

# Clinical Epidemiology & Control of Hepatitis A

Shahid Beheshti University of medical sciences

By: Hatami H. MD. MPH

# Definition History Etiology

#### اصول و مبانی

#### اتیولوژی هپاتیتها

- عوامل غيرعفوني
  - عوامل عفونی
- عوامل غيرويروسي
  - عوامل ويروسى
    - کلاسیک
  - غيركلاسيك

عوامل غیرعفونی مولد هپاتیت حاد داروها (آسپیرین، استامینوفن، ایزونیازید) توکسینها (الکل، تتراکلرید کربن) آسیبهای غیراختصاصی (شوک، ایسکمی).

عوامل عفونی غیر ویروسی مولد هپاتیت حاد

سيفيليس،

لپتوسپيروز،

تب Q،

پنوموکوک...

ویروسهای مولد بیماریهای سیستمیک همراه با هیاتیت

ویروسهای تب زرد، اپشتین بار (EBV)، سیتومگال (CMV)، هرپس، واریسلا زوستر، سرخک، سرخجه، کوکساکی B، آدنوویروسها

عوامل اصلی مولد هپاتیتهای ویروسی کلاسیک

- ويروس هپاتيت A (HAV)
- ويروس هياتيت B (HBV)
- ويروس هياتيت دلتا يا D (HDV)
- ويروس هپاتيت HCV) C عامل هپاتيت NANB منتقله از طريق خون

•ویروس هپاتیت E (HEV) عامل هپاتیت اپیدمیک NANB منتقله از طریق دهانی ـ مدفوعی

عوامل احتمالي موّلد هپاتيتهاي ويروسي كلاسيك

- ويروس هياتيت F (HFV) ?
- ويروس هپاتيت (HGV) G

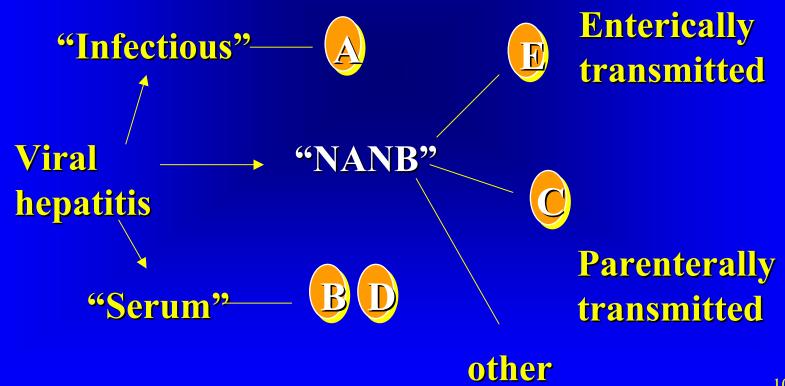
# Definition of Classic hepatitis

- An acute self-limiting infection of the liver
- Classic hepatitis?
- Etiology:

A, B, C, D and E

#### VIRAL HEPATITIS

جایگاه تاریخی هپاتیت A در بین سایر هپاتیتهای کلاسیک



#### Definition of hepatitis A

- Infectious hepatitis
- Epidemic hepatitis
- Epidemic jaundice
- Catarrhal jaundice
- Type A hepatitis

## Viral Hepatitis - Overview

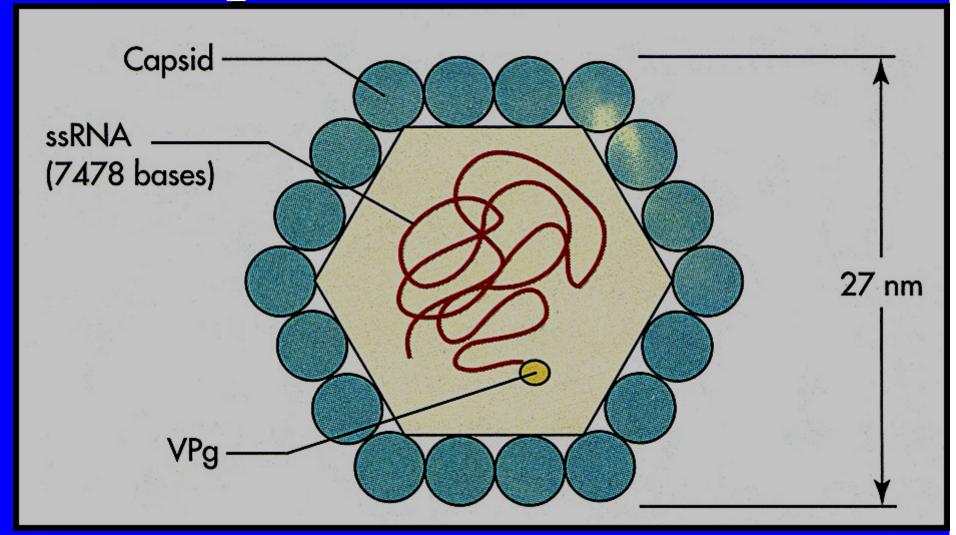
		Type of hepatitis			
	A		C	D	E
Source of virus	feces		blood/ lblood-derived body fluids	blood/ blood-derived body fluids	feces
Route of transmission	fecal-oral	to the state of th	percutaneous permucosal	percutaneous permucosal	fecal-oral
Chronic infection	no	yes	yes	yes	Type 1&2 no Type 3&4 Yo
Prevention	pre/post- exposure immunizatio	pre/post- exposure n immunization	blood donor screening; risk behavior modification	exposure	ensure safe drinking water immunizatio

## Etiology

- Hepatitis A virus (HAV),
- Genus Heparnavirus
- Family Picornaviridae
  - SS RNA
  - Single serotype worldwide
  - Humans only important reservoir

Human HAV strains are divided into 3 genotypes but appear to be of only 1 serotype. (M2015)

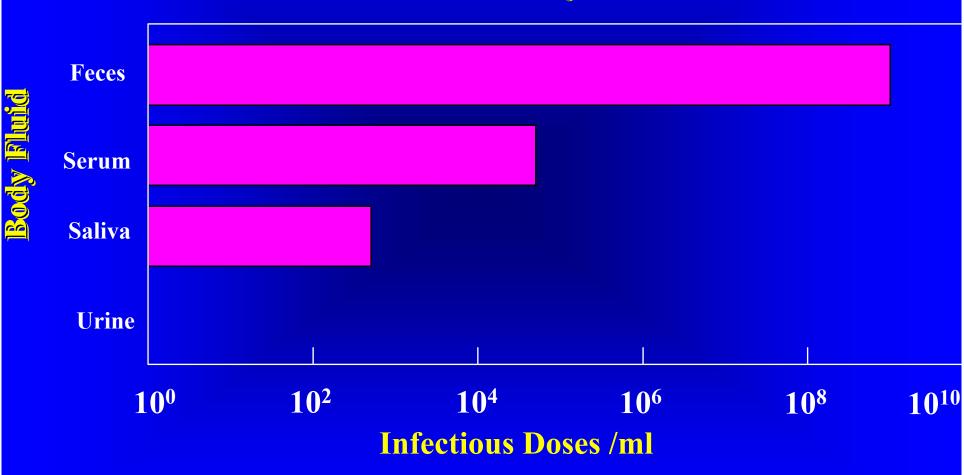
#### Hepatitis A Structure



Nonenveloped, 27 nm RNA Virus

۱ \_ عامل اتيولوژيک /

# Concentration of Hepatitis A Virus in Various Body Fluids



### Stability

- More resistant to heat than picorna.
- Incompletely inactivated by 60°c 12 h.
- Inactivate by autoclaving (121°c, 30 minutes)
- Viable for many years at -20°c
- At room temperature for weeks
- In fecal suspensions are more resistant

### Stability

- Survive for days to weeks in shellfish, water, marine sediment
- Resistant to most solvents and detergents, and PH~3.
- Inactivate by many common disinfecting chemicals (hypochlorite, quaternary amonium

#### Inactivated

#### The most promising techniques are

- Dry heat (80c for 24 h.)
- Ultraviolet irradiation
- γ-irradiation
- Pasteurization at 60c for 10 h.
- Iodine 3 mg/lit
- Potassium permanganate 30 mg/lit
- Formalin 1/4000 for 72 h.
- Formalin 3% for 5 minutes

## Pathogenesis

### The virus is:

- Ingested,
- Replicates in the bowel wall and liver leads to a:
- secondary viremia that infects the liver

## Pathogenesis

- Replicates in hepatocytes (little damage to cells)
- Released via bile to intestines
- Liver damage and clinical syndrome result of immune response and not direct effect of virus

#### ویژگیهای مهم عامل عفونتزا

(Infectivity) \*

(Pathogenicity) \*

(Virolence) \*

(Antigenicity) \*

(Immunogenicity) \*

# Descriptive epidemiology and

OCCUPPENCE

https://sites.google.com/site/emergingreemergingdisappearing/emerging\_ebook/emerging\_index-htm

#### Clinical epidemiology of Hepatitis A

- > Definition and public health importance
- >Etiologic agents
- 1) Incubation period
- 2) Natural couarse
- 3) Geographical distribution
- 4) Timeline trend
- 5) Age, Gender, Occupation, Social situation
- 6) Predisposing factors
- 7) Susceptibility & Resistance
- 8) Secondary attack rate
- 9) Modes of transmission, period of communicability
- > Prevention: primary, secondary, tertiary

OCCURRENCE

#### 1 -Incubation Period

Average 4 weeks

# سیر طبیعی

- میزان موارد بدون علامت (ساب کلینیکال)
  - ميزان موارد حاد
  - میزان موارد مزمن
  - میزان موارد بهبودی خودبخودی
- سیر بعدی بیماری با درمان و بدون درمان
  - میزان مرتالیتی و مربیدیتی
  - میزان مصونیت بعد از بهبودی

#### 2 - Natural course

- Most cases are asymptomatic;
- It does not produce chronic carrier state and has
- No long term sequelae
- Most cases resolve spontaneously in 2-4 weeks
- Complete recovery 99%
- Disease occurs on a sporadic and an epidemic basis.

#### 2 - Natural course

- It typically causes an acute, self-limited illness,
- More often symptomatic in adults than in children.
- HAV is more severe in patients with preexisting chronic hepatitis B or C. (M2015)

# **Acute Viral Hepatitis Clinical Manifestations**



- —An acute illness with:
  - discrete onset of symptoms (e.g. fatigue, abdominal pain, loss of appetite, intermittent nausea, vomiting)
  - jaundice or elevated serum aminotransferase levels, dark urine, light stool
  - Adults usually more symptomatic



# 2 - Natural course: Age

Jaundice by age group:

<6 yrs <10%

6-14 yrs 40%-50%

>14 yrs 70%-80%

Rare complications:

Fulminant hepatitis
Cholestatic hepatitis
Relapsing hepatitis

# Clinical Manifestations of 8647 Hospitalized Patients



Symptom	Percent
Jaundice	84
Weight loss	82
Malaise	80
Fever	76
Nausea	69
Vomiting	47
Abdominal pain	37
Arthralgia	ing shook/smerging index

# Clinical Manifestations of 8647 Hospitalized Patients

Clinical Findings	Percent
Hepatomegaly	87
Splenomegaly	9
Skin rashes	3
Mild edema	2
Petechia	2
Cardiac arrhythmias	0.8

# Clinical Manifestations of 8647 Hospitalized Patients



#### **Complications**

#### Percent

Cholestasis	1.6-5.3
Upper gastrointestinal bleeding	0.5-1.2
Thrombocytopenic purpura	<0.1 (6 cases)
Guillain-Barré syndrome	<0.1 (4 cases)
Pure red cell aplasia	<0.1 (3 cases)
Autoimmune hemolytic anemia	<0.1 (2 cases)
Tranverse mylelitis, optic neuritis	<0.1 (1 case each)

#### سیر طبیعی /سرعت بهبودی / پیش آگهی

- Two thirds of patients recover by 2 months
- 85% by 3 months,
- Nearly all by 6 months.
- Recovery is full and without sequelae, and chronic infection does not occur.



#### Age-specific Mortality Due to Hepatitis A

Age group
(years)

Case-Fatality (per 1000)

<5

5-14

15-29

30-49

>49

Total

3.0

1.6

1.6

3.8

17.5

4.1



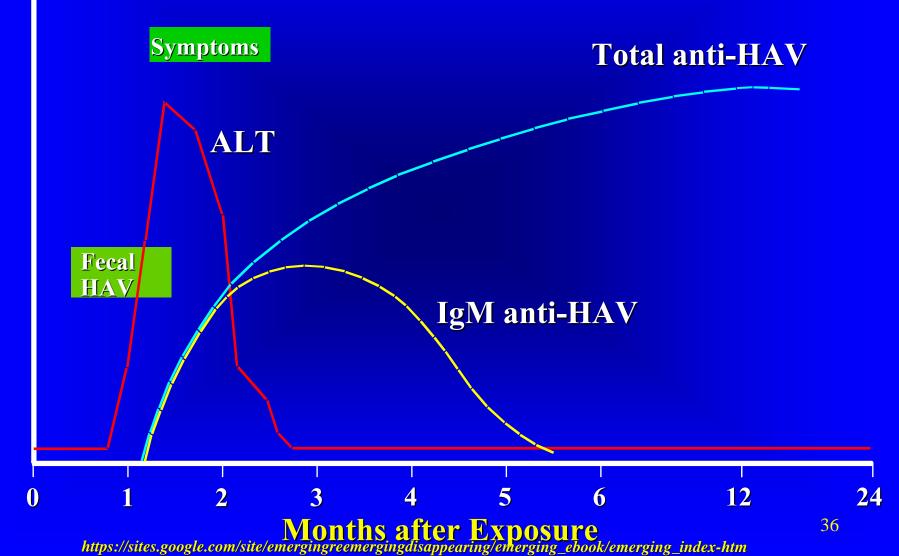
### Host immune response

Immunity after infection lasts for life









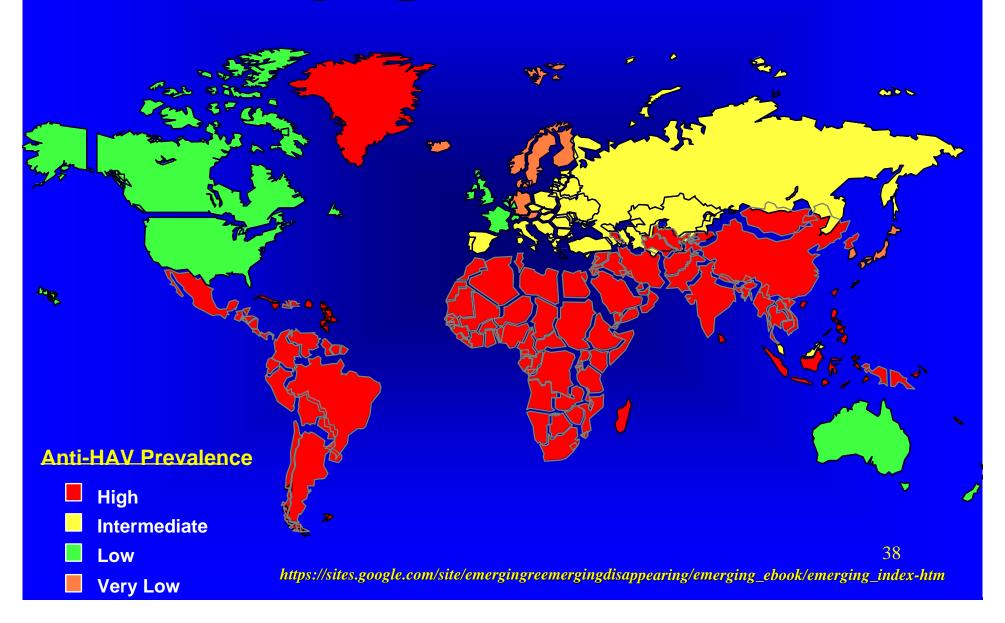
Titer

# سیر طبیعی

- میزان موارد بدون علامت (ساب کلینیکال)
  - ميزان موارد حاد
  - ميزان موارد مزمن
  - میزان موارد بهبودی خودبخودی
- سیر بعدی بیماری با درمان و بدون درمان
  - میزان مرتالیتی و مربیدیتی
  - میزان مصونیت بعد از بهبودی

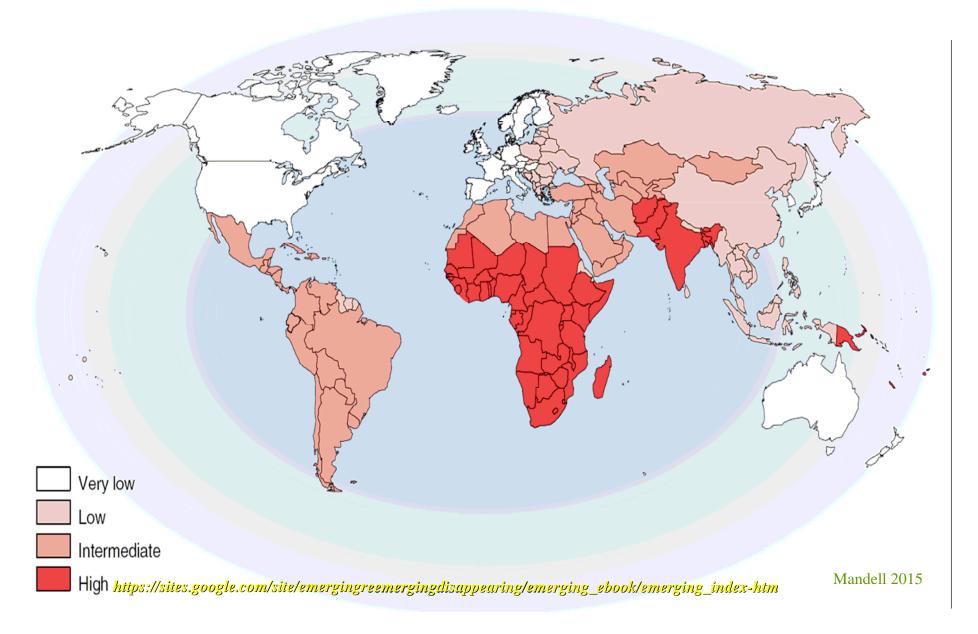
#### ۳\_انتشار جغرافیایی

## 3 – Geographical distribution



#### 2-انتشار جغرافیایی

## 3 – Geographical distribution



## Geographical distribution

- Worldwide
- Endemicity is related to hygienic conditions

# Geographical distribution Areas with high levels of infection

- In developing countries with poor sanitary conditions and hygienic practices
- Most children (90%) have been infected before the age of 10 years.
- Those infected in childhood do not experience any noticeable symptoms.
- Epidemics are uncommon because older children and adults are generally immune.
- Symptomatic disease rates in these areas are low and outbreaks are rare.

WHO, F 2017

# Geographical distribution Areas with intermediate levels of infection

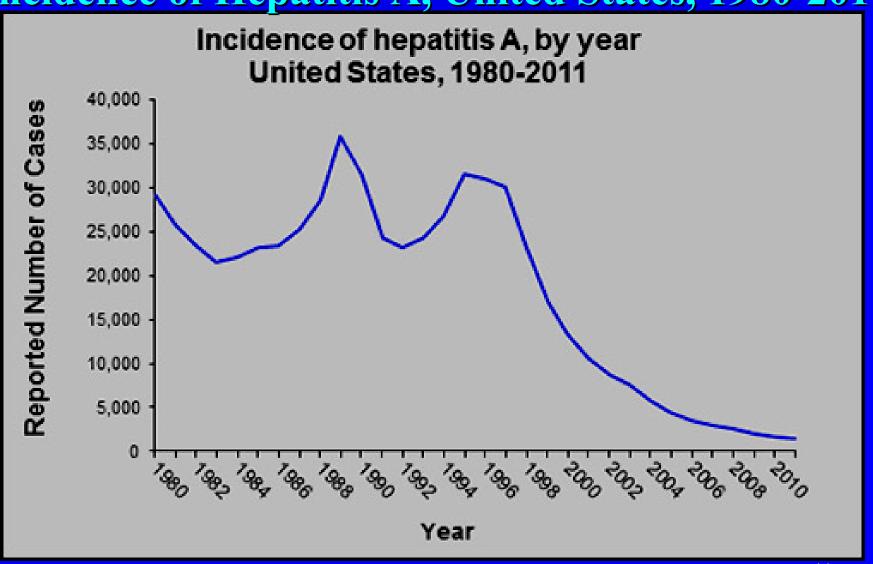
- In developing countries, countries with transitional economies, and regions where sanitary conditions are variable,
- Children often escape infection in early childhood and reach adulthood without immunity.
- Ironically, these improved economic and sanitary conditions may lead to accumulation of adults who have never been infected and who have no immunity.
- May lead to higher disease rates and large outbreaks can occur.

WHO, F 2017

# Geographical distribution Areas with low levels of infection

- In developed countries with good sanitary and hygienic conditions. Infection rates are low.
- May occur among adolescents and adults in high-risk groups, such as injecting-drug users, men who have sex with men, people travelling to areas of high endemicity, and in isolated populations, such as closed religious communities.
- When the virus gets introduced in such communities, high levels of hygiene stops person-to-person transmission and outbreaks die out rapidly.

#### **Incidence of Hepatitis A, United States, 1980-2010**



### Hepatitis A in Iran

- در استان فارس، ۱۰۰٪ افراد کمتر از ۱۰ ساله و ۹۰٪ بزرگسالان
  - در تهران ۲۰٪ مثبت
  - با افزایش سن بر میزان مثبت بودن، افزوده می شود

## 4 - Timeline trend

- Pandemics
- Epidemics
- Outbreaks
- Seasonality

## Seasonality

## Autumn, & early winter

قبالاً در بعضی از کشورهای پیشرفته با شرایط اقلیمی معتدله نظیر ژاپن، المریکا و دانمارک، موج طغیانهای بیماری هر ۱۰–۵ سال به الوج بیماری هر ۱۰–۵ سال به الوج

5 – Age, Gender, Occupation, Social conditions

## Age distribution

- Infected children under 6 years of age do not usually experience noticeable symptoms, and only 10% develop jaundice.
- Among older children and adults, infection usually causes more severe symptoms, with jaundice occurring in more than 70% of cases.

## 6 – Predisposing factors

- Poor sanitation;
- Lack of safe water;
- Use of recreational drugs;
- Living in a household with an infected person;
- Sexual partner of someone with acute hepatitis A infection;
- Travelling to areas of high endemicity without being immunized.

## 7 – Susceptibility and Resistance

- General
- Immunity lifelong

## 8 – Secondary attack rate

- More than hepatitis E
- Family contacts: 24%
- Daycare centers: 18%
- Homosexual : 11%
- Traveling to ...: 4%
- IVDU : 2%

احتمال وقوع همه گیری ناشی از تماس انسان با انسان در کدامیک از بیماریها بیشتر است ۱۶ـ تیفوئید ۲ـ کلرا ۳ـ هپاتیت ٤ هپاتیت

## 9 - Transmission

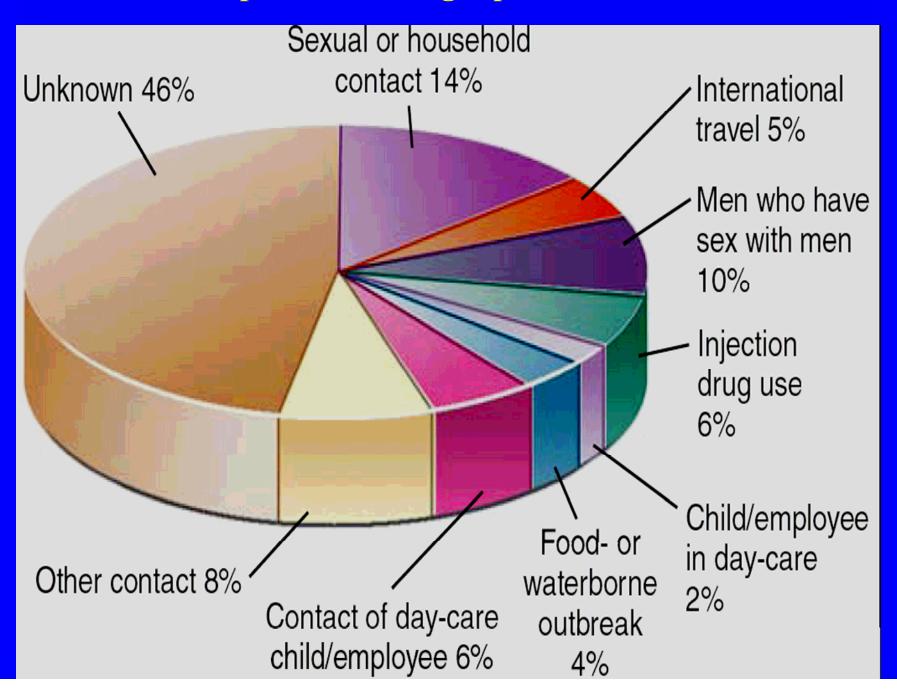
- Close personal contact (household contact, sex contact, child day care centers)
- Contaminated food, water (infected food handlers, raw shellfish)
- Blood exposure (rare)
   (injecting drug use, transfusion)

Person-to-person transmission by the fecal-oral route is the primary means of HAV transmission throughout the world.

# الگوی هپاتیت A با توجه به شدت آندمیسیته آن

Endemicity	Disease Rate	Peak Age of Infection	Transmission Patterns
High	Low to High	Early childhood	Person to person; outbreaks uncommon
Moderate	High	Late childhood/ young adults	Person to person; food and waterborne outbreaks
Low	Low	Young adults	Person to person; food and waterborne outbreaks
Very low	Very low	Adults	Travelers; outbreaks uncommon

#### Risk factors for hepatitis A among reported cases, USA, 1990-2000



## Period of communicability

- During the later half of incubation
- A few days after onset
- Noninfectious after first week of jaundice
- Up to 6 months in infants and children

Infectivity of virus in stool is present from 21 days before to 8 days after onset of jaundice.

The highest concentration of virus in stool is in the 2-week period before jaundice develops (M2015).

### Reservoir

- Human
- Chimpanzees, Marmosets
- Gorillas, Orangutans
- Gibbons, Macaques
- Owl monkey, Rhesus



Human are the only important reservoir of HAV

# Prevention

and

Control

## **Prevention and Control**

- Primary Prevention:
  - Prevention of disease in "well" individuals
- Secondary Prevention:
  - Identification and intervention in early stages of disease
  - **Tertiary Prevention:**
  - Prevention of further deterioration, reduction in complications

## 1 - Primary Prevention:

- Hygiene (e.g., hand washing)
- Sanitation (e.g., clean water sources)
- Hepatitis A vaccine (pre-exposure)
- Immune globulin (pre- and post-exposure)

پیشگیری سطح اوّل

# Primary Prevention: Hygiene

- Educate the public
- Provide safe water and sewage disposal
- Minimize the possibility of fecal- oral transmission

#### THE MAXIME TO PREVENT HEPATITIS A

**Boil** it

**Cook it** 

Peel it

Forget it

## Vaccines

- Inactivated vaccine
- Highly immunogenic
  - •97%-100% of children, adolescents, and adults
- Highly efficacious
  - •In published studies, 94%-100% of children protected against clinical hepatitis A after equivalent of one dose

# HEPATITIS A VACCINES

1st dose at time 0

2<sup>nd</sup> dose 6-12 months afterwards

## Hepatitis A vaccine

- Nearly 100% of people develop protective levels of antibodies to the virus within one month after a single dose of the vaccine.
- Even **after exposure** to the virus, a single dose of the vaccine within **two weeks** of contact with the virus has protective effects.
- Still, manufacturers recommend two vaccine doses to ensure a longer-term protection of about 5 to 8 years after vaccination.
- No vaccine is licensed for children younger than one year of age

# Duration of Protection After Hepatitis A Vaccination

- Protection begins 2-4 weeks after vaccine
- Persistence of antibody
  - At least 5-8 years among adults and children
- Efficacy
  - No cases in vaccinated children at 5-6 years of follow-up
- Mathematical models of antibody decline suggest protective antibody levels persist for at least 20 years
- Other mechanisms, such as cellular memory, may contribute

### Hepatitis A Vaccine

- Vaccine is recommended for the following persons 1 year of age and older:
  - 1. Travelers to areas with increased rates of hepatitis
    A
  - 2. Men who have sex with men
  - 3. Injecting and non-injecting drug users
  - 4. Persons with clotting-factor disorders (e.g. hemophilia)
  - 5. Persons with chronic liver disease

GROUP	COMMENTS
Children	Vaccine should be given to all children at age 1 yr (12-23 mo).* Vaccination of children 2-18 yr may also be warranted.†
International travelers <sup>‡</sup>	IG may be given in addition to or instead of vaccine; children <12 mo should receive IG (see Table 176-2)
Close contacts of newly arriving international adoptees Men who have sex with men	All persons who anticipate close personal contact (e.g., household contact or regular babysitter) during the first 60 days after arrival Includes adolescents
Illicit drug users	Includes adolescents
Persons with chronic liver disease, such as those with hepatitis B or C	Increased risk of fulminant hepatitis A with HAV infection
Persons receiving clotting factor concentrates	
Persons who work with HAV in research laboratory settings	Mandell 2015

## Hep A: Live attenuated Vac.

A live oral vaccine is also available in China WHO, Fact sheet JULY 2017

## Hepatitis A vaccine

- Countries with intermediate endemicity will benefit the most from universal immunization of children.
- Countries with low endemicity may consider vaccinating high-risk adults.
- In countries with high endemicity, the use of vaccine is limited as most adults are naturally immune.

### Hep A: Passive Immunization

- Hepatitis A immune globulin can be given up to 2 weeks after an exposure
- Immunity temporary (4-5 months)
- Also given in travelers leaving for endemic area on short notice (ie not enough time for the vaccine to be effective)

## Preexposure Immunoprophylaxis

Age (yr)	Exposure Duration	Recommended Prophylaxis
<1 <1 <1 >1	Short term (<3 mo) 3-5 mo >5 mo Short or long term	IG 0.02 mL/kg IG 0.06 mL/kg IG 0.06 mL/kg repeated every 5 mo Hepatitis A vaccine Hepatitis A vaccine and IG (0.02 mL/kg) if exposure is
		expected in less than 2-4 weeks Substitute IG as above if vaccine is contraindicated or refused

	EXPOSURE	RECOMMENDED
AGE	DURATION	PROPHYLAXIS
<12 mo	Short term (<3 mo)	IG 0.02 mL/kg
<12 mo	3-5 mo	IG 0.06 mL/kg
<12 mo	>5 mo	IG 0.06 mL/kg repeated every 5 mo
Healthy persons 1-40 yr	Short or long term	Hepatitis A vaccine
Healthy persons >40 yr	Short or long term	Hepatitis A vaccine. Can add IG (0.02 mL/kg) if exposure is expected in ≤2 wk.
Immunocompromised persons and persons with chronic liver disease or other chronic medical conditions	Short or long term	Hepatitis A vaccine. Add IG (0.02 mL/kg) if exposure is expected in ≤2 wk.
Persons for whom vaccine is contraindicated or who refuse vaccine	Depending on expected duration of exposure, substitute IG as described above for children <12 mo of age	Mandell 2015

## 2 - Secondary Prevention:

Identification And intervention in early stages of disease

## Postexposure prophylaxis

- Administer postexposure prophylaxis with hepatitis A vaccine (preferred) or ISG within the previous 2 weeks,
- ISG if patient is immunosuppressed, or if patient is younger than 1 year of age

### Postexposure prophylaxis

Time Since Exposure	Future Exposure Likely or Other Indication for Vaccination*	Recommended Prophylaxis
<2 wk	No	IG 0.02 mL/kg
<2 wk	Yes	IG 0.02 mL/kg and initiate hepatitis A vaccine series <sup>†</sup>
>2 wk	No	None
>2 wk	Yes	Initiate hepatitis A vaccine series

<sup>\*</sup>See Table 170-6.

<sup>†</sup>Children < 1 years of age (for whom vaccine is not licensed) and persons with a contraindication to vaccination should receive immune globulin (IG) 0.06 mL/kg, repeated every 5 months during exposure.

### Postexposure prophylaxis

GROUP*	RECOMMENDED PROPHYLAXIS <sup>†</sup>
Persons 12 mo–40 yr	Single antigen hepatitis A vaccine at age-appropriate dose
Persons >40 yr	IG 0.02 mL/kg is preferred; vaccine can be used if IG cannot be obtained
Children <12 mo	IG 0.02 mL/kg <sup>‡</sup>
Immunocompromised persons, persons who have chronic liver disease, and persons for whom vaccine is contraindicated	IG 0.02 mL/kg <sup>‡</sup>

# Diagnosis Acute Viral Hepatitis

- The most characterisitc markers of infection are the serum aminotransferases
  - ALT and AST
- Increase proportionally during the prodromal phase and can reach 20 x normal.
- Peak when the patients are jaundiced.
- Alk Phos and LDH are usually normal.
- Bilirubin can reach 20 mg/dL

# Diagnosis Acute Viral Hepatitis

- PT is usually normal
- If elevated, for example, INR>1.5, serves as a prognostic marker of fulminant hepatic failure
- Normal CBC
- Viral markers.....

### Diagnosis

- Not clinically distinguishable from other types of acute viral hepatitis.
- Detection of HAV-specific IgM in the blood.
- RT-PCR to detect the hepatitis A virus RNA

### Diagnosis of hepatitis A

- Detection of IgM antibody
- IgG positive 1-3 weeks later; suggests prior infection or vaccination.

### Hepatitis A Treatment

- Supportive- no specific role of antiviral therapy
- Lifelong immunity likely after infection or vaccination

## 3 - Tertiary Prevention:

Liver transplantation

# ACUTE HEPATITIS A CASE DEFINITION FOR SURVEILLANCE

#### Clinical criteria

#### An acute illness with:

- discrete onset of symptoms (e.g. fatigue, abdominal pain, loss of appetite, intermittent nausea, vomiting), and
- jaundice or elevated serum aminotransferase levels
- <u>Laboratory criteria</u>
  - IgM antibody to hepatitis A virus (anti-HAV) positive
- Case Classification
  - <u>Confirmed</u>. A case that meets the clinical case definition and is laboratory confirmed or a case that meets the clinical case definition and occurs in a person who has an epidemiologic link with a person who has laboratory-confirmed hepatitis A (i.e., household or sexual contact with an infected person during the 15-50 days before the onset of symptoms).

• خانواده ۵ نفره فرانسوی که ده روز دیگر قصد مسافرت و اقامت یکساله در افغانستان را دارند دارای ویژگیهای زیر می باشند:

۱ ـ پدر : ۶۰ ساله، حساس در مقابل هپاتیت A قرار است بلافاصله پس از رسیدن به مقصد، بدون توقف با همان هواپیما به فرانسه باز گردد.

• خانواده ۵ نفره فرانسوی که ده روز دیگر قصد مسافرت و اقامت یکساله در افغانستان را دارند دارای ویژگیهای زیر می باشند:

۲ ـ مادر ۳۵ ساله، حساس، دچار آگاماگلوبولینمی

• خانواده ۵ نفره فرانسوی که ده روز دیگر قصد مسافرت و اقامت یکساله در افغانستان را دارند دارای ویژگیهای زیر می باشند:

A ساله با سابقه یکبار ابتلاء حتمی به هپاتیت A

• خانواده ۵ نفره فرانسوی که ده روز دیگر قصد مسافرت و اقامت یکساله در افغانستان را دارند دارای ویژگیهای زیر می باشند:

کے پسر ۱٦ ساله، حساس

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٥ \_ دختر ۱۰ ماهه، حساس

### جدول ۳ ـ ایمونوپروفیلاکسی قبل از تماس با ویروس هپاتیت A

پروفیلاکسی قابل توصیه	مدت تماس	سن (سال)
ایمونوگلوبولین ۰۲/. میلی لیتر / کیلوگرم	کمتر از ۳ ماه	كمتر از ۱ سال
ایمونو گلوبولین ۰۶/. میلی لیتر / کیلوگرم	۵–۳ ماه	كمتر از ۱ سال
ایمونوگلوبولین ۰۶/. میلی لیتر / کیلوگرم و تکرار آن هر ۵ ماه	بیش از ۵ ماه	كمتر از ۱ سال
واکسن هپاتیت A در صورت شروع تماس به فاصله ۴-۲ هفته بعد	کمتر یا بیشتر از ۳ ماه	بیش از ۱ سال
واکسن هپاتیت A + ایمونو گلوبولین ۰۲/. میلی لیتر / کیلوگرم در		
صورت تماس به فاصله کمتر از ۲ هفته بعد		

### جدول ٤ ــ ایمونوپروفیلاکسی بعد از تماس با ویروس هپاتیت ۸

پروفیلاکسی قابل توصیه	احتمال تماس بعدی یا سایر	فاصله كنوني
	اندیکاسیونهای دیگر واکسن	با تماس قبلی
ایمونوگلوبولین ۰۲/. میلی لیتر / کیلوگرم	خير	كمتر از ٢ هفته
ترجیحا استفاده از واکسن و در غیر اینصورت؛	آری	کمتر از ۲ هفته
ایمونوگلوبولین ۰۲/. میلی لیتر / کیلوگرم		
اقدام خاصي لازم نيست	خير	بیش از ۲ هفته
شروع واکسیناسیون هپاتیت A	آری	بیش از ۲ هفته

### Sources:

- CDC, Internet site, 2014
- WHO/CDS/CSR/EDC/2014, Hepatitis E World Health Organization, Department of Communicable Disease Surveillance and, Response
- Control of communicable diseases, 2012.
- Harrison 2015
- Mandell 2015
- Fact sheet JULY 2017.

## اپیدمیولوژی بالینی و کنترل بیماریهای عفونی

آدرس اسلایدها و کتب الکترونیک در سایتهای اینترنتی:

https://sites.google.com/site/drhatamilibrary کو کل سایت

https://t.me/drhatamibooks

تلگرام https://t.me/emergingReemerging

http://eitaa.com/joinchat/1700331527Cc8d03e9182 اينا

سروش https://sapp.ir/emerging