonged PT/INR

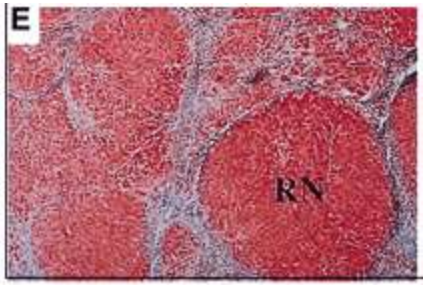
Hepatic biopsy



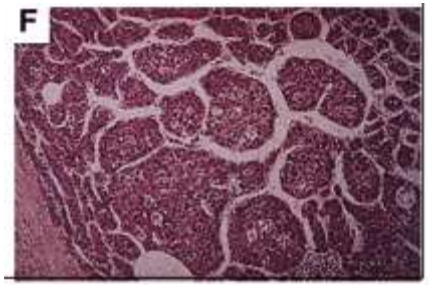
Panel C shows normal liver architecture with scant fibrous tissue (arrows) limited to the portal tracts



During the progressive course of infection, the fibrotic areas expand, and bridging fibrosis develops (arrows in **panel D**)



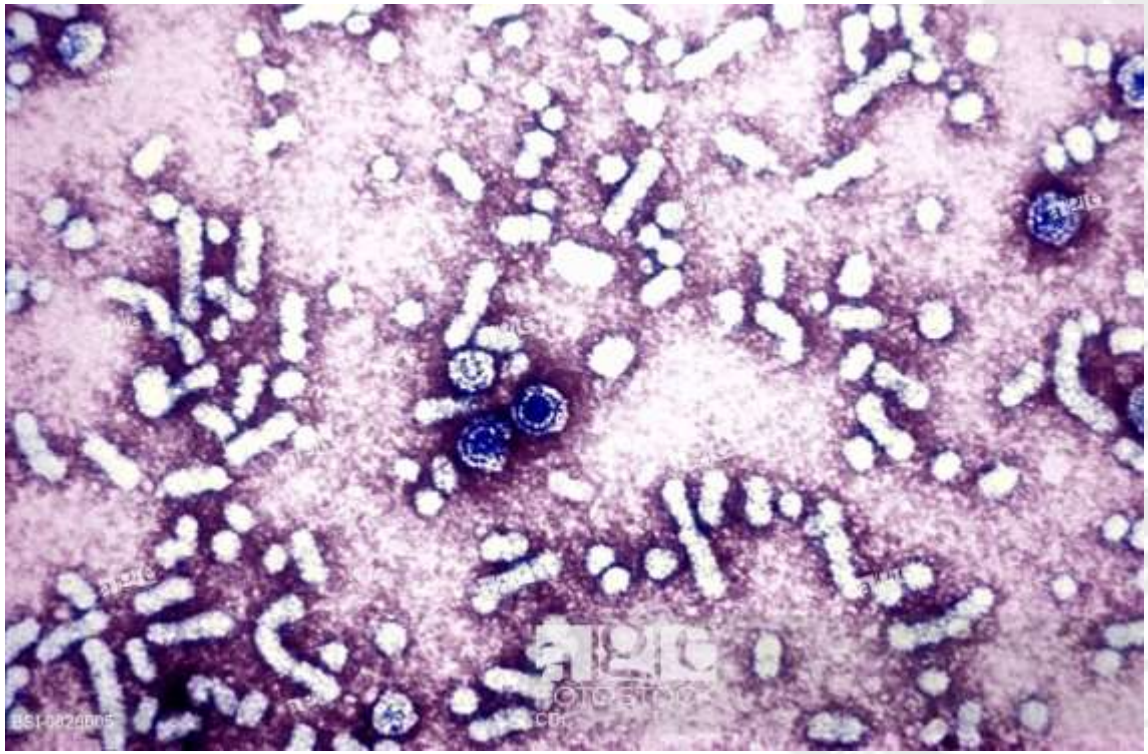
The final stage of cirrhosis (**panel E**) is characterized by marked fibrosis and regenerative nodules



Once cirrhosis has become established, hepatocellular carcinoma (**panel F**) is a feared complication

Lauer GM. *N.Engl J Med*. 2001;345:41-52

Chronic Viral Hepatitis B



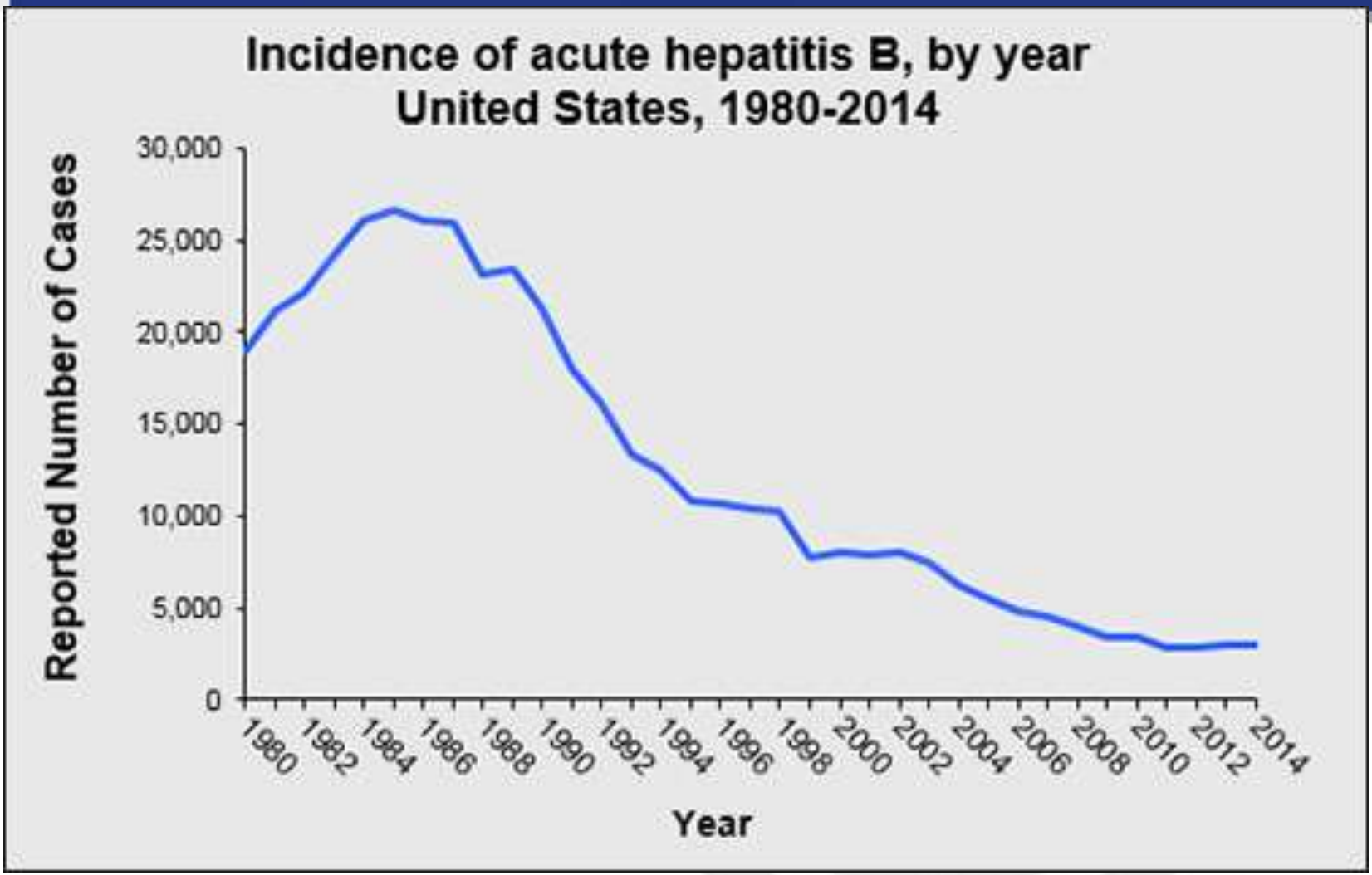
Hepatitis B (HBV) Hepadnaviridae (1970)

Chronic Viral Hepatitis B – Key facts

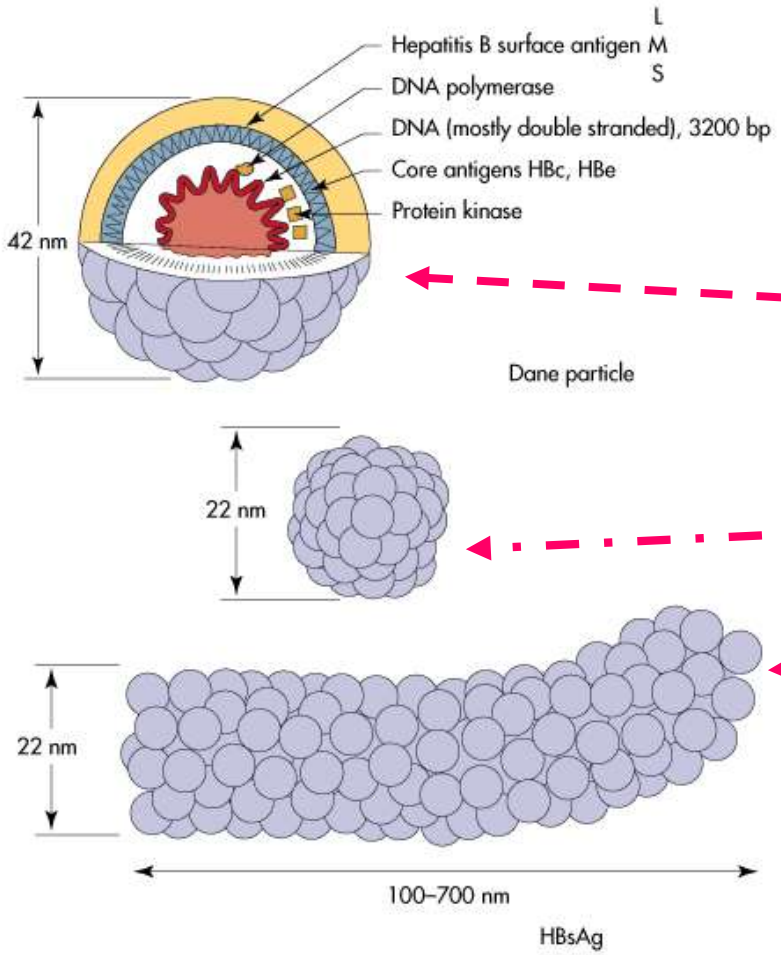
- Hepatitis B is a viral infection that attacks the liver and can cause both acute and chronic disease
- The virus is transmitted through contact with the blood or other body fluids of an infected person
- Hepatitis B virus is 100 times more infectious than the HIV virus
- Chronic hepatitis B is usually diagnosed as a result of a workup for abnormal liver function tests or as a result of screening patients at risk for HBV infection
- Many patients with chronic hepatitis B have no symptoms or have nonspecific symptoms such as fatigue or right upper quadrant discomfort
- However, it can be prevented by currently available safe and effective vaccine

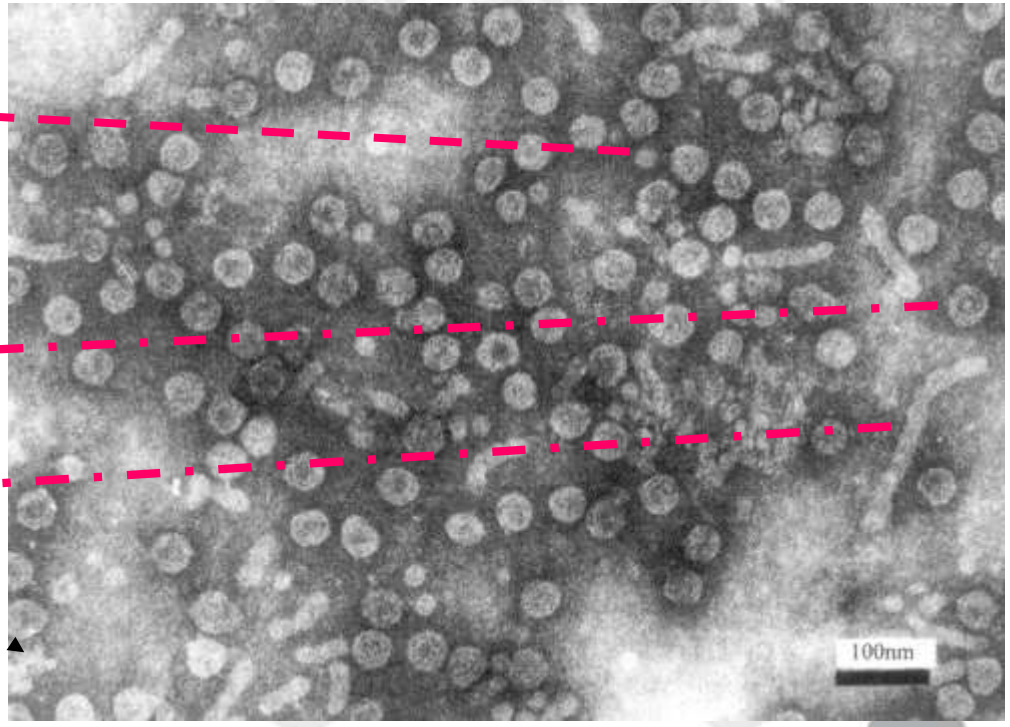
Countries most affected by Hepatitis B

CDC Yellow Book 2020: Health Information for International Travel. New York: Oxford University Press; 2017


Incidence of acute hepatitis B, by year
United States, 1980-2014
Reported Number of Cases
30,000
25,000
20,000
15,000
10,000
5,000
0
1980
1982
1984
1986
1988
1990
1992
1994
1996
1998
2000
2002
2004
2006
2008
2010
2012
2014
Year

Hepatitis B Virus





Transmission routes of HBV

- HVB virus can survive outside the body for at least 7 days
  - During this time, the virus can still cause infection if it enters the body of a person who is not protected by the vaccine.

Incubation period of hepatitis B virus is 75 days on average, but can vary from 30 to 180 days

- The virus may be detected within 30 to 60 days after infection and can persist and develop into chronic hepatitis B

Perinatal transmission – from mother to child at birth

Horizontal transmission (exposure to infected blood), especially from an infected child to an uninfected child during the first 5 years of life

Percutaneous or mucosal exposure to infected blood and various body fluids, as well as through saliva, menstrual, vaginal, and seminal fluids

Infected HBsAg blood during **transfusion** (until 1970)

Transmission of HBV

Perinatal transmission

Perinatal

- 90% of infected infants become chronically infected

Horizontal transmission

- 6% of people infected over the age of 5 become chronically infected

Recipient

Child-to-child
Contaminated needles
Sexual contacts
Healthcare worker
Blood transfusion

CDC. Available at: http://www.cdc.gov/hepatitis. Accessed December 2006.
Lee WM. *N Engl J Med*. 1997;337:1733-1745.
Lavanchy D. *J Viral Hepat*. 2004;11:97-107.

Hepatitis B Perinatal Transmission*

- If mother positive for HBsAg and HBeAg
  - 70-90% of infants infected
  - 90% of infected infants become chronically infected

- If positive for HBsAg only
  - 5-20% of infants infected
  - 90% of infected infants become chronically infected

*in the absence of postexposure prophylaxis

Concentration of Hepatitis B Virus in Various Body Fluids

High	Moderate	Low/Not detectable
blood	semen	urine
serum	vaginal fluid	feces
wound exudates	saliva	sweat
		tears
		breastmilk

CDC: Viral Hepatitis Surveillance Program, 2015

Chronic Hepatitis B Infection in Pediatrics

- Mostly asymptomatic
- Normal growth
- Liver damage mild during childhood
- Cirrhosis, hepatocellular carcinoma at any age

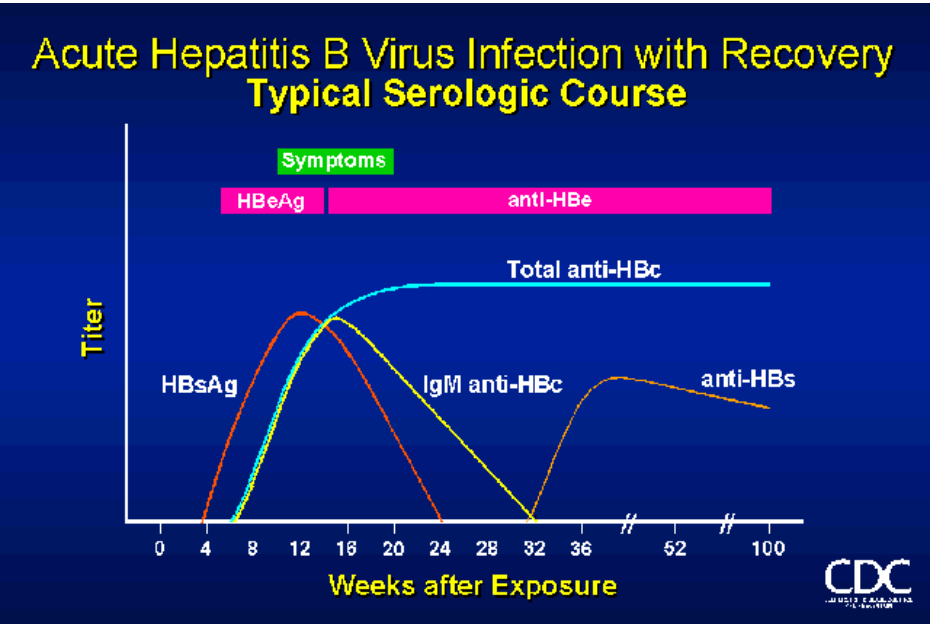
Natural History of Chronic HBV in Pediatrics

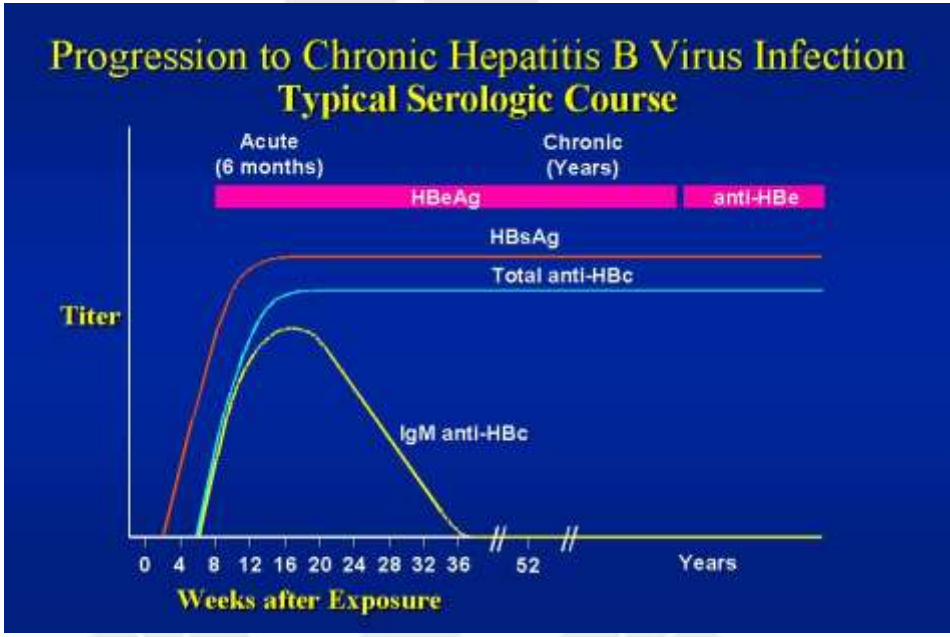
- HBeAb seroconversion rate 55% in 12 years
- Lower seroconversion in vertical transmitted (38.5%) *vs.* horizontal (74%)
- Loss of HBsAg seen in 5%

Diagnostic Interpretations of Hepatitis B markers

HBsAg	Non infectious component of viral coat	Indicator of disease. If > 6 months: chronic HBV
Anti-HBs	Antibody response to HBsAg	Indicates recovery and/or immunity
HBeAg	Antigen that correlates with replication and infectivity	High level of infectivity and replication
Anti-HBe	Antibody response to HBeAg	Decreasing level of replication Remission/resolution
Anti-HBc IgM	Non protective antibody to the HBcAg	Recent HBV infection
Anti-HBc IgG	As above	Acute or remote exposure to HBV
HBV DNA	Replictative genetic material of HBV; infectious agent	Viral replication and continues infection

Immunological events of acute vs. chronic HBV infection





Murray et. al., Medical Microbiology 5th edition, 2005

Common serological pattern in HVB

HBsAg	Anti-HBs	Anti-HBc	HBeAg	Anti-HBe	Interpretation
+	-	IgM	+	-	Acute infection
+	-	IgG	+	-	CHB, active viral replication
+	-	IgG	-	+	CHB, low viral replication
+	+	IgG	+/-	+/-	CHB, heterotypic anti-HBs
-	-	IgM	+/-	-	Acute window
-	+	IgG	-	+/-	Recovery from Hepatitis B (immunity)
-	+	-	-	-	Vaccination (immunity)
-	-	IgG	-	-	False positive, less commonly, infection in remote past

Chronic Carrier State

- 10% / yr lose HBeAg – become noninfectious
- 1-2% / yr lose HBsAg – become non-carriers
- 25 % will develop chronic active disease
- 40% will develop cirrhosis
- 5% will develop hepatocellular cancer

HBV causes 85% of primary liver cancer worldwide

Who to treat?

- Children with chronic HBV (HBsAg > 6 months)
- Children born from mothers with acute or chronic VHB or carrier of HBsAg, must be followed at 2, 3, 6, and 12 month after their discharge fromn the hospital (transaminase activity and blood markers are done after 6 month)

- **Indications**
  - Cytolysis >> 2 x normal values > 12 month
  - Liver biopsy – necrosis, marked inflammation, reduced fibrosis
  - HBeAg + and/or VHB DNA +
  - Functional immune system (no primary or secondary immunodeficiency)
  - No cardiac, renal, immune failures, healthy mental status

- **Better Response to treatment**
  - High ALT
  - Inflammation in biopsy
  - Low HBV DNA
  - Late acquisition of infection

Contraindications for antiviral treatment

- Hepatic decompensation
  - albumin <3.0 g/l
  - bilirubin >51.3 µ mol/l (30 mg/l)
  - prolonged prothrombin time >3.0 s
- Portal hypertension: variceal bleeding, ascites, encephalopathy
- Hypersplenism
  - leukopenia (<2 x 109/l)
  - thrombocytopenia (<7 x 109/l)
- Psychiatric depression: severe, suicide attempt
- Autoimmune disease: polyarteritis nodosa, rheumatoid arthritis, thyroiditis
- Major system impairment: cardiac failure, obstructive airways disease, uncontrolled diabetes
- Pregnancy
- Current intravenous drug abuse
- Hypersensibility to IFN-α

Goals of treatment in Pediatric population

- Reducing the risk of HBV related cirrhosis and HCC
- Elimination of HBeAg may considerable improve prognosis

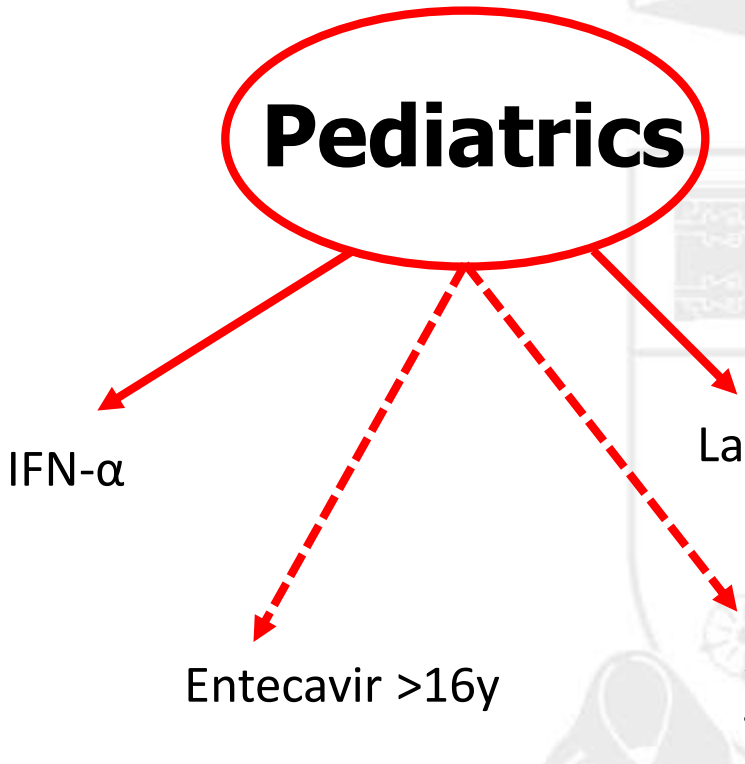
Treatment precautions

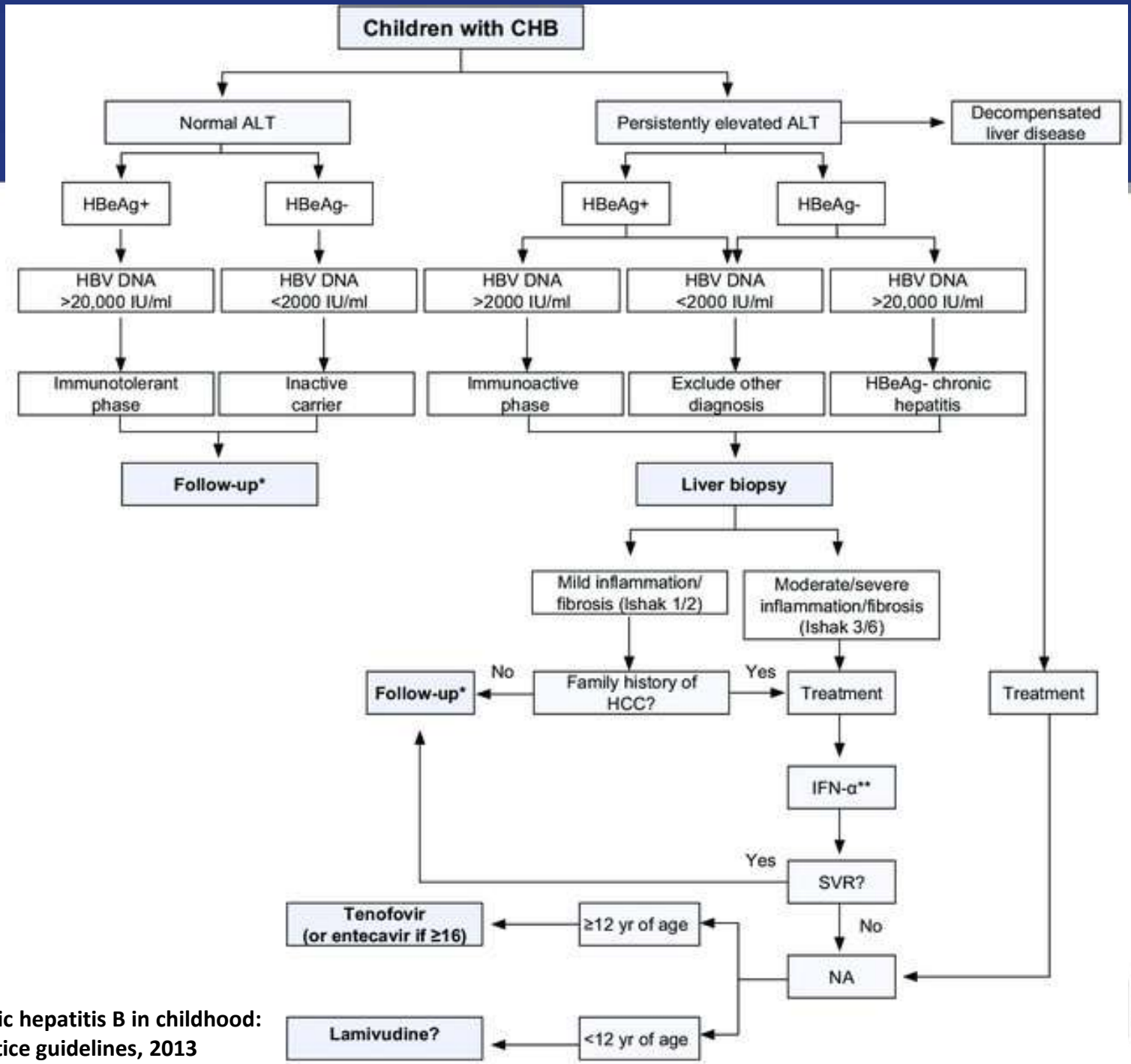
- **Monthly tests:**
  - full blood count,
  - bilirubin, ALT, AST, GGT,
  - blood coagulation

- **Once in 3, 6, 9 month, 1, 2, and 4 years:**
  - HBeAg,
  - DNA VHB viral load

- **Once in 6, 12 month:**
  - abdominal ultrasound (Doppler in hepatosplenomegaly or portal hypertension signs)

How to treat?



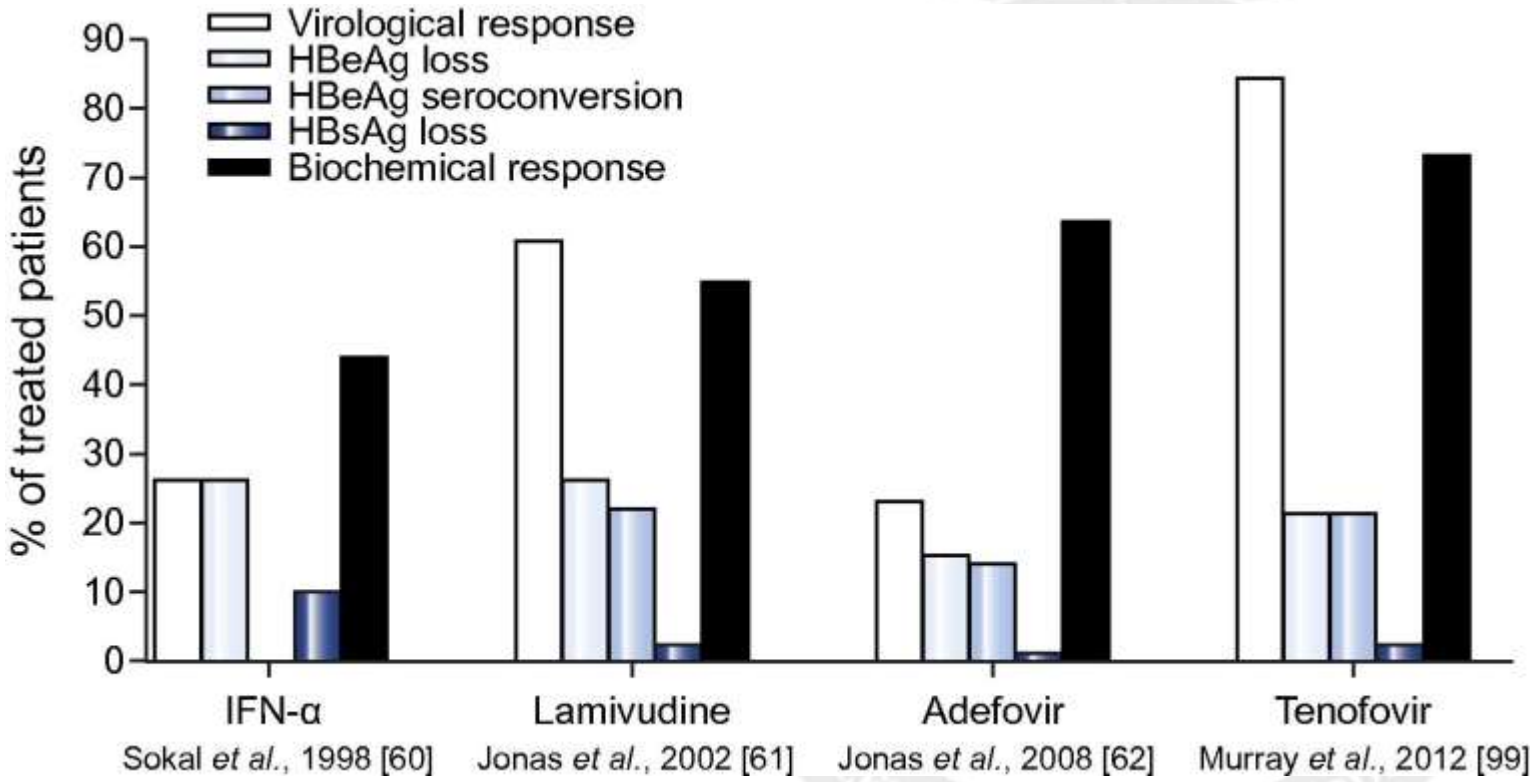


Management of chronic hepatitis B in childhood: ESPGHAN clinical practice guidelines, 2013

Treatment	Licensing	Dose	Duration	Advantages	Disadvantages
IFN-α	≥12 mo	5-10 M units/m² sc three times weekly	6 mo	• No resistance • Licensed for young children • Short treatment	• Side effects • Parenteral administration • Not usable if decompensated cirrhosis or transplantation
Lamivudine	≥3 yr	3 mg/kg po once daily (max 100 mg/die)	≥1 yr	• Few side effects • Oral administration • Usable in 3rd trimester of pregnancy	• High resistance rate (increasing with time of treatment)
Adefovir	≥12 yr	10 mg po once daily	≥1 yr (+ 6 mo after HBeAg seroconversion)	• Partially effective in lamivudine resistant patients • Oral administration	• Not approved for children <12 yr • High resistance rate (increasing with time of treatment)
Entecavir	≥16 yr + phase III (2-17 yr)	0.5 mg po once daily (1 mg/day for lamivudine-resistant pts)	≥1 yr (+ 6 mo after HBeAg seroconversion)	• Low resistance rate • Oral administration	• Not approved for children <16 yr
Tenofovir	≥12 yr	300 mg po once daily	≥1 yr	• High response rate • No resistance identified • Few side effects • Oral administration • Usable in 3rd trimester of pregnancy	• Not approved for children <12 yr • Reduced mineral density in children
PegIFNα	Phase III (2-18 yr)	180 µg/wk	6 mo	• No resistance • Once weekly administration • Short treatment	• Side effects • Parenteral administration • Not usable if decompensated cirrhosis or transplantation
Telbivudine	Phase I (2-18 yr)	600 mg po once daily	≥1 yr	• Few side effects • Oral administration • Usable in 3rd trimester of pregnancy	• High resistance rate

Management of chronic hepatitis B in childhood: ESPGHAN clinical practice guidelines, 2013

Efficacy of currently available therapies



Journal of Hepatology 2013 59814-829DOI: (10.1016/j.jhep.2013.05.016)

Prevention of Hepatitis B

Universal precautions

- Obligatory examination of blood donors for HBsAg detection
- Prohibition of hemotransfusion and use of blood derivatives marked positive for HBsAg
- Use of disposable instruments
- Education (needles, sex)

Hepatitis B Immunoglobulin (HBIG)

- May be used to protect persons who are exposed to hepatitis B
- It is particular efficient within 48 hours from the moment of incident
- It may also be given to neonates whose mothers are HBsAg and HBeAg positive

Hepatitis B vaccine (HepB)

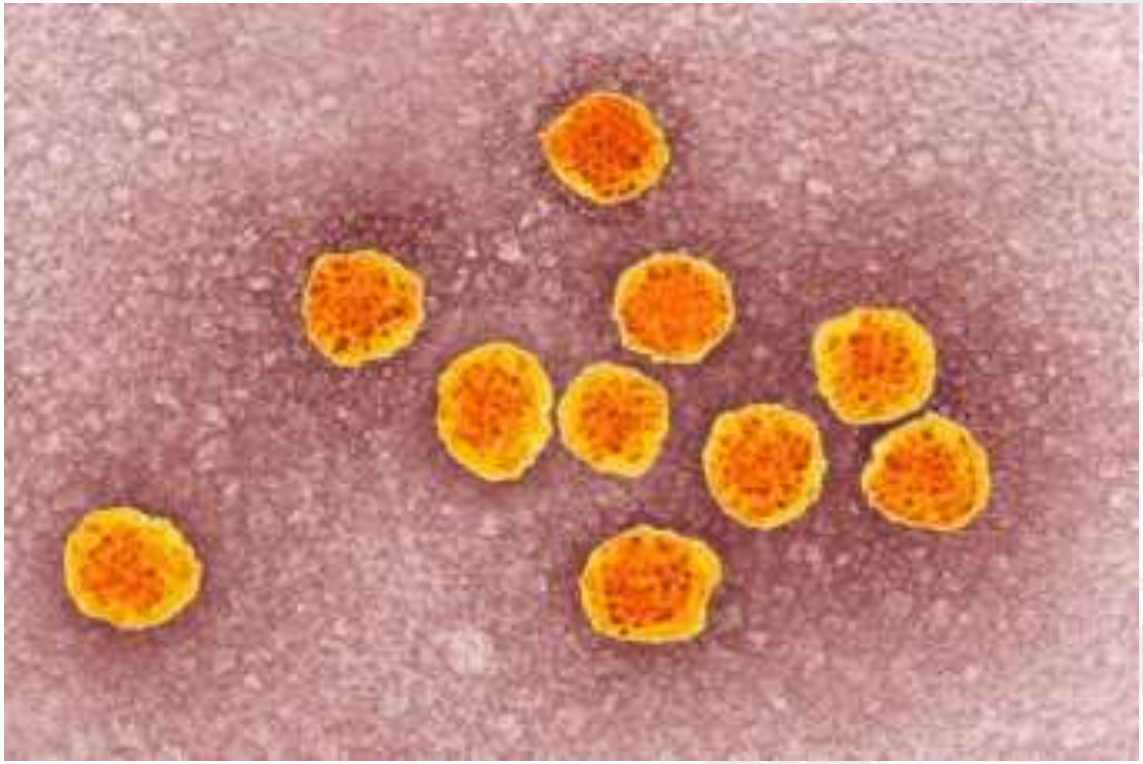
- 1965 – discovery of hepatitis B virus ("Australia Antigen“, now HBsAg)
- 1971 – developing a blood test for the hepatitis B, used by blood banks to screen donors → decreased VHB risk transfusion 25%
- 1981 – FDA approved plasma-derived hepatitis B vaccine (“inactivated” type of vaccine), discontinued in 1990
- 1986 – genetically engineered (or DNA recombinant) hepatitis B vaccines
- A primary 2 to 3-dose series induces **protective antibody concentrations in >95%** of healthy infants, children and young adults

Calendarul vaccinărilor 2016-2020

Vîrsta efectuării vaccinării	Imunizarea împotriva										Note
	Hepatitei virale B **(HepB)**	Tuberculozei **(BCG)**	Poliomielitei **(bVPO/ VPI)**	Infecţiei cu rotavirus **(RV)**	Infecţiei Hib **(Hib)**	Infecţiei cu pneumococi **(PC)**	Difteriei, tetanosului pertusei **(DTP)**	Difteriei, tetanosului **(DT/Td)**	Rujeola oreion rubeola **(ROR)**	Papiloma- virusul uman **(PVU)**	
24 ore	HepB-0										În maternitate
2-5 zile		BCG 1									În maternitate
2 luni	HepB-1*		bVPO-1	RV-1	Hib-1*	PC-1	DTP-1*				*Concomitent în aceeaşi zi: injectabil intramuscular HepB+DTP+Hib în componenţa vaccinului pentavalent, PC şi VPI separat cu diferite seringi şi în diferite locuri anatomice; bVPO şi RV picături în gură
4 luni	HepB-2*		bVPO-2	RV-2	Hib-2*	PC-2	DTP-2*				
6 luni	HepB-3*		bVPO-3 VPI		Hib-3*		DTP-3*				
12 luni						PC-3			ROR-1		Separat cu diferite seringi şi în diferite locuri anatomice
22-24 luni			bVPO-4				DTP-4				Concomitent, peste 16-18 luni după vaccinare
6-7 ani			bVPO-5					DT	ROR-2		bVPO-5 şi DT – concomitent primăvara, pînă la admiterea copiilor la şcoală; ROR-2 toamna (în clasa I)
12 ani fetele										PVU-1 PVU-2	Conform instrucţiunii de utilizare a vaccinului
15-16 ani								Td	ROR-3		Concomitent (clasa 9), separat cu diferite seringi şi în diferite locuri anatomice
Adulţii: la 20, 30, 40, 50 şi 60 ani								Td			Imunizarea este efectuată la atingerea vîrstei indicate

Notă:
1.Vaccinările opţionale împotriva altor boli infecţioase (rabia, gripa, hepatita virală A, infecţia meningococică, varicela, holera, tularemia, febra tifoidă, bruceloza etc.) va fi efectuată grupelor de populaţie cu risc sporit de infectare, în funcţie de situaţia epidemiologică şi în conformitate cu deciziile Ministerului Sănătăţii, precum şi în mod individual, inclusiv contra plată.
2. Imunizarea împotriva febrei galbene, encefalitei acariene, pestei va fi aplicată persoanelor care pleacă în regiunile endemice în mod individual, inclusiv contra plată.

Hepatitis C Virus (HCV)



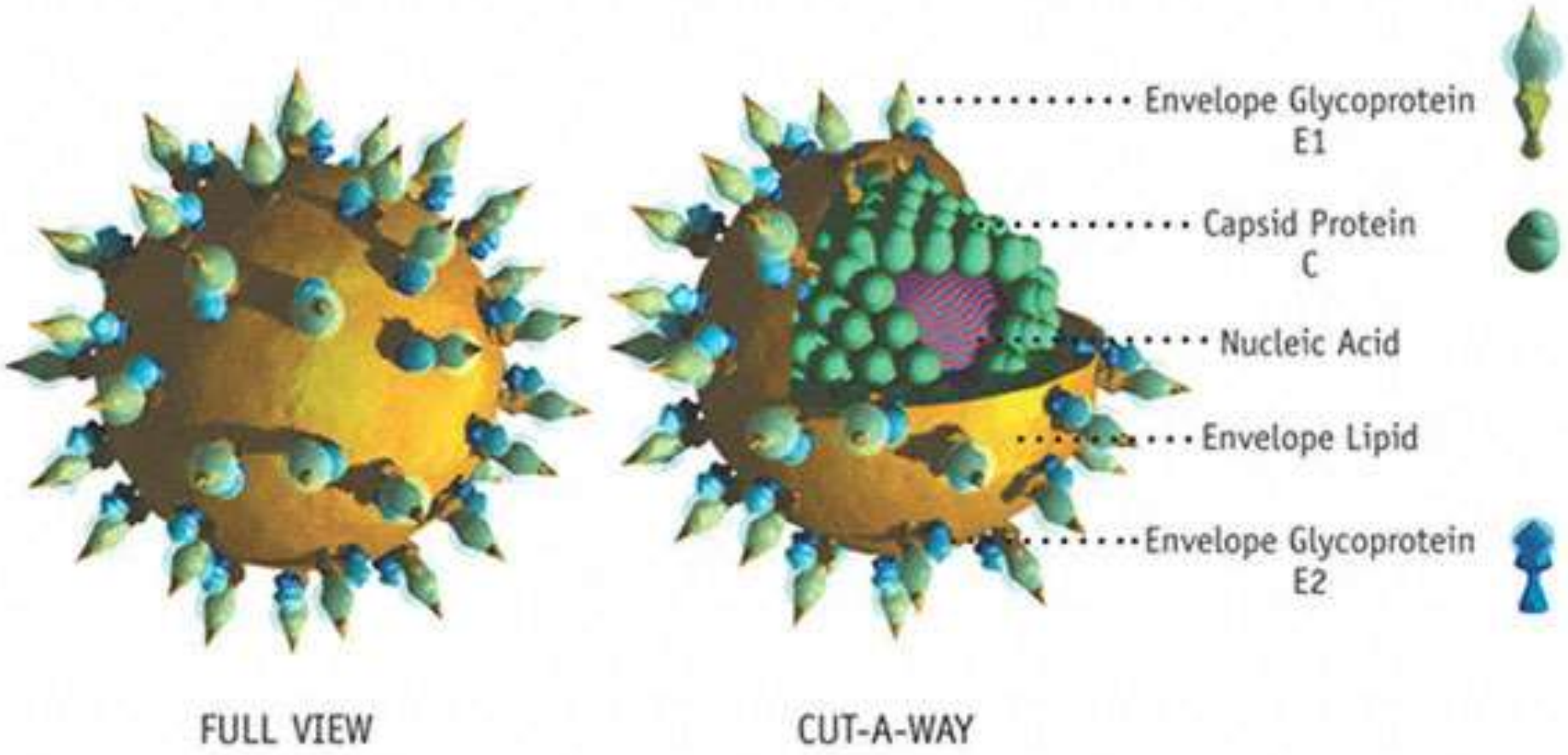
Hepatitis C (HcV) Flaviviridae (1989)

Hepatitis C

"transfusion related non-A, non-B hepatitis"

- **No vaccine available!**
- 6 genotypes worldwide, many subtypes and isolates based on nucleotide diversity
- Genotype does not influence disease progression but does affect response to antiviral treatment (Genotypes 2 and 3 more responsive to alpha-interferon therapy than Genotype 1)
- Affects each person differently
- Usually asymptomatic or mild disease
- Chronic infection very common
- 20% of community acquired hepatitis
- 90% post-transfusion hepatitis (prior to 1992)
  - Blood banks started screening in 1992: <1% risk now

Model of the Human Hepatitis C Virus



- The lipid envelope contains glycoproteins E1 and E2 (as a heterodimer)
- Inside the envelope is the viral capsid which contains the HCV genome

Prevalence of Hepatitis C

- 10 000-60 000 newborn will be infected worldwide yearly
- 115 M subjects globally (1.6% world's population) - 11 M < 15 years
- 5 M viremic and in need of therapy
- China, Pakistan, Nigeria, Egypt, India, and Russia account for >50% of the total pediatric infections
- Prevalence varies ranging from 0.05% to 0.36% in the US and Europe to 1.8% to 5.8% in some developing countries
- Children : adults varies from 1:25 in high income countries, to 1:4 in middle-income countries, as high as 1:2 in low-income countries

El-Kamary SS. *J Pediatr*. **143**:54-9, 2003.
Jonas MM. *J Pediatr*. **131**:314-6, 1997.
Yeung LT. *Hepatology*. **34**:223-9, 2001.
Aletr MJ. N Engl J Med. 341; 556-62. 1999

Countries most affected by hepatitis C

CDC Yellow Book 2020: Health Information for International Travel. New York: Oxford University Press; 2017

Transmission of HCV

Perinatal Transmission of Hepatitis C

- 3.7% of the infants acquired HCV
- Infection rate in HIV positive mothers, 25%
- Role of viral titer unclear
- Infected infants do well – severe hepatitis is rare

Risk Factors for Vertical Transmission of Hepatitis C

Does not increase vertical transmission

- Breast feeding
  - HCV detected in breast milk and colostrum
  - Rate of transmission identical to bottle-fed infants
  - Safety based on the absence of traumatized, cracked or bleeding nipples
- Delivery method

Does increase vertical transmission

- Use of internal fetal monitoring devices
- High viral loads
- Prolonged rupture of membranes (>6 h)
- HIV co-infection

Clinical Features of VHC

- Incubation period: Average 6-7 wks
  Range 2-26 wks
- Clinical illness (jaundice): 30-40% (20-30%)
- Chronic hepatitis: 75-85%
- Persistent infection: 85-100%
- Immunity: No protective antibody response
- Case fatality rate Low, no fulminant forms
- Cirrhosis 10-20%
- Chronic Liver Disease Mortality 1%-5%
  - Chronic disease often improves after 2-3 years
  - Increases risk of liver cancer

Clinical Features of VHC in Pediatrics

- Normal growth
- Mostly are asymptomatic
- Hepatomegaly 2-61%
- Elevated liver enzymes 44-93%

Hepatitis C Diagnosis

1. Symptoms
2. Elevated level of liver enzymes
3. Rule out other causes of hepatitis
4. Confirmed by serology
   - Serologic test detects HCV antibody
   - Positive in chronic cases
   - May not be positive in acute phase
   - Rule out other causes of acute hepatitis

Laboratory Diagnosis

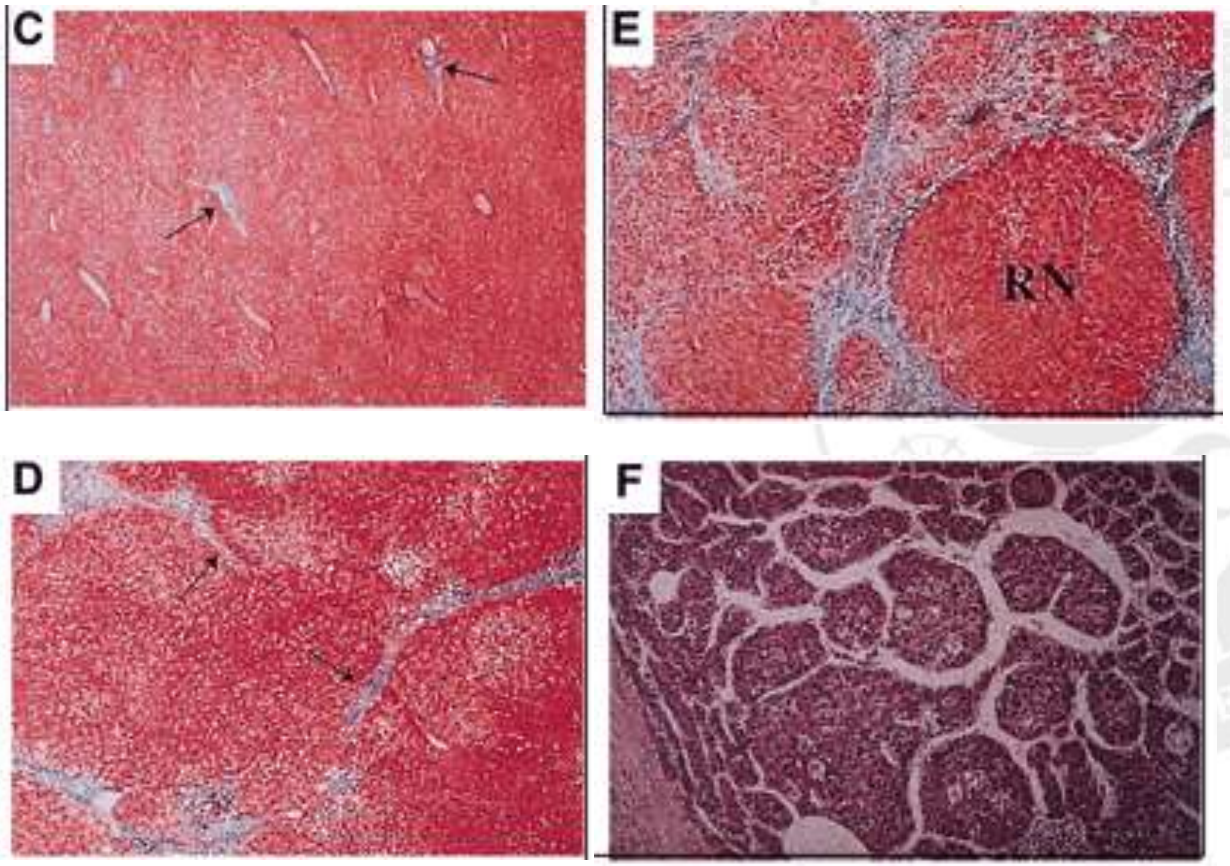
- HCV antibody
  - generally used to diagnose hepatitis C infection
  - not useful in the acute phase as it takes at least 4 weeks (10-30 weeks) after infection before antibody appears
- HCV-RNA
  - various techniques are available e.g. PCR and branched DNA
  - may be used to diagnose HCV infection in the acute phase
  - however, its main use is in monitoring the response to antiviral therapy
  - HCV-RNA disappear after 6 month of treatment in 50-95%
- HCV-antigen
  - an EIA for HCV antigen is available
  - it is used in the same capacity as HCV-RNA tests but is much easier to carry out

Biochemical Indicators of Hepatitis C Virus Infection

- In chronic hepatitis C, **increases in the alanine and aspartate aminotransferases** range from 0 to 20 times (but usually less than 5 times) the upper limit of normal
- **ALT levels are usually higher than AST levels**, but that finding may be reversed in patients who have cirrhosis
- **Alkaline phosphatase** and **gamma glutamyl transpeptidase** are usually normal, if elevated, they may indicate cirrhosis
- **Rheumatoid factor, low platelet and white blood cell counts** are frequent in patients with cirrhosis, providing clues to the presence of advanced disease
- The enzymes **lactate dehydrogenase** and **creatine kinase** are usually normal
- **Albumin levels** and **prothrombin time** are normal until late-stage disease
- **Iron** and **ferritin** levels may be slightly elevated

Liver biopsy

- Liver biopsy is not necessary for diagnosis but is helpful for grading the severity of disease and staging the degree of fibrosis and permanent architectural damage



Diagnosis of Hepatitis C

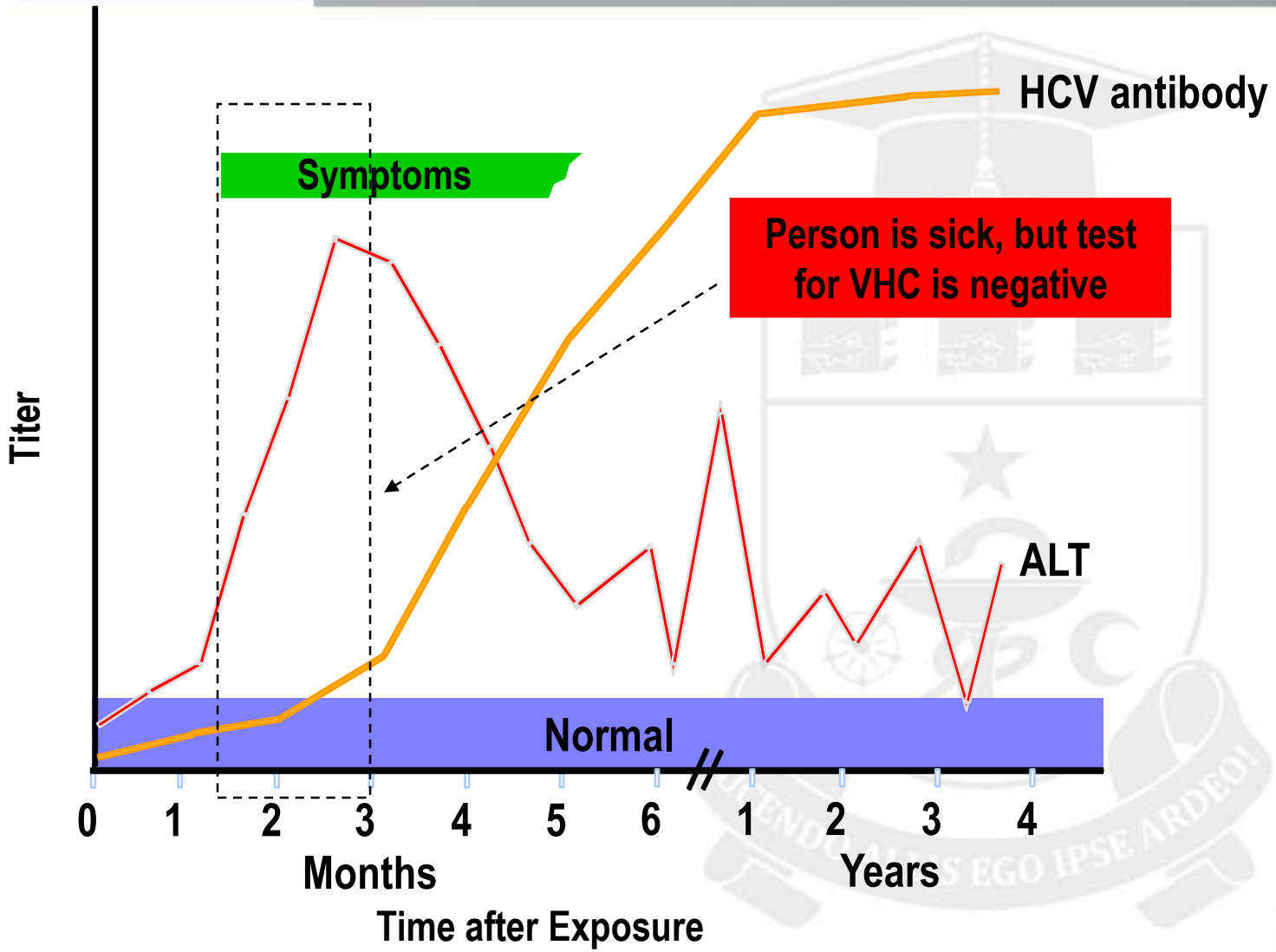
HCV antibodies (IgG)

- Initial screening
- Diagnosis

HCV RNA PCR
(quantitative/qualitative)

- Confirmation of Diagnosis (qualitative)
- Pretreatment evaluation
- Post treatment monitor

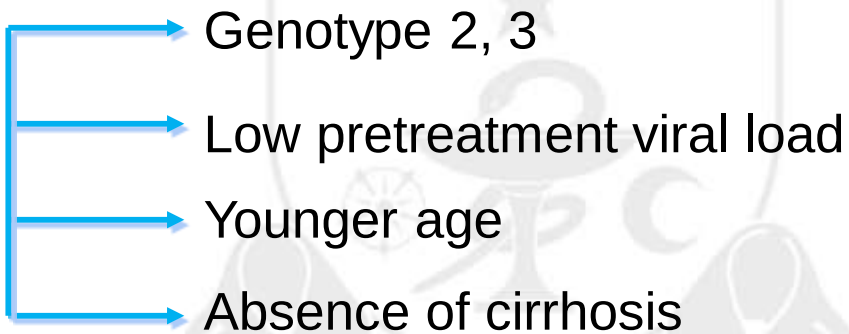
Typical Serologic Course in VHC



Antiviral Therapy for Chronic Hepatitis C
Old recomendations

- Presently available treatments for pediatric CHC (1-12 years)

- **Combined PEG interferon and Ribavarin**
  - 45-62% sustained virological response
  - Better response



Pediatric Hepatitis C Infection. EPSGHAN. JPGN, 2012

Interferon-A

- May be considered for patients with chronic active hepatitis
- 3 million units/ 3 times weekly for 6-12 month
- The response rate is around 50%, but ½ of responders will relapse upon withdrawal of treatment
- **Side effects**
  - with immunomediated mechanism: autoimmune thyroiditis, autoimmune hepatitis
  - other autoimmune manifestations: lupus-like disease, rheumatoid arthritis, diabetes melitus, autoimmune hemolytic anemia, immune thrombocytopenia)
- If autoimmune manifestations appear after initiation of interferon-A therapy the clinical and serological changes should be investigated, the diagnostic should be reconsidered and than the therapy with INF must be stopped if needed

Ribavirin

- Ribavirin is an oral nucleoside analogue with broad activity against viral pathogens and has immunomodulatory effects
- The addition of ribavirin to IFN-a treatment dramatically improved SVR (up to 30-40%) and the end-of-treatment response
- Combination treatment also results in a significant decrease in the relapse rate of HCV infection as compared with PEG-IFN-a monotherapy

- **Side effects**
  - Anemia/Thrombocytopenia
  - Fetal malformations

Antiviral Therapy for Hepatitis C

New recomendations

- Preferred regimens in the WHO guidelines – **direct-acting antivirals based on genotype and cirrhosis status**
  - **Sofosbuvir, daclatasvir** and **sofosbuvir/ledipasvir**
- Can achieve cure rates above 95%
- Are much more effective, safer and better-tolerated than the older therapies
- WHO is currently updating its treatment guidelines to include pangenotypic

Treatment of Chronic Hepatitis C Virus Infection in Children. ESPGHAN, 2018

Direct-acting antivirals based on genotype of hepatitis C virus

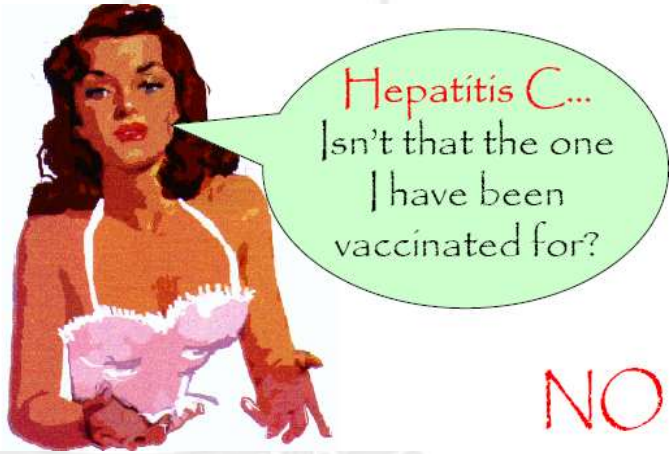
In 2017, the European Medicines Agency and the Food and Drug Administration approved for the treatment of adolescents (12-17 years or weighing >35 kg) with chronic hepatitis C virus the use of

- the fixed-dose combination of ledipasvir/sofosbuvir for genotype 1, 4, 5, and 6
- the combination of sofosbuvir and ribavirin for genotype 2 and 3
- Although trials with direct-acting antivirals are ongoing for younger children, the only available treatment in the United States and Europe for those **<12 years is still the dual therapy of pegylated interferon and ribavirin**.

Treatment of Chronic Hepatitis C Virus Infection in Children. ESPGHAN, 2018

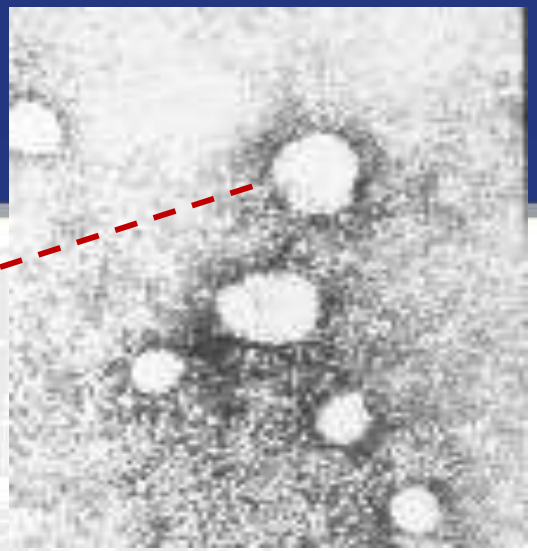
Prevention of Hepatitis C

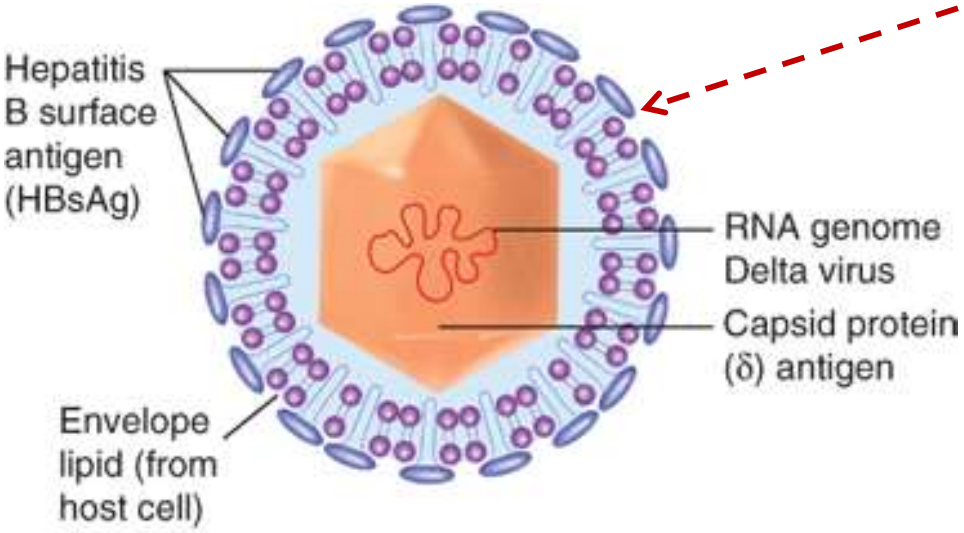
- Screening of blood, organ, tissue donors
- Household contacts: avoid sharing of shavers, toothbrushes, nail clippers, tweezers
- Education
  - High-risk behavior modification
  - Same risk factors as hepatitis B
  - Blood > sex > Perinatal



- HCV vaccine: none available
- HCV immune globulin: none available

Viral Hepatitis D



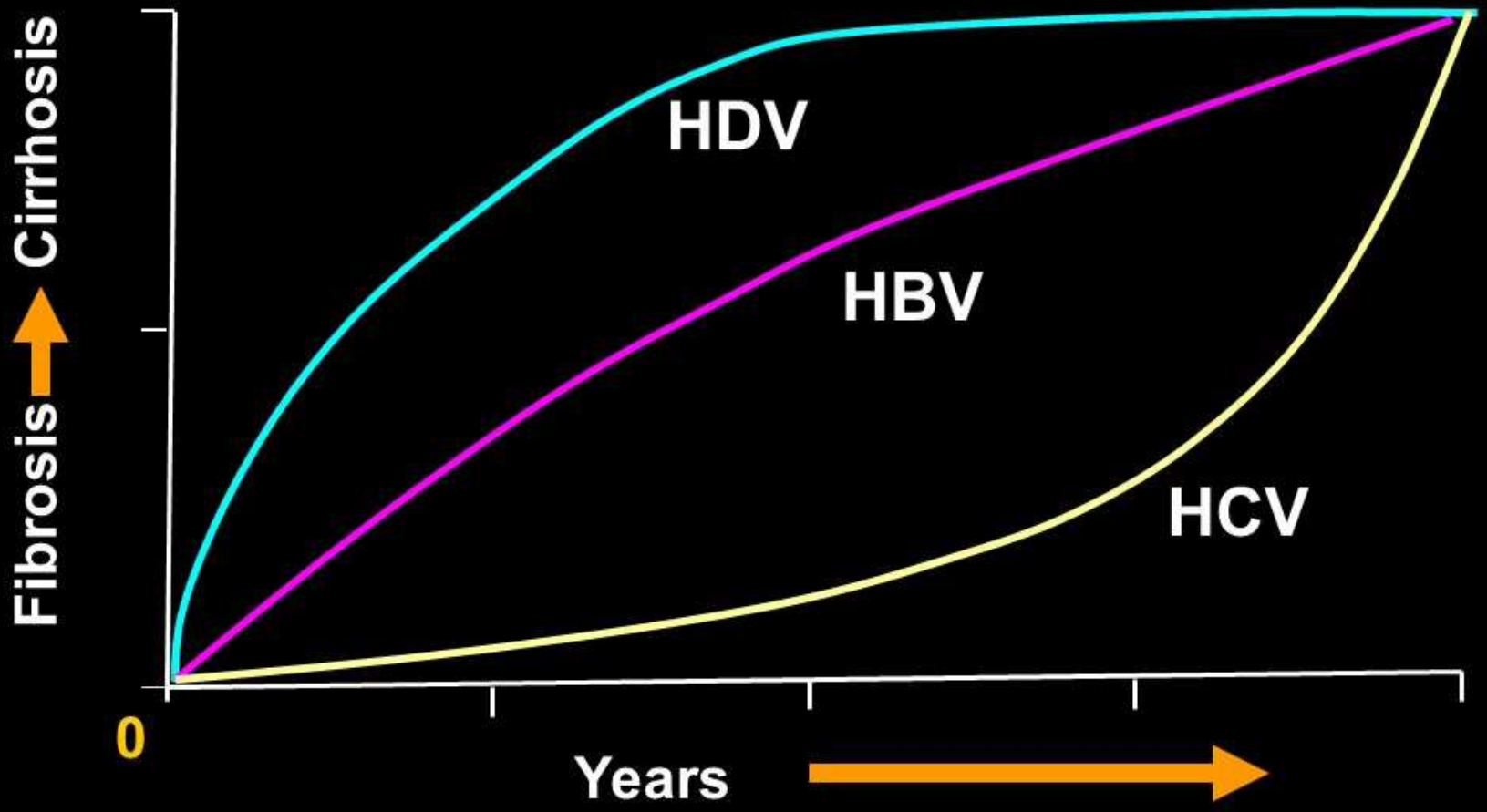


Hepatitis D (HDV) (1977)

- Virus-like particle
- Defective RNA virus
- VHD genome is covered by HBsAg
- Requires HBV co-infection to replicate
- Incubation phase: 20-90 days
- Highly pathogenic

ANYONE WHO IS HBsAg(+) IS AT RISK

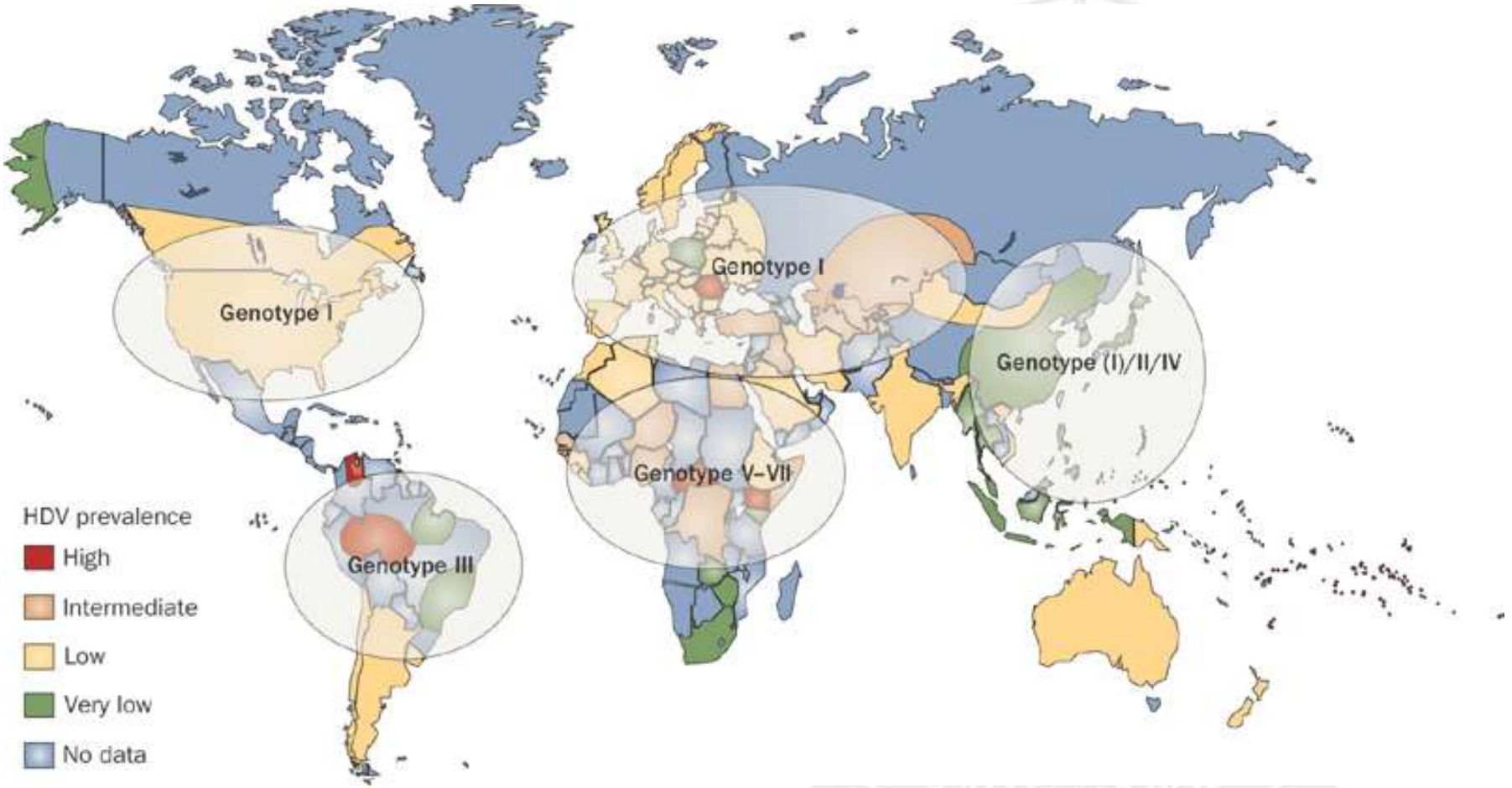
Evolution of Hepatitis D Compared to Hepatitis B and C



Viral Hepatitis D

- Transmission
  - Similar to Hepatitis B
  - No fecal-oral transmission
  - Highest rates in Italy, Venezuela, Africa, Russia, Romania, central Asia and the Middle East
- Co-infection
  - severe acute disease
  - low risk of chronic infection
- Superinfection
  - usually develop chronic HDV infection
  - high risk of severe chronic liver disease
  - may present as an acute hepatitis

Geographic distribution of HDV infection



Wedemeyer, H. et al. "Geographic distribution of HDV genotypes," *Nat Rev Gastroenterol Hepatol* 2010

Clinical features

- Fever < 38ºC
- Severe pain in hepatic region
- Arthralgias in large joints
- Hepatosplenomegaly
- Urticarial rash

- On 15th-32nd day of the icteric phase can appear:
  - Weakness
  - high Bi, ALT, AST
  - serum prothrombin and β-lipoprotein decrease

- Probability of evolution to chronic VHD is the same as in VHB because of the main pathogenic development mechanism – failure of immune system to eliminate HBsAg from the human body

Diagnosis of VHD

- Serological test for hepatitis D antibody

Hepatitis D Complications

- 10-15% - develop cirrhosis within two years
- 70% - eventually develop cirrhosis
- 2-20% - fatality rate
- 25-50% - fulminant liver failure in hepatitis B actually due to hepatitis D co-infection

Hepatitis D Prevention

- Hepatitis B vaccine

AUTOIMMUNE HEPATITIS

Pediatric autoimmune liver diseases

- are diagnosed more frequently than in the past
  - enhanced awareness,
  - real increase in their prevalence,
  - decrease in viral hepatitis-related disease.
- A scoring system for the diagnosis of autoimmune liver disease in pediatric age is proposed for testing and validation
  - scoring systems for autoimmune hepatitis diagnosis in adults are not applicable to pediatric patients

Diagnosis and Management of Pediatric Autoimmune Liver Disease: ESPGHAN, 2018

Autoimmune hepatitis

- AIH is the prototype autoimmune liver disease both in adults and children, first described in the 1950s
- It is a **progressive inflammatory hepatopathy**, which, if untreated, evolves to end-stage liver disease, liver failure requiring transplantation
  - is more aggressive in childhood than in adulthood
- The most typical features of AIH are
  - female preponderance,
  - hypergammaglobulinemia/increased immunoglobulin G (IgG),
  - seropositivity for circulating autoantibodies,
  - a picture of interface hepatitis on histology
- AIH responds to immunosuppressive treatment in the majority of cases
  - Treatment should be instituted promptly upon diagnosis

Autoimmune hepatitis

- **Three forms** of pediatric liver disease recognize an autoimmune component to their pathogenesis:
  - autoimmune hepatitis
  - autoimmune sclerosing cholangitis
  - *de novo* AIH after liver transplant
- **Trigger factors** – infection, drugs, toxins in a genetically susceptible host
- 25-30 % children – mimic viral hepatitis
- Patients can be asymptomatic or have fatigue, malaise, behavioural changes, anorexia

Autoimmune hepatitis serology

- **Two types of AIH** are distinguished according to serological profile:
  - ***type 1 AIH*** (AIH-1) is positive for antinuclear antibody (ANA) and/or anti-smooth muscle antibody (SMA)
  - ***type 2 AIH*** (AIH-2) is defined by positivity for anti-liver kidney microsomal type 1 antibody (anti-LKM-1) and/or for anti-liver cytosol type 1 antibody (anti-LC-1)
- **ASC** is serologically (ANA/SMA) and histologically similar to autoimmune hepatitis type 1, but in addition has ***bile duct damage*** demonstrable by cholangiography, often already at presentation
  - Positivity for peripheral anti-nuclear neutrophil antibodies is more frequent in ASC than AIH
  - Rare patients with ASC are anti-LKM-1-positive
- **De novo AIH** after LT is characterized by autoantibody seropositivity (ANA, SMA, and typical or atypical anti-LKM-1)

Clinical Features

- **acute presentation** resembling that of viral hepatitis, with nonspecific symptoms of malaise, nausea/vomiting, anorexia, joint and abdominal pain, followed by jaundice, dark urine, and pale stools (40-50% of patients with AIH-1 or AIH-2)
- **grade II to IV hepatic encephalopathy** developing 2 weeks to 2 months after the onset of symptoms (3% of patients with AIH-1 and 25% of patients with AIH-2)
- **insidious onset**, characterized by nonspecific symptoms (progressive fatigue, relapsing jaundice, amenorrhea, headache, anorexia, joint and abdominal pain, diarrhea, weight loss), lasting from 6 months to a few years before diagnosis (40% of patients with AIH-1 and 25% of patients with AIH-2)
- **complications of cirrhosis and portal hypertension** (hematemesis from oesophageal/gastric varices, bleeding diathesis, splenomegaly), without previous history of jaundice or liver disease
- incidental finding of **raised hepatic aminotransferases**, without any symptoms or signs (rare)

Diagnostic Criteria

- The diagnosis of AIH is based on a ***combination of clinical, biochemical, immunological, and histological features***
- Should be excluded other known causes of liver disease (viral hepatitis, Wilson disease, nonalcoholic steatohepatitis, and drug-induced liver disease)
- **Liver biopsy is needed** to confirm the diagnosis and to evaluate the severity of liver damage

IAIHG simplified scoring system (2008)

- Diagnostic criteria for routine clinical use

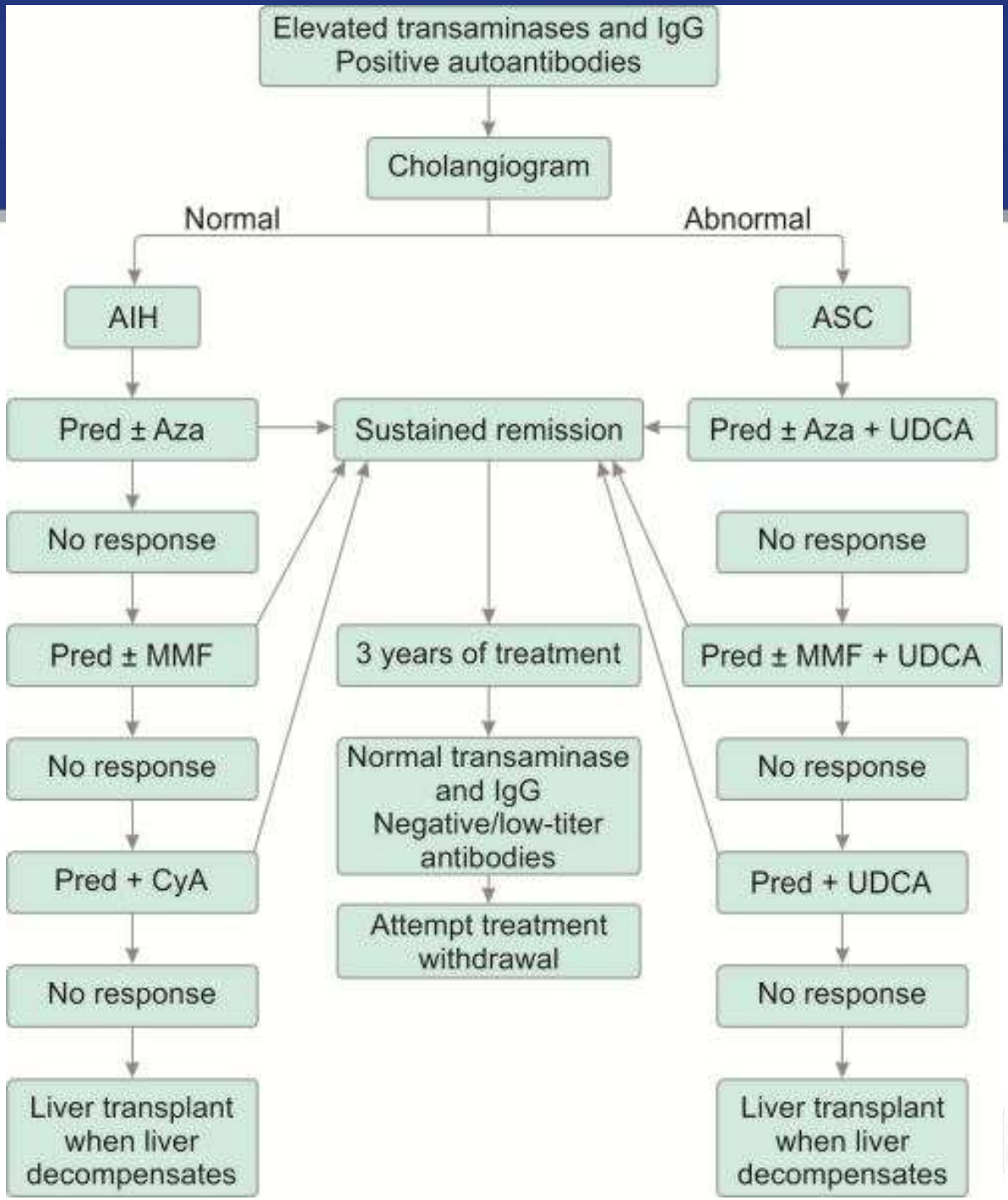
Feature/parameter	Discriminator	Score
Antibodies (max 2 points)		(0–2 points total)
ANA or SMA+	≥1:40	+1
ANA or SMA+	≥1:80	+2
or LKM+	≥1:40	+2
or SLA/LP+	Any titre	+2
IgG or γ-globulins level	>ULN	+1
	>1.1x ULN	+2
Liver histology (evidence of hepatitis is required)	Compatible with AIH	+1
	Typical of AIH	+2
	Atypical	0
Absence of viral hepatitis	No	0
	Yes	+2

Score ≥7 = Definite AIH
Score ≥6 = Probable AIH

Hennes EM, et al. Hepatology 2008;48:169–76; EASL CPG AIH. J Hepatol 2015;63:971–1004

When to Treat

- AIH should be suspected in all children with evidence of liver disease after exclusion of infectious and metabolic etiologies
- AIH is exquisitely responsive to immunosuppression and treatment should be initiated promptly to avoid progression of disease
- The goal of treatment is to reduce or eliminate liver inflammation, to induce remission, improve symptoms, and prolong life expectancy
- Although cirrhosis is present in 44-80% of children at the time at diagnosis



Diagnosis and Management of Pediatric Autoimmune Liver Disease: ESPGHAN, 2018

Immunosuppressive treatment regimens for juvenile autoimmune liver disease

	Initial regimen	
AIH	Predni(so)lone	Azathioprine
	2 mg · kg^{-1} · day^{-1} (up to 60 mg/daily) decreased weekly in parallel to transaminase levels decrease to a minimum maintenance dose of 2.5 to 5 mg daily	1–2 mg · kg^{-1} · day^{-1} added gradually if transaminase levels plateau or increase. Alternatively, added in all patients after 2 weeks of predniso(lo)ne treatment
ASC	Predniso(lo)ne ± azathioprine as above, plus ursodeoxycholic acid 15 mg/Kg/day	

Diagnosis and Management of Pediatric Autoimmune Liver Disease: ESPGHAN, 2018

Immunosuppressive treatment regimens for juvenile autoimmune liver disease

	Maintenance		
AIH	Prednis(ol)one	Azathioprine	Azathioprine mono therapy (in AIH-1)
	0.1–0.2 mg · kg^{-1} · day^{-1} or 5 mg/day	1–2 mg/kg/day if required	1.2–1.6 mg/kg/day
ASC	Predniso(lo)ne ± azathioprine as above, plus ursodeoxycholic acid 15 mg · kg^{-1} · day^{-1}		

Diagnosis and Management of Pediatric Autoimmune Liver Disease: ESPGHAN, 2018

AIH	Definition of remission	Treatment length	Before attempting treatment withdrawal
	Normal transaminase and IgG levels; - Negative or low titer (< 1:20) ANA/ SMA -negative anti-LKM-1/anti-LC-1	3 y Before considering suspension	Remission for at least 3 years + follow up liver biopsy showing no inflammatory changes
ASC	As above	As above	As above

Diagnosis and Management of Pediatric Autoimmune Liver Disease: ESPGHAN, 2018

DRUG INDUCED LIVER INJURY

Reye syndrome

- Reye's syndrome describes an **acute encephalopathy** combined **with liver injury** that occurs in children treated with **acetyl salicylic acid** (aspirin), usually in the context of a viral infection such as influenza or varicella
- Aspirin can uncouple mitochondria and inhibit mitochondrial fatty acid oxidation, resulting in mainly **microvesicular steatosis**
- Laboratory findings include **hyperammonaemia, hypoprothrombinaemia** and **hypoglycaemia**
- Since the restriction of use of aspirin in children, the incidence of Reye's syndrome has declined sharply

Drug induced liver injury

- Drug-induced liver injury refers to liver injury induced by all types of prescription or non-prescription drugs, including
  - small chemical molecules,
  - biological agents,
  - traditional Chinese medicines,
  - natural medicines,
  - health products,
  - dietary supplements

DILI

Intrinsic DILI (direct toxic effect)

- Dose-dependent
- No specific predisposition (predictable)
- Onset is within a short time span (hours to days)
- Distinctive liver pathology
- High incidence
- Experimental reproducibility

Idiosyncratic DILI

- Dose-independent
- Only genetically predisposed individuals (unpredictable)
- Exhibits a variable latency to onset (days to weeks)
- Variable liver pathology (usually reverses after drug withdrawal)
- Low incidence
- Lack of experimental reproducibility

Metabolic type

Duration of exposure: 1 week to several month
Lack of hypersensitivity features
Delayed response to reexposure (weeks)

Immunologic type

Duration of exposure: few weeks
Hypersensitivity features
Prompt response to reexposure (1 or 2 doses)

EASL Clinical Practice Guidelines: Drug-induced liver injury. Journal of Hepatology, 2019

Drugs associated with intrinsic vs. idiosyncratic DILI

Intrinsic	Idiosyncratic	
Acetaminophen	Allopurinol	Lapatinib
Amiodarone[§]	Amiodarone[§]	Methyldopa
Anabolic steroids	Amoxicillin-clavulanate	Minocycline
Antimetabolites	Bosentan	Nitrofurantoin
Cholestyramine**	Dantrolene	Pazopanib
Cyclosporine	Diclofenac	Phenytoin
Valproic acid	Disulfiram	Pyrazinamide
HAART drugs	Felbamate	Propylthiouracil
Heparins**	Fenofibrate	Statins[§]
Nicotinic acid	Flucloxacillin	Sulfonamides
Statins[§]	Flutamide	Terbinafine
Tacrine**	Halothane	Ticlopidine
	Isoniazid	Tolvaptan
	Ketoconazole	Tolcapone
	Leflunomide	Trovafloxacin
	Lisinopril	

ALT, alanine aminotransferase; DILI, drug-induced liver injury; HAART, highly active antiretroviral therapy.
*Known examples; withdrawn or unapproved drugs not listed
**Mild ALT elevations without jaundice
§Both intrinsic and idiosyncratic.

EASL Clinical Practice Guidelines:
Drug-induced liver injury. Journal of Hepatology, 2019

Definition and classification of DILI

- Serum aminotransferases (ALT/AST), ALP, and TBL levels remain the mainstay for detecting and classifying liver damage in suspected DILI
  - Liver biopsy is not available in most instances
- DILI should be classified as **hepatocellular**, **cholestatic** or **mixed** according to the pattern of elevation of liver enzymes
- ALT, ALP and TBL are the standard analytes to define liver damage and liver dysfunction in DILI
- Persistently elevated TBL and ALP in the second month from DILI onset should be used as a marker for chronic DILI

EASL Clinical Practice Guidelines:
Drug-induced liver injury. Journal of Hepatology, 2019

DILI qualification

- Qualification of liver injury for practical and scientific purposes is made by liver biochemistry
  - ALT ≥5x ULN
  - ALP ≥2x ULN
  - ALT ≥3x ULN + TBL >2x ULN

- Pattern of liver injury is classified according to **R (ALT x ULN/ALP x ULN)**
  - Hepatocellular = R≥5
  - Cholestatic = R≤2
  - Mixed = 2>R<5

EASL Clinical Practice Guidelines:
Drug-induced liver injury. Journal of Hepatology, 2019

Diagnosis of DILI relies largely on exclusion of alternative causes of liver damage

Laboratory work-up

- Tests for viral hepatitis, particularly in those cases not compatible with the drug signature of the suspected causative agent and/or with high transaminase levels

Imaging

- An abdominal ultrasound should be undertaken in all patients suspected of DILI

Liver biopsy

- Liver biopsy may be considered during the investigation of selected patients suspected to suffer DILI, as liver histology can provide information that can support the diagnosis of DILI or an alternative diagnosis
- Liver biopsy may be performed in patients suspected to have DILI when serology raises the possibility of AIH
- Liver biopsy may be considered in patients when suspected DILI progresses or fails to resolve on withdrawal of the causal agent as the liver histology may provide prognostic information assisting clinical management

EASL Clinical Practice Guidelines:
Drug-induced liver injury. Journal of Hepatology, 2019

Stepwise approach to DILI diagnosis

Abnormal biochemistry/acute hepatitis

DILI suspicion

Features supporting toxic aetiology
Skin involvement, kidney injury, previous DILI episodes

Careful enquiry of exposure to HDS, drugs, OTC drugs

Potential pitfalls
Lack of information (eg. dose, duration), several medications, hidden HDS and OTC drug intake

Discontinue non-essential drugs/HDS treatment

Search in hepatotoxicity resources (Liver tox)

Calculate biochemical pattern of liver injury

$R = \frac{ALT/ULN}{ALP/ULN}$

Hepatocellular	Mixed	Cholestatic
R ≥ 5	2 > R < 5	≤ 2

Search for alternative causes

- Viral infections (HAV, HBV, HCV, HEV, EBV, CMV)
- Alcohol-related liver disease, hepatic ischaemia
- Autoantibody titres, ↑ IgG

- Benign/malignant biliary obstruction
- Primary biliary cholangitis
- Primary sclerosing cholangitis

Consider liver biopsy if
- Negative or incomplete rechallenge
- Acute or chronic atypical presentation
- Autoimmune hepatitis

EASL Clinical Practice Guidelines: Drug-induced liver injury. Journal of Hepatology, 2019

DILI severity classifications

Category	Severity	Description
US Drug-Induced Liver Injury Network[310]		
1	Mild	Elevated ALT and/or ALP but TBL <2.5 mg/dl and INR <1.5
2	Moderate	Elevated ALT and/or ALP and TBL ≥2.5 mg/dl or INR ≥1.5
3	Moderate-severe	Elevated ALT, ALP, TBL and/or INR and hospitalization or ongoing hospitalization prolonged due to DILI
4	Severe	Elevated ALT and/or ALP and TBL ≥2.5 mg/dl and at least 1 of the following criteria: - Hepatic failure (INR >1.5, ascites or encephalopathy) - Other organ failure due to DILI
5	Fatal	Death or liver transplantation due to DILI
International DILI Expert Working Group[160]		
1	Mild	ALT ≥5 or ALP ≥2 and TBL <2 × ULN
2	Moderate	ALT ≥5 or ALP ≥2 and TBL ≥2 × ULN, or symptomatic hepatitis
3	Severe	ALT ≥5 or ALP ≥2 and TBL ≥2 × ULN, or symptomatic hepatitis and 1 of the following criteria: - INR ≥1.5 - Ascites and/or encephalopathy, disease duration <26 weeks, and absence of underlying cirrhosis - Other organ failure due to DILI
4	Fatal/transplantation	Death or liver transplantation due to DILI

ALP, alkaline phosphatase; ALT, alanine aminotransferase; INR, international normalized ratio; TBL, total bilirubin, ULN, upper limit of normal.

EASL Clinical Practice Guidelines: Drug-induced liver injury. Journal of Hepatology,

Treatment of DILI

Non-specific treatment

- Treatment is mainly supportive
- Withdraw the offending agent

Specific treatment

There are 2 main treatment approaches for drug-induced ALF:

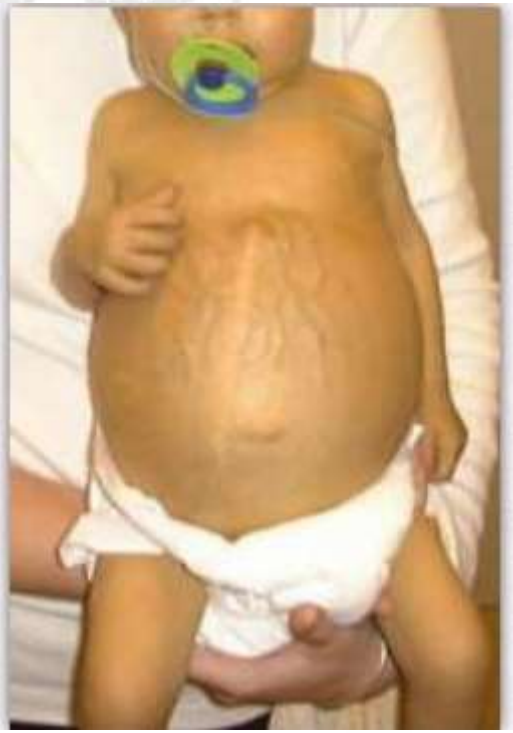
- rapid depuration of the body from the toxic drug to stop further aggression before the agent may reach the liver
- administration of an antidote to prevent and/or stop the aggression once the drug has reached the liver
  - Paracetamol overdose – antidote **N-Acetyl Cystiene**
  - Valproate overdose – antidote **Carnitine**
- Corticosteroids may have a role in immune mediated disease

METABOLIC-GENETIC HEPATITIS

Metabolic-genetic hepatitis

- Wilson disease
- cystic fibrosis
- α1-antitrypsin deficiency
- haemochromatosis
- glycogen storage dsease type IV

LIVER CIRRHOSIS IN CHILDREN



General considerations

- **Cirrhosis** is a diffuse process characterized by **fibrosis and nodular regeneration**, which lead to the disorganization of liver architecture
  - is the final stage of progressive liver disease

- Cirrhosis was long thought to be irreversible and associated with limited life expectancy
- However, it is now considered a dynamic condition, which can be reversed if adequately treated

Etiology

Neonates/infants

- **Bile duct diseases**
  - Biliary artresia
  - Sclerosing cholangitis
  - Congenital hepatic fibrosis
  - Choledochal cysts
- **Inherited diseases**
  - Glycogen storage disease
  - Tyrosinemia
  - Wilson disease
  - Alpha1-antitrypsin deficiency
  - Cystic fibrosis

Children/adolescents

- **Viral hepatitis**
  - VHB and VHD
  - VHC
- **Autoimmune hepatitis**
- **Drugs and toxins**
  - Isoniazid
  - Methotrexate
  - Excess vitamin A
- **Vascular alterations**
  - Congenital cardiopathy
  - Congestive heart failure
  - Budd-Chiari syndrome
- **Fatty liver disease**

Cryptogenic cirrhosis 5-15% cases

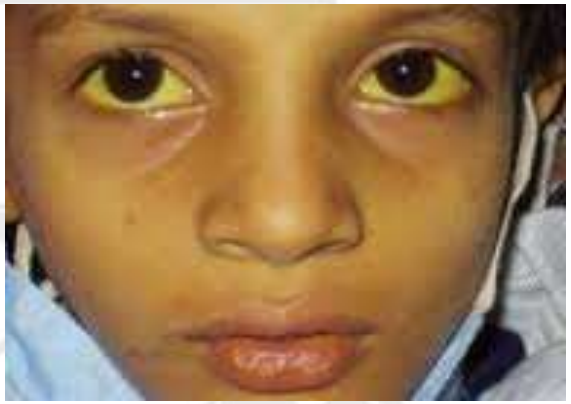
Clinical findings

- depends on the primary cause of liver disease and on whether the cirrhosis is compensated or decompensated
- may be asymptomatic before liver failure occurs (40% of cases)
  - early: fatigue, weakness, weight loss
- In decompensated cirrhosis, there may be a cascade of progressive complications such as
  - gastrointestinal bleeding
  - ascites
  - hepatic encephalopathy
- The diagnosis is often predictable since it is part of the natural progression of chronic liver conditions such as biliary atresia
- However, cirrhosis may already be present when diseases such as AIH are diagnosed
  - approximately 40-80% of children with AIH present with cirrhosis

Symptoms of cirrhosis in children

Hepatocellular failure

- pallor, **jaundice**, itchy skin, xanthomatosis
- edema, fatigue,
- dark urine, pale stool
- weight loss
- palmar erythema, spider nevi, pigmentation



Portal Hypertension

- ascites, distended vein (*caput medussa*),
- splenomegally
- varices: hematemesis, bloody stool

Symptoms of cirrhosis in children

Hepatocellular failure

- pallor, jaundice, itchy skin, **xanthomatosis**
- edema, fatigue,
- dark urine, pale stool
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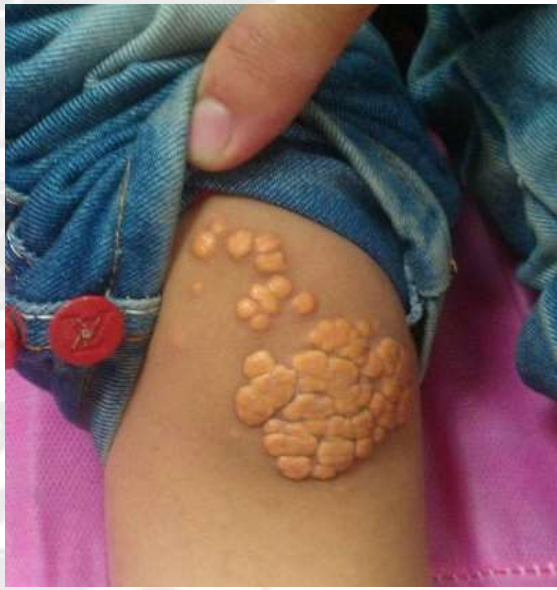

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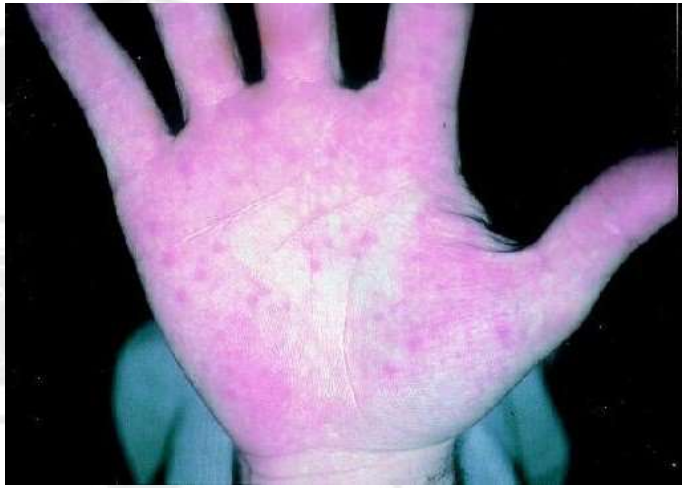

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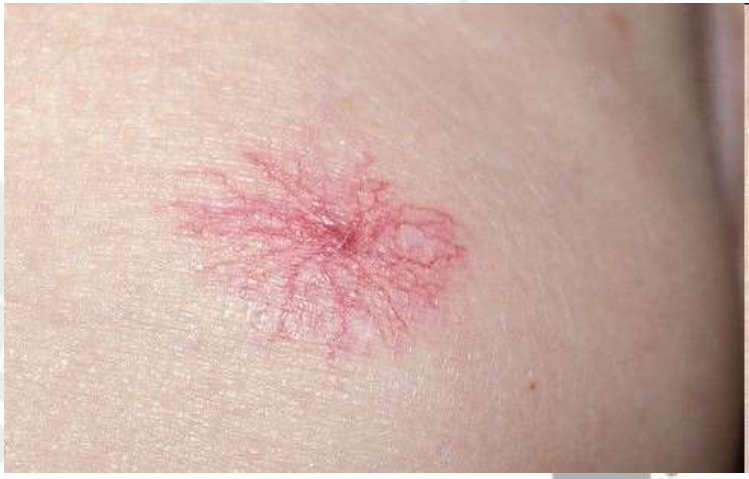

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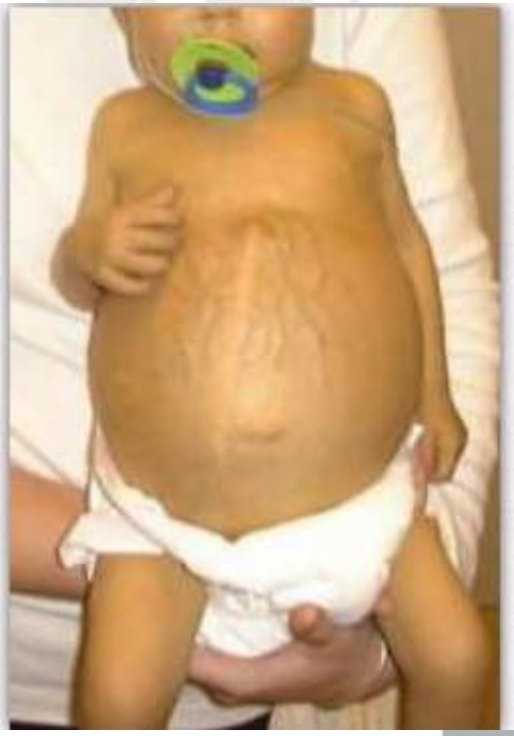

Laboratory work up

- Biochemical tests indicating liver damage
- Investigations to find underlying etiology
- Liver function status evaluation
- Liver Biopsy

Biochemical tests indicating liver damage

- **Liver Function Tests (LFTs)**
  - Serum Bilirubin
    - Total
    - Fractionated (direct and Indirect)
  - Alanine aminotransferase/Aspartate aminotransferase
  - Alkaline phosphatase
  - GGTP

Investigations for Liver Function Status

- Serum albumin levels
- Coagulation Profile
- Plasma glucose

Investigations for identification of etiology

- **Infectious causes**
  - Hepatitis serology
  - Toxoplasma and cytomegalovirus screening
- **Autoimmune causes**
  - Anti Nuclear Antibodies (ANAs)
  - Anti Smooth Muscle Antibodies (Anti SMA)
  - Anti Liver Kidney Microsomal Antibodies (Anti LKM)
  - Total Immunoglobulins levels
- **Metabolic causes**
  - α-1 antitrypsin levels (protease inhibitor typing)
  - Copper studies (Wilson disease)
  - Sweat test (cystic fibrosis)
  - Plasma amino acid levels (tyrosinemia)

Radiology and Imaging

- Liver Ultrasound with Doppler
- Computed Tomography (CT Scan)
- Magnetic Resonane Imaging (MRI)
- Radionucleide liver scan (HIDA)
- Fibroscan
- Cholangiography (MRCP)

Liver Biopsy

- **Types**
  - percutaneous
  - transvenous
  - open biopsy

- **Indication**
  - Diagnosis of metabolic and autoimmune diseases
  - To assess severity of liver damage
  - Monitoring progress of treatment

Principles of Management

- General management including nutritional support
- Specific treatment of underlying etiology
- Prevention, early detection and treatment of complications
- Liver transplantation

New hopes for the future

- Extracorporeal liver support devices
  - The molecular adsorbent recirculating system (MARS®)
- Hepatocyte transplant
- Gene therapy & genetically engineered enzymes
- Modulating fibrogenesis
- Hepatopoeitin

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