Hepatitis Viruses

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Introduction

- Hepatitis: inflammation of liver; presence of inflammatory cells in organ tissue
- The causes of hepatitis are varied and include viruses, bacteria, and protozoa, as well as drugs and toxins (eg, isoniazid, carbon tetrachloride, and ethanol).
- Acute hepatitis: symptoms last less than 6 months
- Viral Hepatitis: is inflammation of the liver induced by viral infections
- The clinical symptoms and course of acute viral hepatitis can be similar, regardless of etiology, and determination of a specific cause depends on laboratory tests.

Scope of the lecture

Dr. Means hepatitis viruses here

Viral hepatitis *types:*

These exclusively infect the liver unlike

Although they have the same target & they all have the same basic hepatitis symptoms they differ in:
1-mood of replication and transmission
2-time course and sequela of the disease they cause

- *A:* Picornavirus: +ssRNA, Non enveloped

  family

- B: Hepadnavirus Ds DNA, Partial, has enzyme, enveloped

- C: Flavivirus, +ssRNA genome, enveloped

- *D: Deltaviruses, Defective –ssRNA virus*

  defective virus (cant cause infection unless HBV is present

- E: Hepevirus, +ssRNA non enveloped

in addition to those viruses there are other viruses that causes sporadic cases of hepatitis :
1- yellow fever virus
2-CytoMegaloVirus
3-Epstein Burr Virus
4-Rubella virus
5-herpes simplex virus
and other enteroviruses

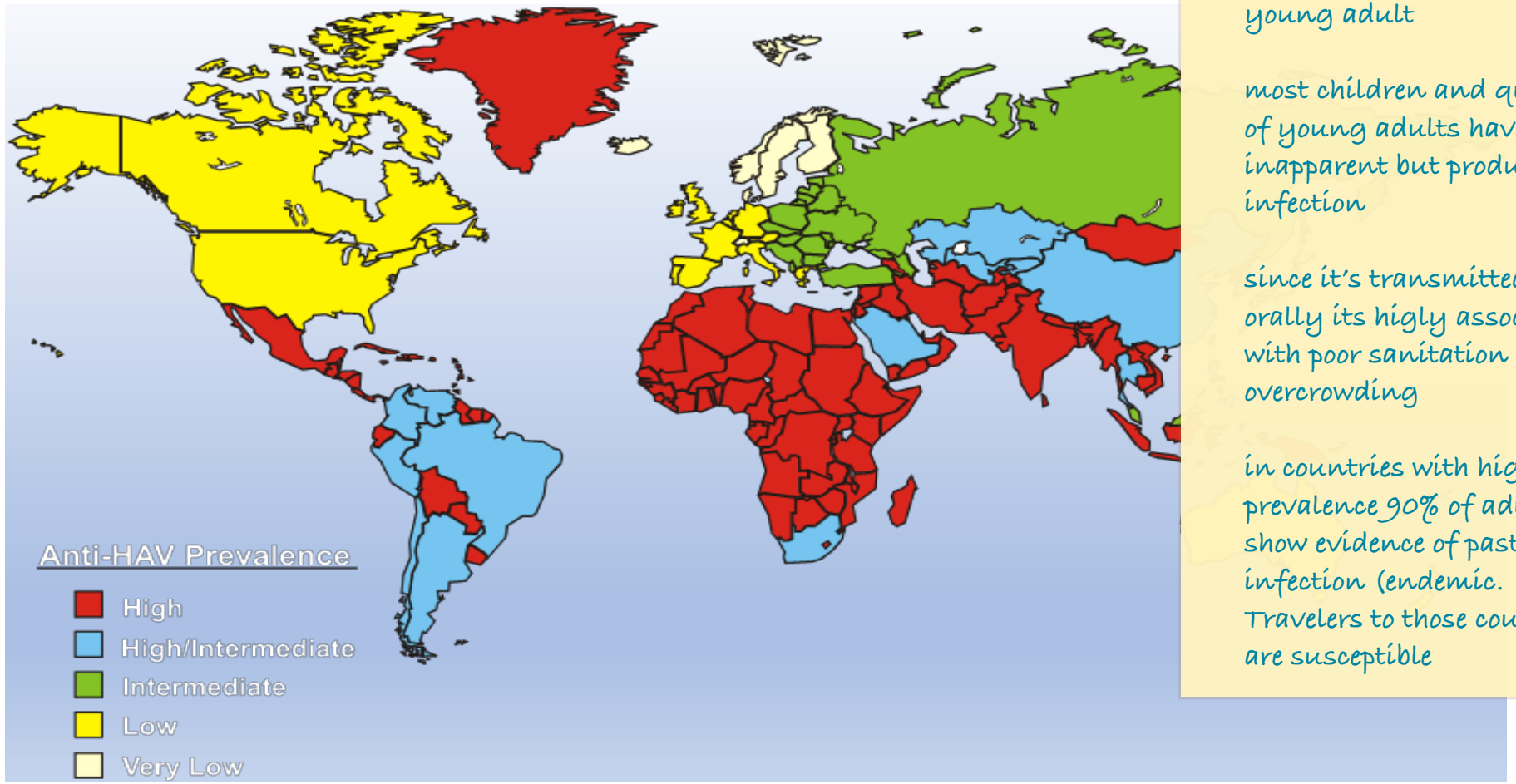
Hepatitis A

Etiologic agent of viral hepatitis A (aka Infectious hepatitis)

- A typical Enterovirus , also known as entervirus 72
- Naked Icosahedral nucleocapsid virus with a single stranded positive polarity RNA. No virion polymerase. One serotype → But 7 genotypes
- Enterically transmitted (fecal/oral route)
  - replicates in liver > excreted in bile > feces [2weeks pre illness & 1 week post illness]
  - outbreaks in contaminated food cases.
  - humans are the reservoir
- *Ingestion* > Multiplies in oropharynx and intestinal epithelial cells > blood > Liver > Periportal necrosis + mononuclear infiltrates
- Virus is not cytopathic but the CMI causes cell necrosis
  - Like all hepatitis viruses
  - CMI = Cell-mediated immunity

Epidemiology of *Hepatitis A*

40-50 % of all acute hepatitis thus the most common viral hepatitis virus



mostly in children and young adult

most children and quarter of young adults have inapparent but productive infection

since it's transmitted feco-orally its higly associated with poor sanitation and overcrowding

in countries with high prevalence 90% of adults show evidence of past infection (endemic. Travelers to those countries are susceptible

Clinical Manifestations

100 virions are enough to establish the disease

it only causes acute hepatitis it doesn't progress to chronic (similar to HEV)

- Incubation period: 2-6 WEEKS

most contagious in 2 weeks prior to symptoms

- Most HAV infections are asymptomatic. → most adults are symptomatic while most children are asymptomatic
- fever; anorexia; nausea, vomiting and jaundice . → icteric phase
  - pre-icteric phase
- Abdominal pain, hepatomegally, spenomegally, Dark urine and clay-colored stools and elevated transaminase levels.

- Resolve spontaneously in 2-4 weeks.
  - 99% of cases ——— 1% suffer from fulminant hepatitis
    - (0.1 – 0.2% mortality)

Hepatitis A Diagnosis:

- Clinically
- *Liver enzyme: High AST and ALT, mild elevation of bilirubin.*

Due to cytoplasmic damage

leukopenia, lymphocytosis and elevated Erythrocytes Sedimentation Rate (ESR)

- *Serology: IgM, IgG (life long immunity)* Anti HAV

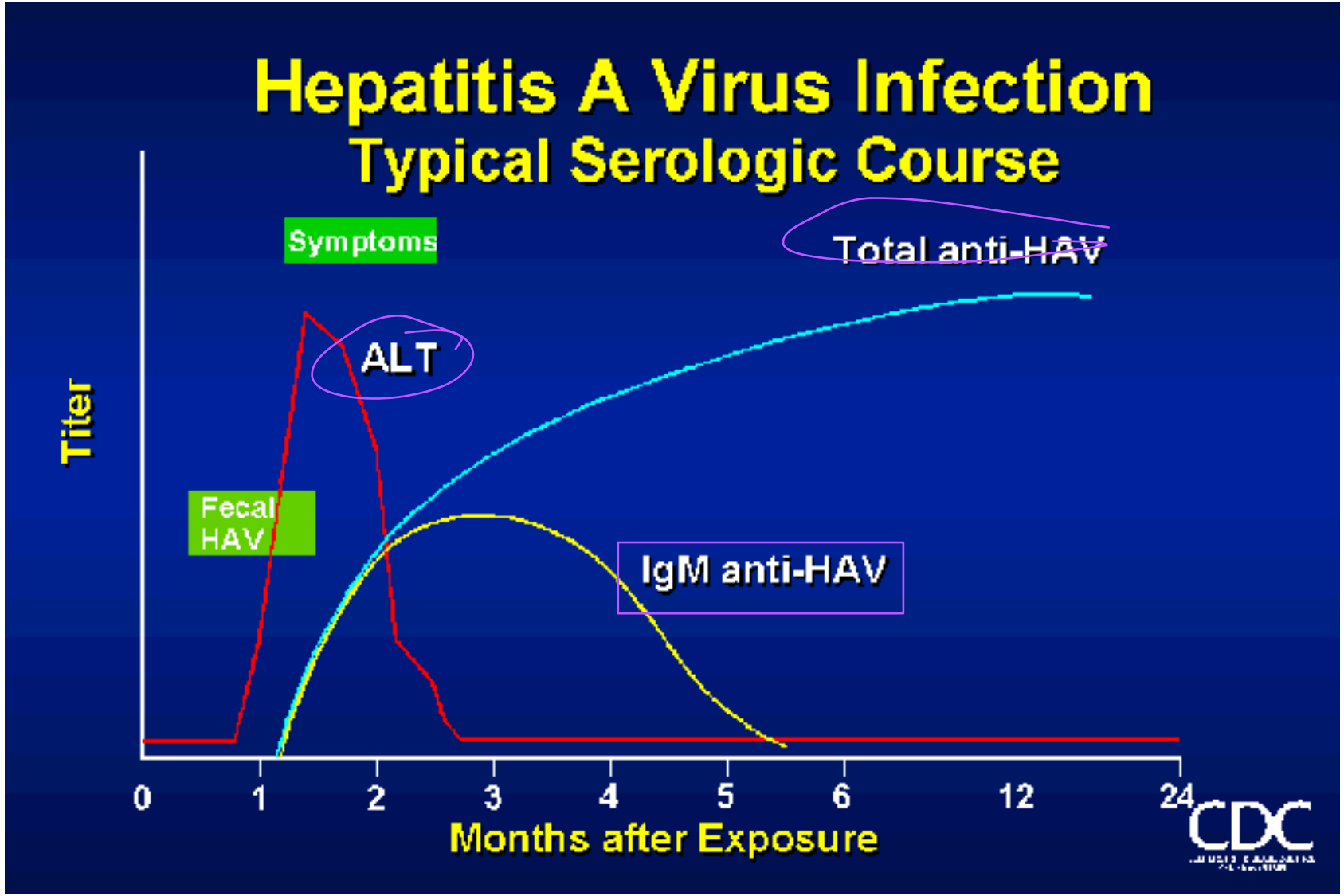
➢ *IgM: Acute infection remains high for 3-6 months* (initial)

➢ *IgG: Past infection or vaccine*

viral particles and can be seen by TEM in feces

culture is usually for research purposes only

Hepatitis A


Hepatitis A Virus Infection
Typical Serologic Course
Symptoms
Total anti-HAV
ALT
Titer
Fecal HAV
IgM anti-HAV
0
1
2
3
4
5
6
12
24
Months after Exposure
CDC

- *Rx: Usually full recovery in 90% of patients in 3-6m*

➢ *Acute:*

- *Supportive: Do not give Paracetamol and Alcohol*
- *Immunoglobulins* — Passive immunity (given as prophylactic given early in the incubation period)

➢ *Fulminat hepatitis:*

- *Supportive, but may need liver transplantation*
- *Prevention:*
- *Hygiene, Vaccine: killed, IM 2 doses separated by 3- 6 months*

Active immunization (long life immunity)

Hepatitis E Virus

- Hepatitis E virus is a none enveloped, single stranded RNA virus. ↗ Similar but distinct from Calicivirus
- The viral particles in stool are spherical, 27 to ~~34~~ 30 nm in size, and unenveloped and exhibit spikes on their surface.

- Feco-oral transmission → same features of HAV

- Waterborne epidemics of hepatitis

- High mortality rate in pregnant women. → mostly subclinical but can be symptomatic and in rare occurrences cause fulminant hepatitis (especially in high risk groups [pregnant women and malnourished ppl])
- No chronicity , No carrier state.

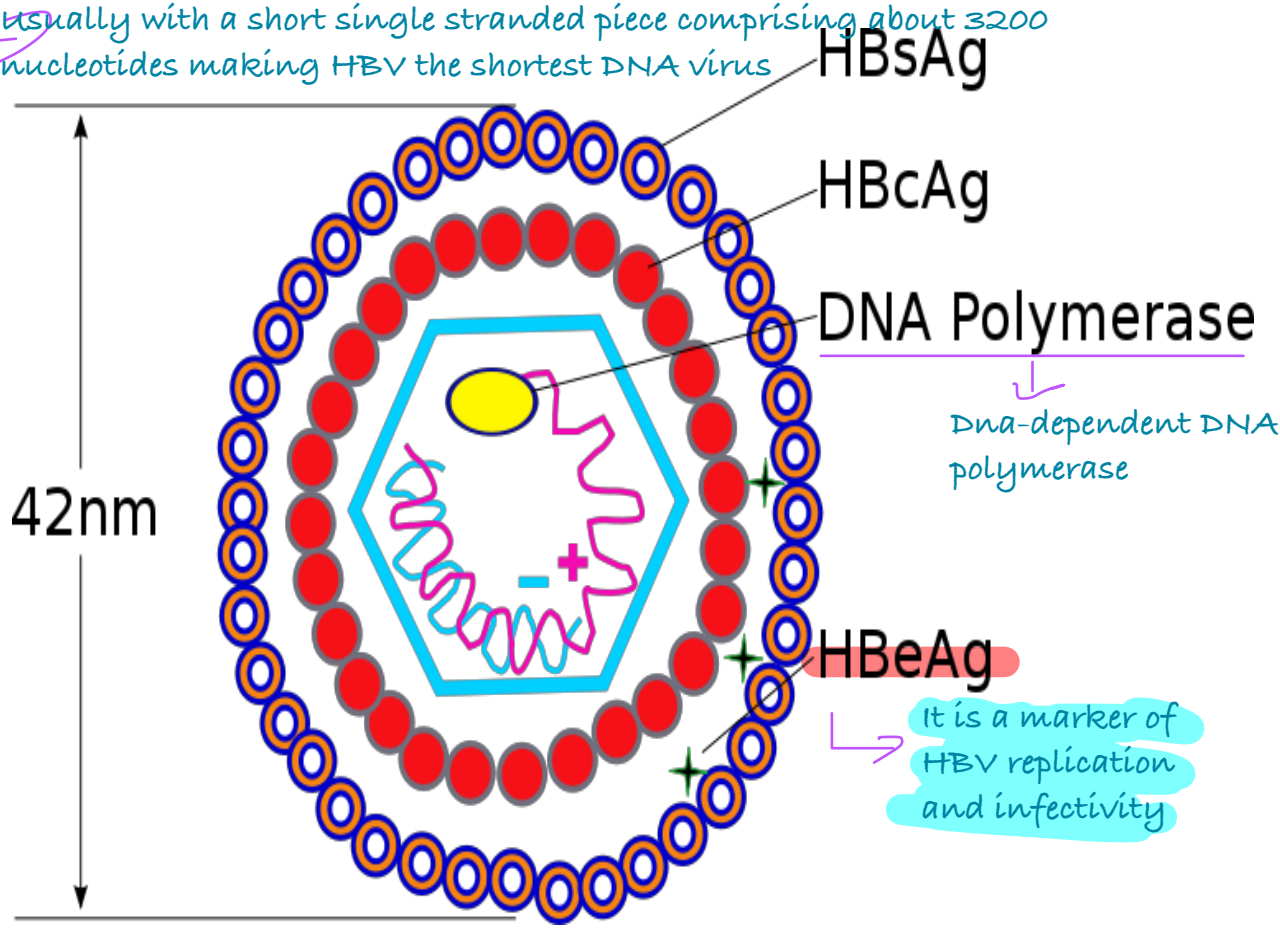
Incubation period is 2-8 weeks and diagnosis by Anti-HEV AB
usually bilirubin is higher thus deeper jaundice when compared to HAV
treatment is Supportive

Hepatitis B virus

Etiologic agent of viral hepatitis B (aka Serum Hepatitis)
it has 1 serotype only

- Hepadnavirus , Partially –Double stranded circular DNA genome.
- Enveloped
- Icosahedral nucleocapsid
- Antigens:
- The main components of the virus include the core - hepatitis B core antigen (HBcAg) and the pre-corehepatitis B e antigen (HBeAg), and the envelope of the virus contains the hepatitis B surface antigen (HBsAg)

usually with a short single stranded piece comprising about 3200 nucleotides making HBV the shortest DNA virus



Dna-dependent DNA polymerase

It is a marker of HBV replication and infectivity

Notes :

- HBV has 3 different types of particles : Virions / filaments / spheres
- for epidemiological and medico-legal purposes and based on the serologic sub-typing of HBV surface antigen it has 4 strains each of them contains
    1-a group-specific antigen (usually abbreviated a)
    2- two set of mutually-exclusive sets of epitopes d/y and w/r
    so the possible combinations will be (adw/adr/ayw/ayr)

- epidemiology:
    -it's distributed worldwide
    -2 billion ppl have markers of infection
    -400 million ppl with chronic infection of HBV (carriers of HBV)
    -1 Million deaths annually

Hepatitis B virus

➢ Transmission:

That's why it's called serum hepatitis

- Parenteral via blood or plasma, needle stick injury & Sexually especially in homosexuals
- Vertically: mother to baby → Main mode of transmission worldwide
- Body fluids → Semen and saliva

➢ Risk groups:

- Health care workers
- Drug abusers
- Recipients of blood or its products (blood should be ideally screened)
- Dialysis patients, Homosexual men...

Hepatitis B virus

- Pathogenesis:
- Blood borne > liver cells > hepatocytes injury and necrosis (piecemeal necrosis) ---Largely cell mediated.
- Clinically :
- Incubation period: 1-4 months (infectious dose)

Cytotoxic T cells

7 - 160 days usually 10 weeks

Aka interface hepatitis
charactized by inflammation extending from the portal tract to periportal zone with necrosis of periportal hepatocytes and disrubtion of the limiting plate

✓Asymptomatic: 90% of children and 50% of adults (increased liver enzymes)

✓Symptomatic:

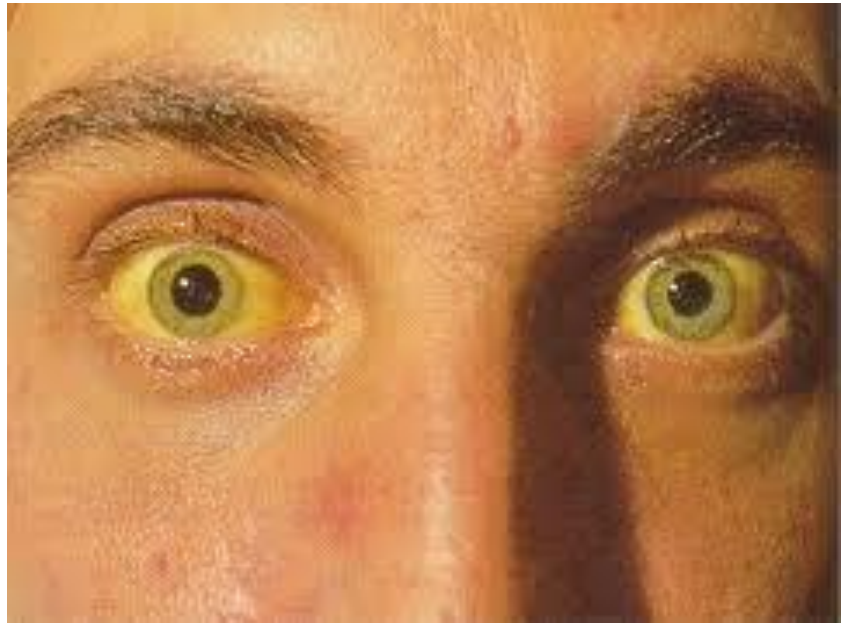
Early in the disease pain in joints and arthritis may occur via ag-ab complex mechanism

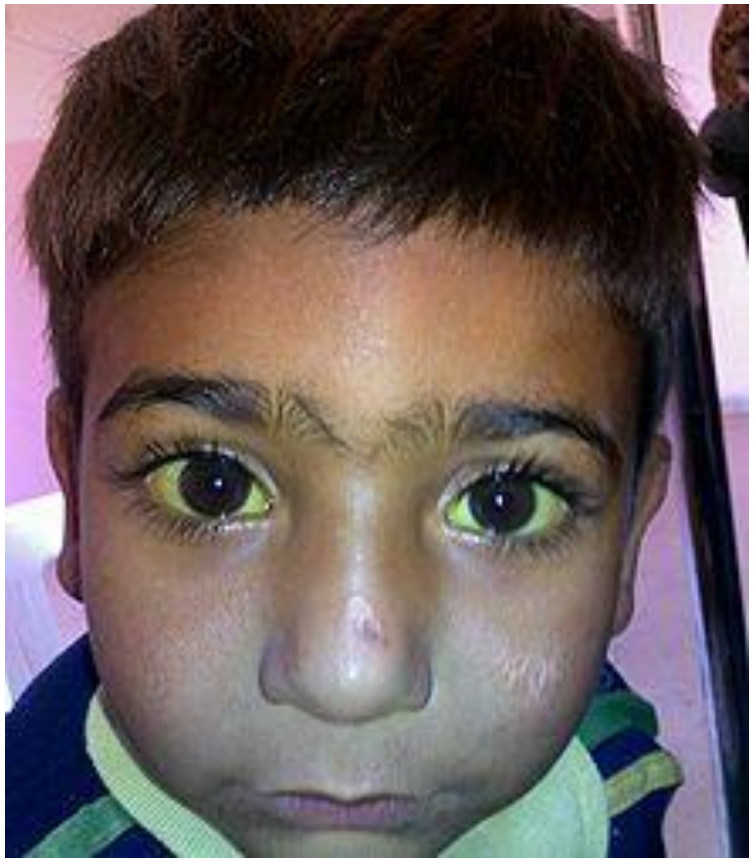
- Preicteric phase: flu like symptoms nausea, anorexia, malaise
- Icteric phase: Jaundice, pale stool, dark- coloured urine, increased liver enzymes and billirubin

With more & more involvement of the liver

Hepatitis B

These cases are clearly in their icteric phase





Hepatitis B virus

➢Outcome:

- 90-95% recovery — It may take several months
- 5-10% chronic carriers (sAg > 6 months): — 90% of neonates infected become chronic carriers — Major source of spread

Chronic passive carriers → less likely to have symptoms / discovered incidentally (elevated liver enzymes)

- chronic active hepatitis (more fatal) — A third of chronic carriers

Necrosis → scarring → cirrhosis → liver failure or primary HCC

- 1% fatality

Fulminant hepatitis in 1% of pts

- 1% of HBV chronic carriers develop hepatocellular carcinoma — Due to integration of viral DNA into cellular DNA

- Diagnosis of HBV :

1. Clinical picture

2. Liver, kidney function tests, other tests to role out other causes e.g: CMV, EBV infection

elevated Alt / AST / bilirubin

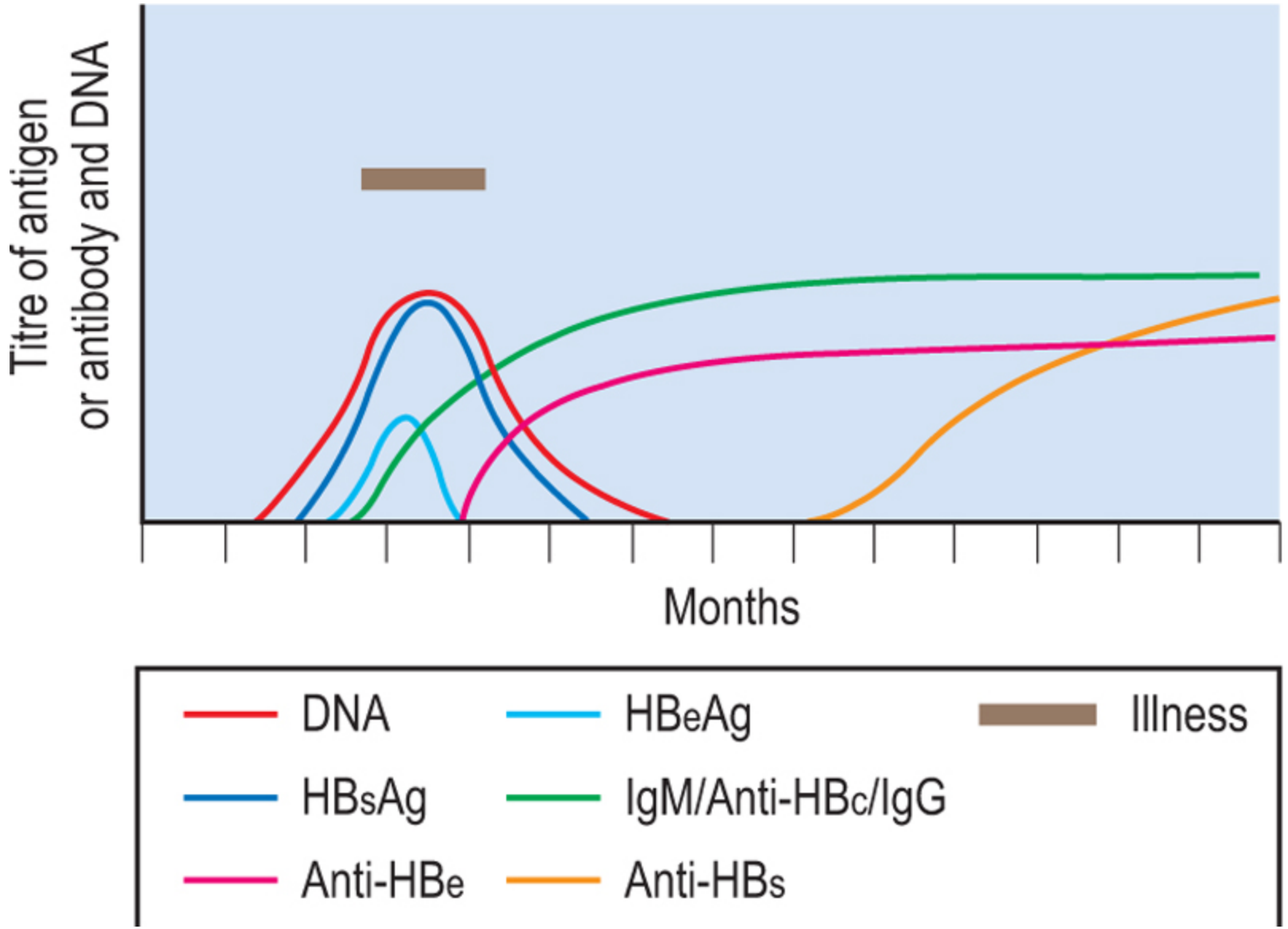
3. Serology:

- We rely on:

- S, e antigens and antibodies
- Anti core antibodies
- DNA detection

Anti-HBcAg IgM (almost into all who developed jaundice)
Anti-HBcAg IgG /Anti-HBsAg IgG or both (in past infections)

HBV VIRAL DNA detected by PCR


Titre of antigen
or antibody and DNA
Months
DNA
HBeAg
Illness
HBsAg
IgM/Anti-HBc/IgG
Anti-HBe
Anti-HBs

Anti-HBcAg IgM —>acute hepatitis
Anti-HBcAg IgG —>past or chronic infection
HBsAg is general marker of infection —>if longer than 6 months —>chronic infection
HBsAb is used to document recovery or immunity to HBV infection
HBeAg indicate active replication and infectiveness of the virus
HBeAb indicates that there's no longer replication but still the pts will be +very for HBsAg which is made by the integrated HBV

viral DNA is more accurate than HBeAg especially in cases of escaped mutants (used in monitoring response to therapy)

video for bettser understanding:
https://youtu.be/h_9EBVPADNE?t=114

TABLE 41-4 Serologic Test Results in Four Stages of HBV Infection

Test	Acute Disease	Window Phase	Complete Recovery	Chronic Carrier State
HBsAg	Positive	Negative	Negative	Positive
HBsAb	Negative	Negative	Positive	Negative[1]
HBcAb	Positive[2]	Positive	Positive	Positive

extra note:
*window phase of a test means the time between the first exposure to an etiologic agent and the detection of the disease
so only HBcAB being +ve indicates that it's the first Antibody released by the body.

	HBsAg HBeAg* HBV-DNA	HBcAb IgM	HBcAb IgG	HBeAb	HBsAb
Acute infection	+	+	–	–	–
Window period	–	+/–	+	+	–
Prior infection	–	–	+	+	+
Immunization	–	–	–	–	+
Chronic infection	+	–	+	+/–	–

Hepatitis B virus

Treatment:

- There's no specific treatment for acute hep B , high calorie diet is desirable
- corticosteroid therapy hasn't shown effectiveness in uncomplicated acute viral hepatitis

1. Peg Interferon alpha — For chronic hepatitis
2. Lamivudine, Tenofovir, entecavir

Lamivudine is a potent HIV inhibitor it also has activity against HBV but resistance develops in some pts after 12 months of therapy so we switch to the other mentioned drugs those are nucleoside analogs

Prevention:

1. Immunoglobulin / passive

Accidental exposure in non vaccinated

Newborns of infected mothers

Passive immunization post exposure as prophylaxis is effective

Given to high risk individuals & to neonates in many countries

2. Vaccine (Recombinnt HBsAg) 3 I.M doses at 0, 1, 2 OR 6 months

- Fridge storage
- Check response by measuring anti HBsAg antibodies 2 months after last dose (>10mIU/ml is protective)

To check whether someone is immunized

- Part of ministry of health vaccination program (2, 3, 4 months)

Hepatitis D virus

causes Delta Hepatitis
it's a small ssRNA virus

- It needs HBV to replicate (provide the envelop)
- Route of transmission:

it requires HBsAGfor it's transsmission so it's only found in pts with acute or chronic Hep B infections

✓ As HBV

so it's also mostly prevalent in ppl with high risk of Hep B (injection drug users / dialysis pts)

- conditions:

2 types of Hep D infections have been noted:

✓1 Co- infection with HBv

* simultaneously infected by HBV & HDV resulting in acute hepatitis that's indistinguishable from those caused by HBV and HAV
* Fulminant Hepatitis is much more common than in cases with Hep B alone

✓2 Super infection of HBV chronically infected patients (High risk of liver failure)

in these cases pts will be suffering from relapse of jaundice and have a high likely-hood of developing of cirrhosis

- Diagnosis: serology

Anti-Delta IgM (in 3 weeks) or IgG (appear after and remain for years)

- Rx: as HBV

treatment with interferons isn't as effective as in infections with HBV alone

since the capsid antigen of delta Hep is HBsAG, in order to prevent transsmision infected indviduals shouldn't donate blood or serum

prevention is by decreased use of contaminated needles among injection drugs users and more safety measures when using needles among health care workers

Hepatitis C virus

Etiologic agent of viral hepatitis C

- Flavivirus, Enveloped , single stranded , positive sense RNA virus
- No polymerase in the virion

very simple genome having 3 stuctural and 5 non-structural genes

- 6 genotypes: needed for Rx and medicolegal

also there's multiple subtypes.
there's a hypervariable region in the envelope glycol protein and it's called quasispecies.

- Spread via infected blood and sexual contact

*transmission is not as understood as Hep a/b/d
*it was major cause for hepatitis post-transfusion before there were screening for donated blood

sexually is much less than HBV

- 6 - 8 week incubation period / most infections are sub-clinical

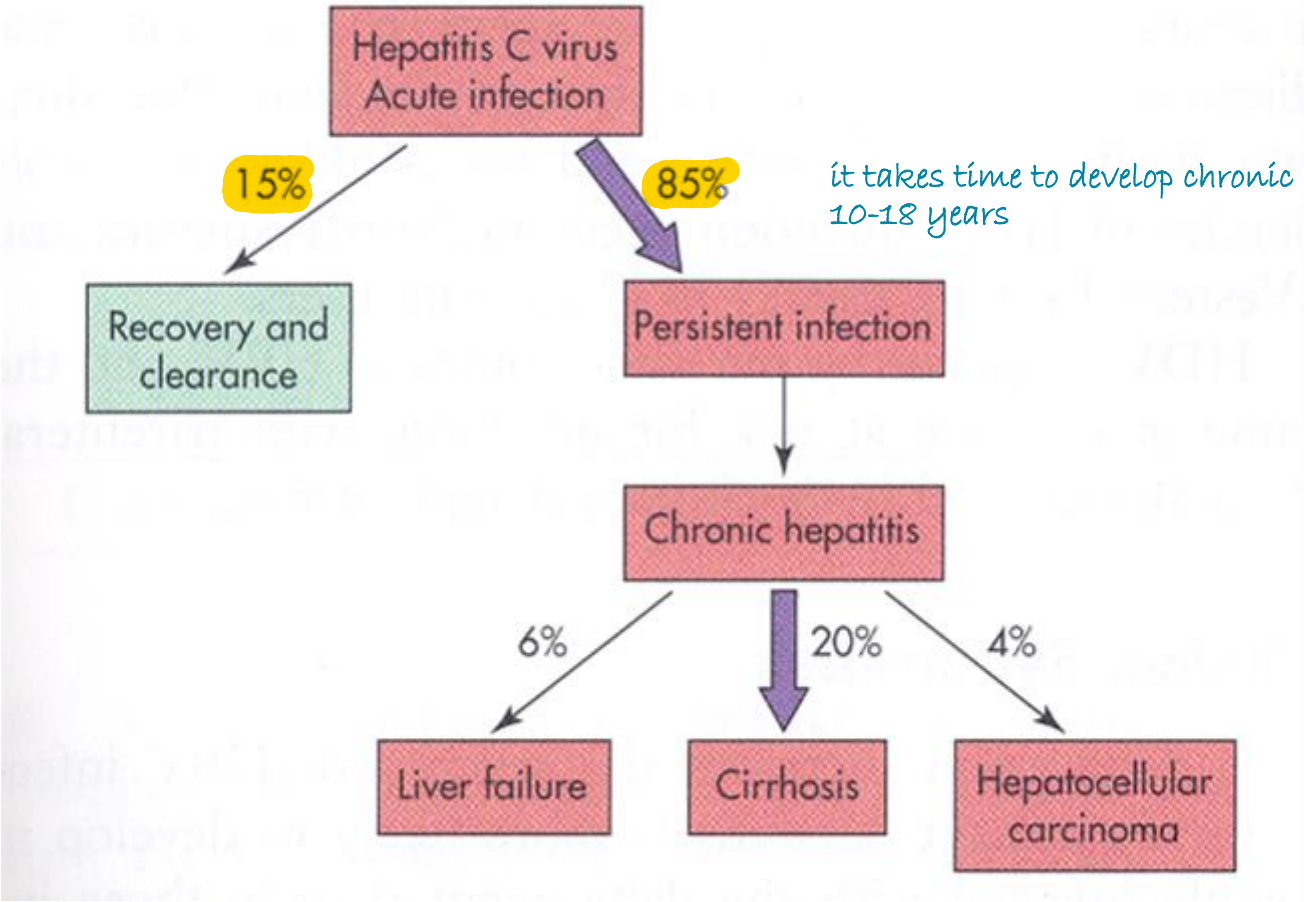
- Clinical infections are generally less severe than HBV, damage due to cell mediated immune response

Hep C is incidious disease that it doesn't usually cause clinically evident acute hepatitis instead it's present in quarter of infected individuals as smoldering Chronic hepatitis that may lead to liver failure

- HVC has *a higher incidence of chronic liver disease than HBV* (70-80% of patients remain viremic for more than 1 year)

- 170 million cases globally

Hepatitis C virus



it takes time to develop chronic hepatitis
10-18 years

Hepatitis C virus

Diagnosis:

*antigens tend to not be detectable in blood so serologic tests aim for Antibodies
*antibodies against HCV takes long time to develop or may not even develop in some pts making the sero-diagnosis very difficult

1. Anti HCV IgM
2. RNA detection

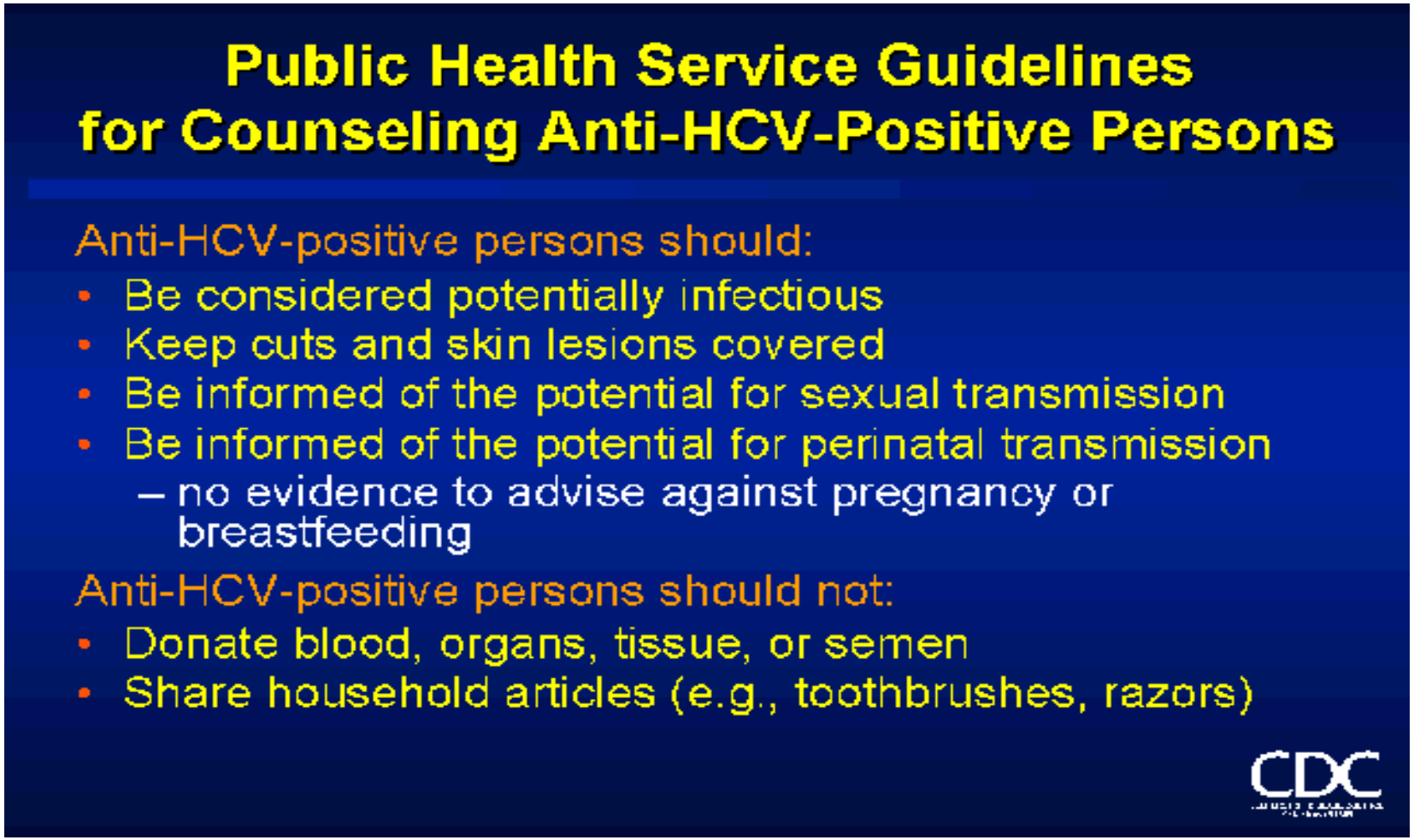
quantitative assays might be used for diagnosis / estimating prognosis / monitoring therapy

Treatment:

antivirals interferon alpha and ribavirin (aka tribavirin) are the drugs of choice of Hep C infections

Hepatitis C virus / prevention

- No vaccine
- Blood screening



Post exposure prophylaxis

جدول رقم (9) الاجراءات الفورية بعد اصابة عمل

المريض مصدر الاصابة	الوضع التطعيمي للموظف	الاجراء
التهاب الكبد (B) موجب HBsAg (positive)	- لم يتم تطعيمه - غير مكتمل الجرعات - ثلاث جرعات من التطعيم	-اعطاء التطعيم فورا + جرعة جليوبيولين مناعي* - إكمال كل الجرعات و اعطاء جليوبيولين مناعي* - فحص الاجسام المناعية (اذا كان أكثر أو يساوي 10 وحدة دولية لا شيء) **
التهاب الكبد (B) سالب HBsAg (negative)	- لم يتم تطعيمه - تم تطعيمه	- يتم تطعيمه - لا شئ
غير معروف اصابته بالتهاب الكبد ب	- لم يتم تطعيمه - غير مكتمل الجرعات - ثلاث جرعات من التطعيم	- -يعامل كما لو كان مصدر الاصابة ايجابيا - يعامل كما لو كان مصدر الاصابة ايجابيا - يعامل كما لو كان مصدر الاصابة ايجابيا
حامل لمضاد فيروس التهاب الكبد (C)	لا يوجد لقاح للالتهاب الكبد (C)	فحص الموظف بعد الاصابة مباشرة ثم بعد اسبوعين و بعد شهر ثم بعد 3 اشهر بطريقة HCV-Abو PCR و اذا ظهرت بوادر اصابته يحول الى أخصائي جهاز هضمي
غير معروف اصابته بالتهاب الكبد (C)	لا يوجد لقاح للالتهاب الكبد (C)	فحص الموظف بعد الاصابة مباشرة ثم بعد اسبوعين و بعد شهر ثم بعد 3 اشهر بطريقة HCV-Abو PCR و اذا ظهرت بوادر اصابته يحول الى أخصائي جهاز هضمي
حامل لفيروس العوز المناعي البشري HIV	لا يوجد لقاح لفيروس العوز المناعي البشري HIV	- مدة اربعة اسابيع يتم فيه تناول ثلاثة ادوية مضادة للفيروسات (مثل زيدوفودين ولاميفودين) ويجب الرجوع الى البرنامج الوطني لمكافحة الايدز*** - يبدأ العلاج فوراً(خلال ساعات)

* يتم ذلك خلال 24 ساعة من التعرض للعدوى

* *تقاس الاستجابة المناعية لمطعوم الكبد (B) بفحص الاجسام المضادة (Hbs Ab) وتعتبر ايجابية اذا كانت أكبر أو يساوي 10 وحدة دولية

Table 1 summary

Comparison of A, B, D (Delta), C, and E Hepatitis

Feature	A	B	D	C[a]	E
Virus type	Single-stranded RNA	Double-stranded DNA	Single-stranded RNA	RNA	RNA
Percent of viral hepatitis	50	41	<1	5	<1
Incubation period (days)	15–45 (mean, 25)	7–160 (mean, 60–90)	28–45	15–160 (mean, 50)	?
Onset	Usually sudden	Usually slow	Variable	Insidious	?
Age preference	Children, young adults	All ages	All ages	All ages	Young adult
Transmission					
Fecal–oral	+++	±	±	–	+++
Sexual	+	++	++	+	+?
Transfusion	–	++	+++	+++	–
Severity	Usually mild	Moderate	Often severe	Mild	Variable
Chronicity (%)	None	10	50–70	>50%	None
Carrier state	None	Yes	Yes	Yes	?
Immune serum globulin protective	Yes	Yes[b]	Yes[c]	Uncertain	?

Abbreviation: Plus and minus signs indicate relative frequencies.

[a] Many individuals with hepatitis C virus are also infected with the hepatitis G virus, which is similar to hepatitis C.

[b] Hyperimmune globulin more protective.

[c] Prevention of hepatitis B prevents hepatitis D.

The End