Hepatitis A, B and C Prevention and Treatment

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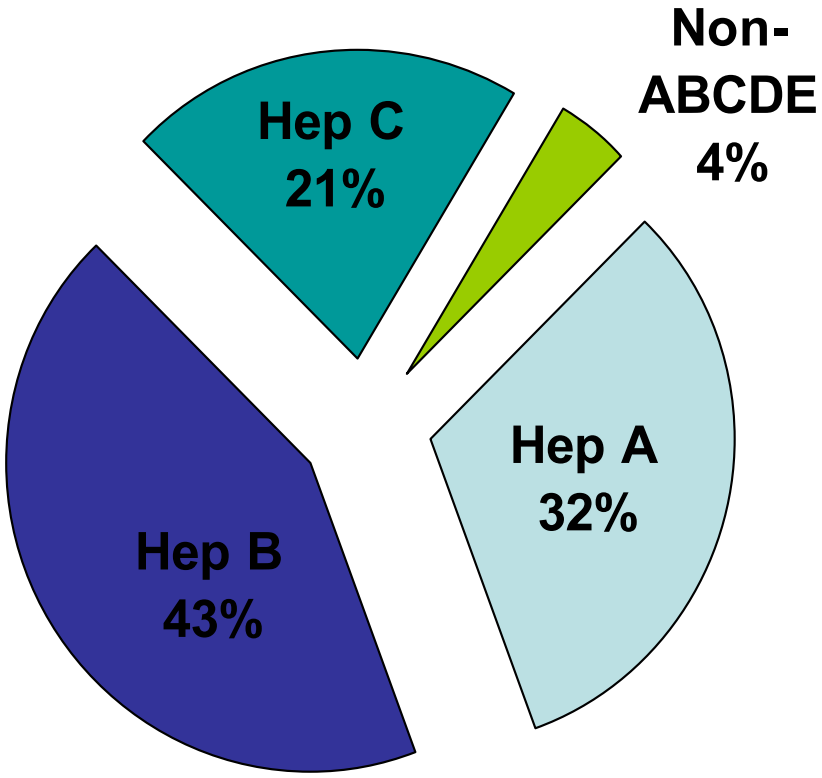
AMERICAN ACADEMY OF FAMILY PHYSICIANS

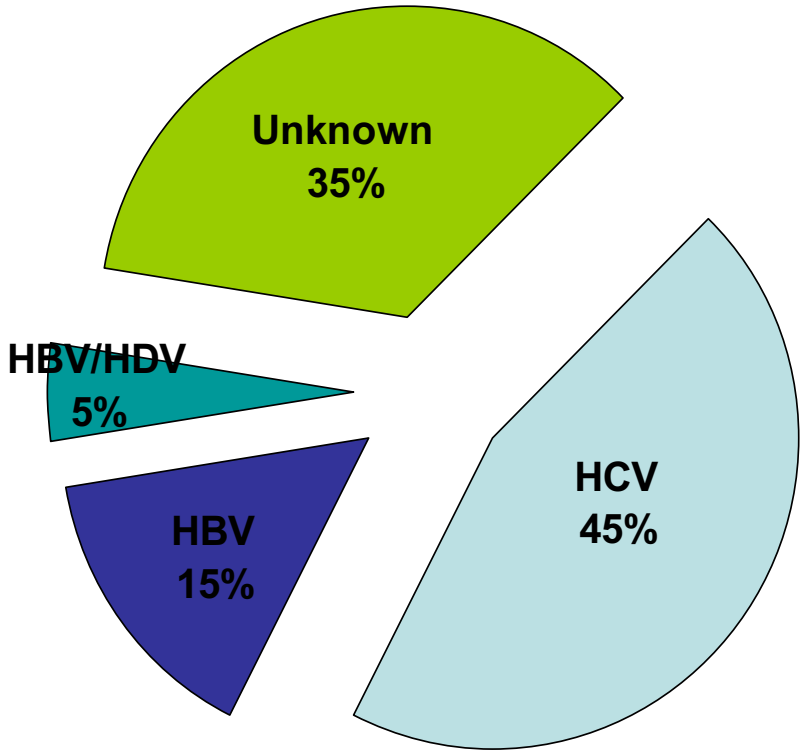
STRONG MEDICINE FOR AMERICA

Causes of Acute Viral Hepatitis in the United States

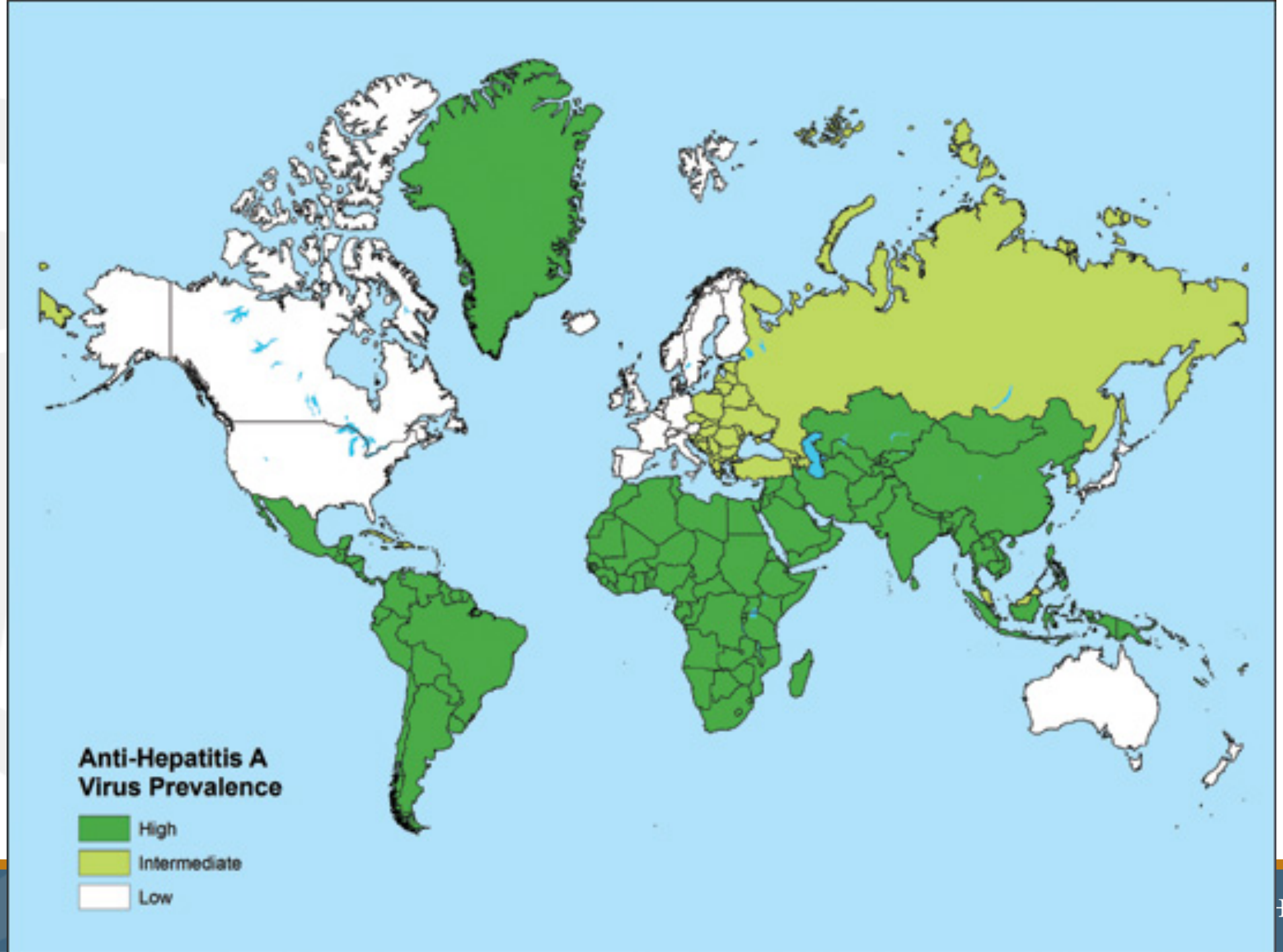


Alter MJ, et al. N Engl J Med. 1997;336:741.
Alter MJ, Mast EE. Gastroenterol Clin North Ame. 1994;23:437.

Etiologic Agents of Chronic Viral Hepatitis



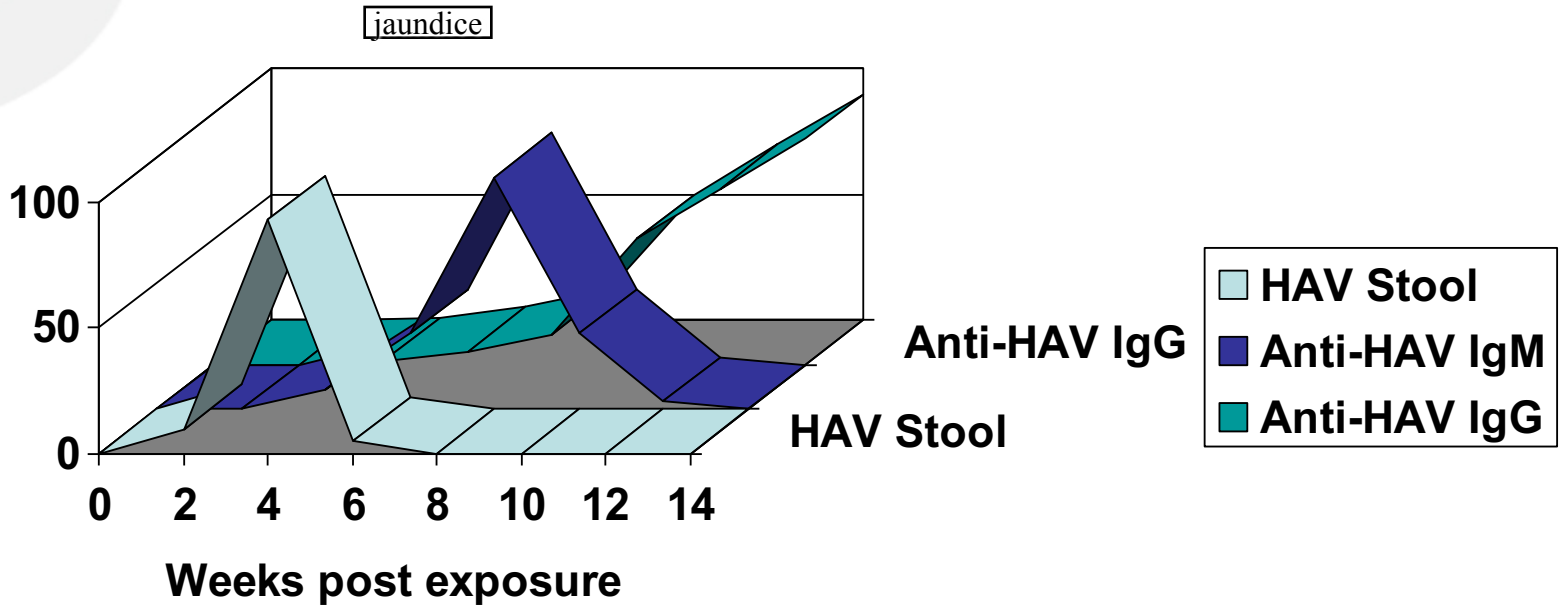
Alter MJ, Hadler SC. In: Hepatitis Delta Virus. Molecular Biology, Pathogenesis, and Clinical Aspects. 1993:243.


Anti-Hepatitis A
Virus Prevalence
High
Intermediate
Low

Hepatitis A - facts

- Mode of transmission: fecal-oral route
- Incubation period is about 1 month
- Symptoms are usually constitutional and maybe pruritic. Self limiting.
- No chronic carrier state. Rarely cause acute fulminant liver failure.
- Lab: IgM anti-HAV

Hepatitis A Serology



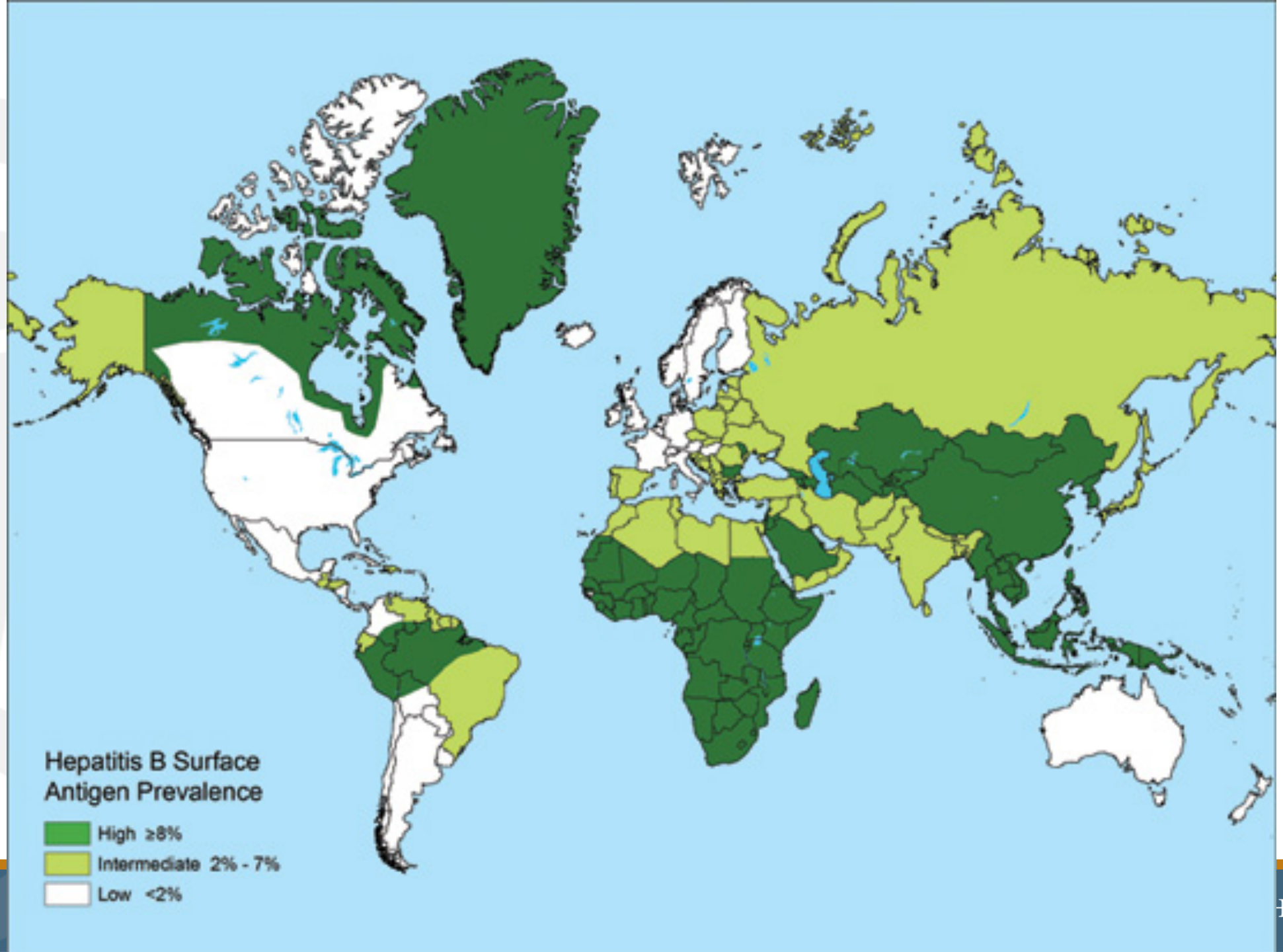
Hep. A Vaccination

1. Travelers to endemic areas.
2. All children age 12- 23 months.
3. Children (2-18 y/o) living in high prevalence areas;
   - Native Americans or Alaskans natives
4. IV drug abusers.
5. MSM
6. Occupational risk
7. Chronic liver disease, esp., over 30 y/o.
8. Clotting factors disorder, eg., hemophiliacs.
9. Anyone who request the vaccine.

Vaccines and Immunoglobulin

- Two different inactivated vaccines; Havrix & Vaqta
  - All children > 1 y/o
- Twinrix is a bivalent vaccine – Hep A &B
  - 18 y/o or older
- Seroconversion rate of 97%-99% in 1 mth

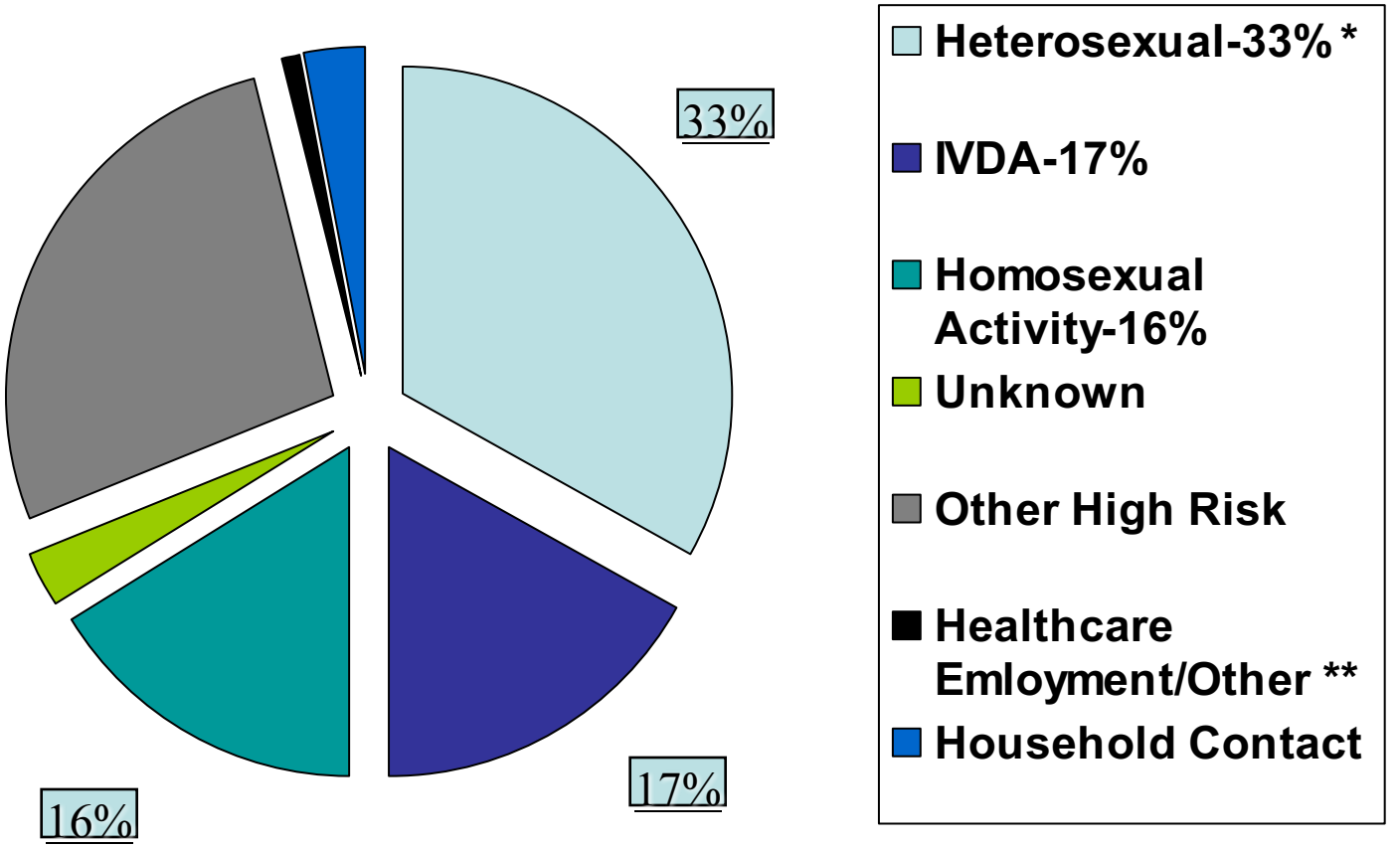
- Give **within two weeks** of post-exposure
- Dose: 0.02-0.06 mL/kg of body weight
- Only gives 3-5 months transient protection


Hepatitis B Surface Antigen Prevalence
High ≥8%
Intermediate 2% - 7%
Low <2%

Hepatitis B facts

- DNA virus
- Blood borne transmission
- 2 billion people worldwide have been infected
- 350 million live with chronic infection
- Incubation period is wide – 30 to 180 days
- Risk factors: Born in Asia or Africa, heterosexual, IVDA, homosexual, household contact, healthcare employment, HIV and HCV infected

Risk Factors Associated With Reported Cases of Acute Hepatitis B

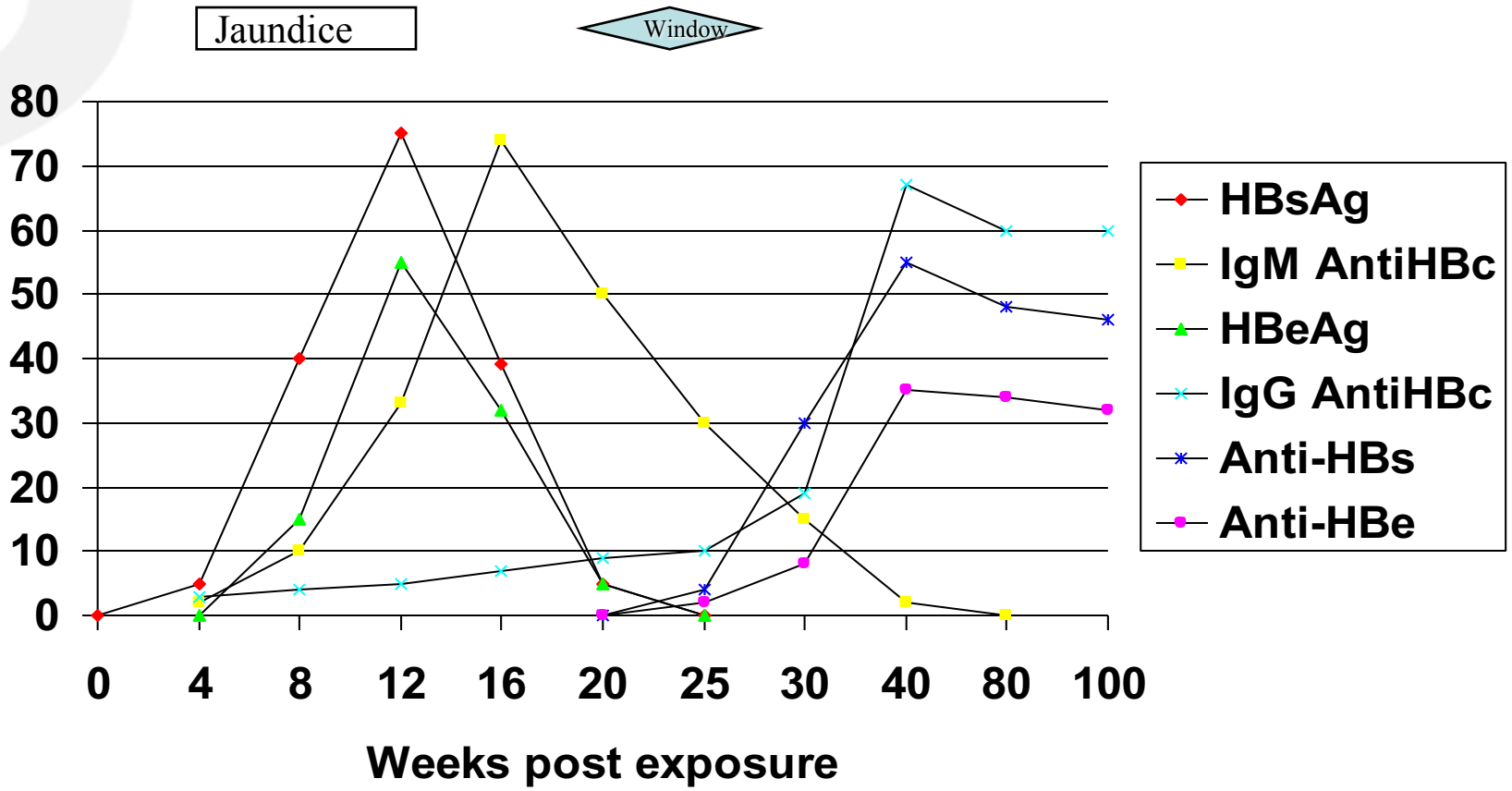


CDC, Sentinel Counties study

Diagnosis of Hepatitis B

- Acute
  - *HBsAg
  - *Anti-HBc IgM
- Chronic
  - *HBsAg-positive > 6 mo
  - *HBeAg
  - *HBV DNA

Acute Hepatitis B Serology



Interpretation of Hepatitis B Panel

HBsAg	Anti-HBs	Anti-HBc	HBeAg	Anti-HBe
+	-	**IgM**	+	-
+	-	**IgG**	+	-
+	-	**IgG**	-	+
+	+	+	+/-	+/-
-	-	**IgM**	+/-	+/-
-	-	**IgG**	-	+/-
-	+	**IgG**	-	+/-
-	+	-	-	-

Phases Chronic Hep B (CHB)

	ALT	HBV DNA	HBeAg	Liver Histology
Immune-tolerant phase	Normal	Typically > 1 million IU/mL	Positive	Minimal inflammation and fibrosis
HBeAg-positive immune-active phase	Elevated	> 20,000	Positive	Moderate-to-severe
Inactive CHB phase	Normal	< 2,000	Negative	Minimal
HBeAg-negative immune reactivation phase	Elevated	> 2,000	Negative	Moderate-to-severe

Terrault NA, Bzowej NH, Chang K, et al. Hepatology;2016,(63):261-283.

Hepatitis B vaccination - indications

- Infant: Birth, 1-2 mths, 6-18 mths
- All adolescents (before age 12)
- Any household contact, sexual partner or staff on nonresidential child care of HBV carrier
- IVDA
- Health care workers
- International travelers to high endemic area
- Sexually active homo- or bi- sexual
- HIV or HCV infection
- ESRD

Treatment of Chronic Hep B

- Pegylated interferons
- Entecavir 0.5 mg po daily
- Tenofovir 300 mg po daily
- Telbuvidine 600 mg po daily
- Others: Lamuvidine, Adefovir

Terrault NA, Bzowej NH, Chang K, et al. Hepatology;2016, (63):261-283.

Prevention of Perinatal Transmission

- Infants born to mother known to be HBsAg
  - Give 1st vaccine dose & HBIG within 12 hrs, then 2nd dose at 1-2 mths, and 3rd dose at 6 month
- Infant born to mother not screened for HBsAg
  - Give 1st vaccine dose within 12 hrs & HBIG if mother is HBsAg +, not later than 1 week after birth. 2nd dose at 1-2 mths, and 3rd dose at 6 months

Pickering LK, et al. 2003 Red Book: Report of the Comm. on Infect. Dis.; 2003:318-336.

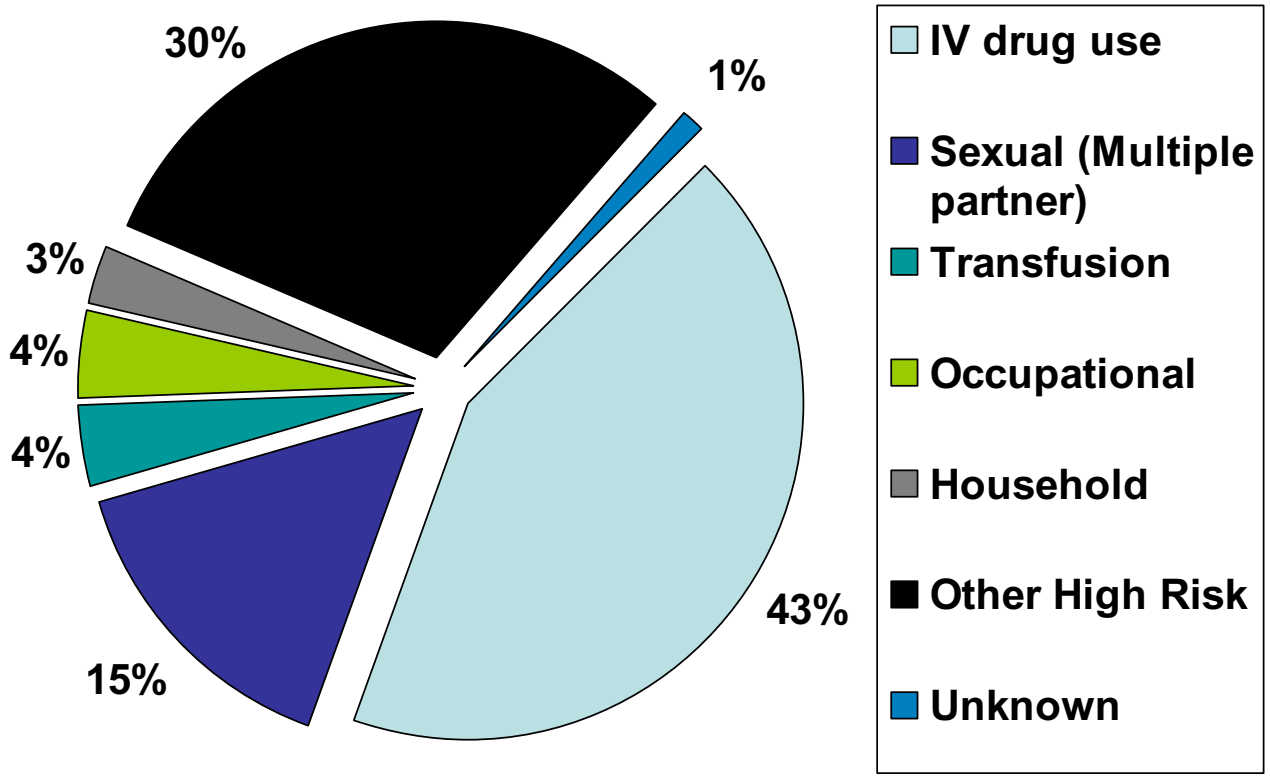
Pregnancy

- Screen pregnant women for HBsAg
- If HBsAg is positive, check HBV DNA, HBeAg, ALT
  - If HBV DNA > 20,000 IU/ml, HBeAg + or ALT > 19 IU/L – Refer to specialist

Hepatitis C facts

- Estimated 170 million persons with chronic hepatitis C globally
- Estimated 3-4 million persons are newly infected per year
- A RNA virus with 6 genotypes (type 1 most common in US)
- Blood-borne viral infection
- Incubation period is wide – 15 to 150 days

Risk Factors for Acute Hep. C



AASLD-IDSA. Hepatology 2015;(62):932-954.

Other Risk Factors for Hepatitis C

- Medical
  *Blood transfusion/Organ transplant (before 1992)
  *Clotting factor concentrates (before 1987)
  *Long term dialysis
- HIV positive
- CDC recommendations, 2012:
  - All persons born 1945-1965 needs one-time HCV testing
- Lifestyle
  *Intravenous drug use
  *Intranasal cocaine use
  *Tattooing, extensive body piercing

Acute Hepatitis C

- Incubation period averages 6-7 wks
- Symptoms develop in only 25%-35% patients
  *Nonspecific - constitutional
  *Jaundice in only 20-30%
  *Diagnosis rarely established thru symptoms
- ALT level by itself is not reliable
- >85% develop persistent infection
  *Majority develop chronic hepatitis

CDC
Management of Hepatitis C. NIH Consensus Statement, 2002.

Hepatitis C Antibody (Anti-HCV) Test

- EIA-2 or 3 test for detection of hepatitis C antibodies
- Positive test suggests viremia until refuted
- Sensitivity 92%-95%
- Detection of anti-HCV following infection averages 12 weeks
- Positive test usually diagnostic in patients with elevated levels of liver enzymes and presence of risk factors

Alter MJ, Semin Liver Dis. 1995; 15:5
de Medina M. et al. Semin Liver Dis. 1995; 15:33
Management of Hepatitis C. NIH Consensus Statement, 2002

Hepatitis C Antibody Test Results

- False Positives
  - *Autoimmune hepatitis
  - *Hypergammaglobulinemia
  - *Normal liver enzymes and no risk factors for hepatitis C
- False negatives
  - *Immunosuppressed patients (e.g. organ transplant recipients)
  - *Chronic dialysis patients

Herrera JL. Postgrad Med. 1993; 93:119.
Hsu HH, et al. Gastroenterology. 1991; 101:1724.

Available HCV RNA Tests

- Polymerase chain reaction (PCR)

  *May be ordered as qualitative or quantitative

  *Qualitative is most sensitive and specific to detect HCV viremia

  *Although, more variability between labs

- Branched DNA amplification (bDNA)

  Quantitative test

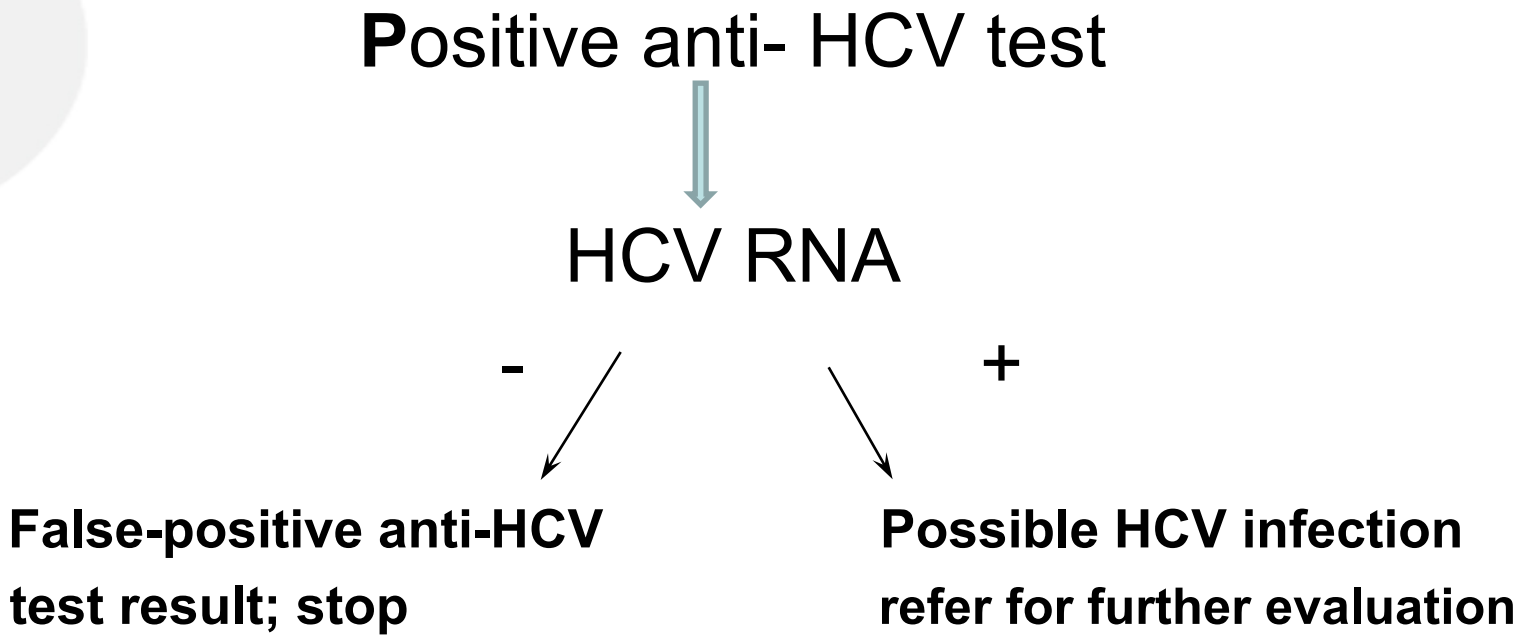
  Less sensitive than PCR method

  Concentrations of $<2.0 \times 10^5$ Eq/mL are undetectable

  Easier to perform, less variability in results

de Medina M. Schiff ER. Semin Liver Dis. 1995; 15:33.
Gish RB, Lau JYN. Viral Hepatitis Reviews. 1997; 2: 17-37.
Urdea MS. Bio/Technology. 1994; 12:926.

Diagnostic Approach to Chronic Hepatitis C



Diagnostic Approach to Chronic Hepatitis C

+ Risk factors for hepatitis
Anti-HCV (EIA) testing

-

<8% chance of chronic hepatitis C (Consider HCV RNA)

+

Diagnosis of chronic hepatitis C 92%-95%

↓

Refer to specialist for evaluation and treatment

Other associated conditions

- Lymphoproliferative disorders – cryoglobulinemia, Waldenstrom's macroglobulinemia & non-Hodgkin lymphoma
- End-stage renal disease
- Diabetes mellitus type 2

Giordano TP, Henderson L, et al. JAMA 2007;297(18):2010-2017
Tsui JI, Vittinghoff E, et al. Arch Intern Med 2007;167(12):1271-1276

Liver fibrosis/cirrhosis assessment

- Liver biopsy is the gold standard although invasive
- APRI

$$\text{APRI} = \frac{\dfrac{\text{AST Level}}{\text{AST (Upper Limit of Normal)}}}{\text{Platelet Count } (10^9/\text{L})} \times 100$$

- FIB-4

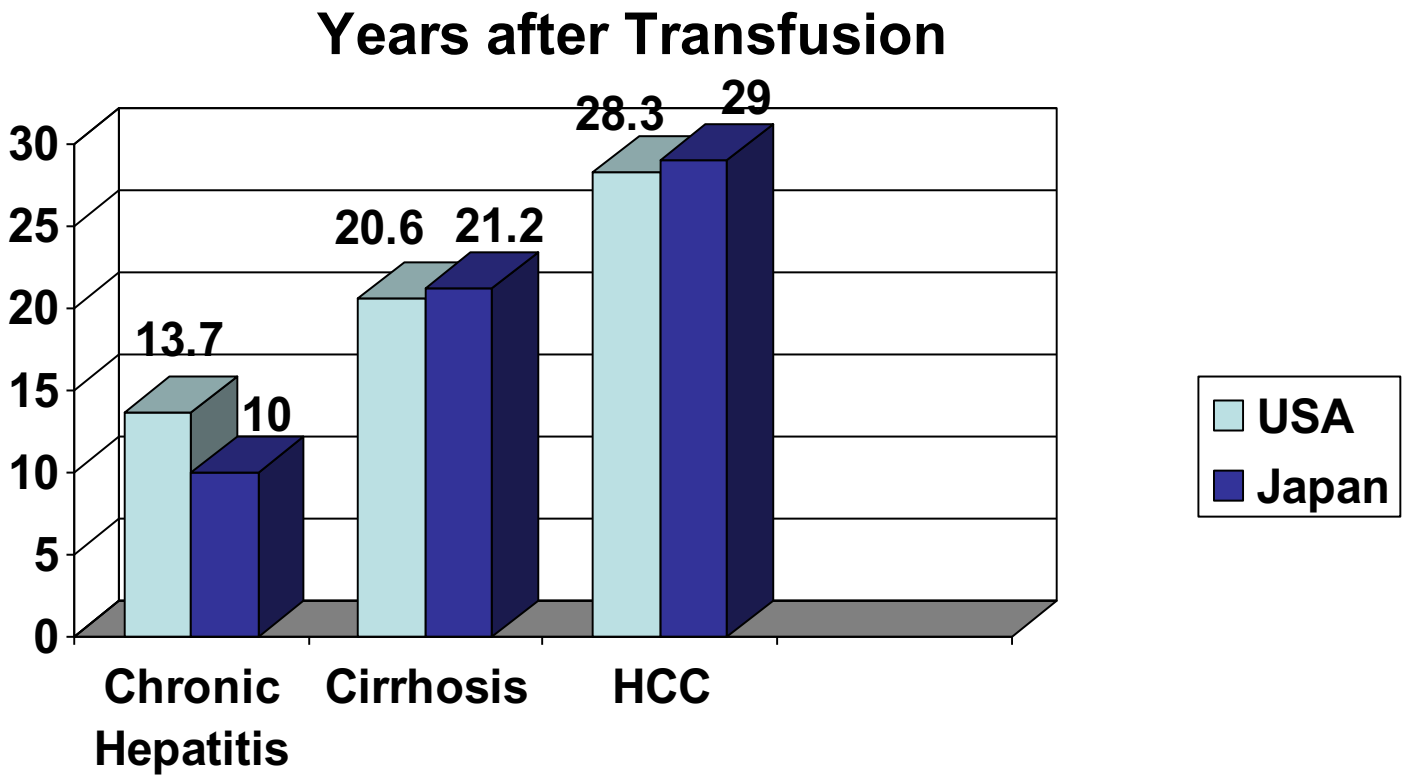
$$\text{FIB-4} = \frac{\text{Age (years)} \times \text{AST (U/L)}}{\text{Platelet Count } (10^9/\text{L}) \times \sqrt{\text{ALT (U/L)}}}$$

Image obtain from hepatitisc.uw.edu

Acute hepatitis C

- Systematic review of 22 studies (5 randomized trials, 11 nonrandomized trials and 6 observational studies) comparing treatment vs. no treatment with data on timing of treatment in 1,075 patients (mean age 36 years) with acute hepatitis C infection
  - 417 patients began treatment within 12 weeks of diagnosis
  - 110 patients began treatment 12-24 weeks after diagnosis
  - 46 patients began treatment > 24 weeks after diagnosis
- 77% of treated patients received peginterferon monotherapy
  - rates of sustained viral response in treated patients 82.5% in patients treated within 12 weeks
  - 66.9% in patients treated at 12-24 weeks
  - 62.5% in patients treated after 24 weeks
- Clearance in 55% of untreated patients

Progression of Chronic Hepatitis C



Kiyosawa K, et al. Hepatology. 1990; 12:671.
Tong MJ, et al. N Engl J Med. 1995;332:1463.

Treatment Terms

- Sustained virologic response (SVR)
- End-of-treatment response (ETR)
- Rapid virologic response (RVR)
- Early virologic response (EVR)
- Null responder
- Non responder
- Partial responder

Treatment of Chronic Hep C

- Interferon 3 MIU SC or IM TIW **OR**
- Pegylated interferon alfa 2a 180 ug/kg/ Q week or
- Pegylated interferon alfa 2b 1.5 ug/kg/ Q week

PLUS

- Ribavirin (dose depends on genotype and weight), as a combination therapy with interferon, increases virologic response to both naïve and INF relapse pts

Most Common Adverse Experiences With Interferon Therapy* for Hepatitis C

- Flu-like symptoms
- Gastrointestinal symptoms
- Alopecia
- Somnolence, depression
- ***Suicidal behavior (ideation, attempt, & completed suicides)**
- Ribavirin - anemia, bone marrow suppression, category X on pregnant pts.

ION Investigator

- Multicenter, randomized, open-label study in US and Europe from Oct 2012 to May 2013. 865 chronic hepatitis C pts who previously are untreated underwent 1:1:1:1 randomization to receive fixed dose combination of ledipasvir & sofosbuvir for 12 wks, or ledipasvir-sofosbuvir + ribavirin for 12 wks, or ledipasvir & sofosbuvir for 24 wks, ledipasvir-sofosbuvir + ribavirin for 24 wks.
  - Primary end point: sustained virologic response at 12 wks after the end of therapy
- Results:
  - LS12 – 99% (CI 96-100)
  - LSR12 – 97% (94-99)
  - LS24 – 98% (95-99)
  - LSR24 – 99% (97-100)
- Conclusion: Once-daily ledipasvir-sofosbuvir with or without ribavirin for 12 or 24 wks was highly effective

Ritonavir-ombitasvir-dasabuvir+ ribavirin study

- Phase 3 trial of 394 pts with HCV genotype 1 and no cirrhosis who had been treated with unsuccessful peginterferon-ribavirin therapy.
- Pt was given ritonavir 100 mg daily, ombitasvir 25 mg daily, dasabuvir 250 mg twice daily with ribavirin 1000 or 1200 mg daily vs matching placebo during the 12 wks double-blind period (3:1 ratio).
  - Primary end point: Sustained virologic response (svr) 12 wks after the end of the study treatment.
- Results: SVR of 96.3%. Historical response rate is 65% in retreatment with peginterferon-ribavirin and telaprevir.
  - Pruritus occurred more frequently in treatment group 13.8 vs 5.2%
- Conclusion: Rates of response to a 12-wk interferon-free combination regimen were more than 95% among previously treated patient with HCV genotype 1 infection, including patients with a prior null response.

Direct acting antivirals (DAA)

- Oral agents
- Usually 12 weeks
- Usually high SVR rates - > 90%
- Check CBC, Creat, GFR, hepatic function panel and Quantitative HCV viral load after 4 weeks on treatment
- A 10-fold increase in ALT should prompt discontinuation or < 10-fold with any weakness, vomiting, jaundice
- Side effects includes headache, fatigue

DAA

- Declatasvir (Daklinza) plus sofosbuvir
- Elbasvir-grazoprevir (Zepatier)
- Ledipasvir-sofosbuvir (Harvoni)
- Ombitasvir-paritaprevir-ritonavir (Technivie) plus dasabuvir
- Sofosbuvir-velpatasvir (Epclusa)
- Glecaprevir-pibrentasvir (Mavyret)

Factors Associated with Accelerated Fibrosis

- Fibrosis stage / Inflammation grade
- Older age at time of infection
- Male sex
- Organ transplant
- Alcohol consumption
- Obesity
- Nonalcoholic fatty liver disease
- Insulin resistance
- Genotype 3 infection
- Coinfection with hep B or HIV

Follow ups on Hepatitis C patients

- Vaccinate against Hep A and B
- Liver function test – ALT, Bili, PT & Alb
- Tsh
- Hep C with cirrhosis
  - Liver ultrasound at intervals of 6 or 12 months

Recommendations to Avoid Transmission of HCV

- Adherence to universal healthcare precautions
- Sterilization of medical and dental equipment
- No donation of blood, organs, tissues, or semen by individuals who are HCV +
- Use of condoms by individuals who have multiple sexual partners
- Testing for HCV recommended for sexual partners of infected patients

Recommendations to Avoid Transmission of HCV (cont.)

- Avoiding household transmission:
  *Avoid sharing razors, toothbrushes
  *Cover open wounds
- Abstinence from alcohol
- Evaluate for HBV and HIV
- Vaccination against hepatitis A and B
- Vaccination against pneumococcal infection to all pts with cirrhosis

QUESTIONS???