A, B, C's of Hepatitis

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KAOM Mid-Year Conference

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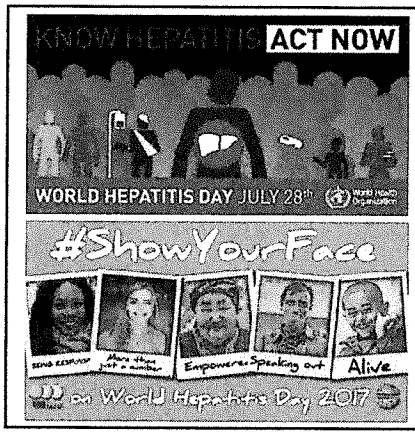
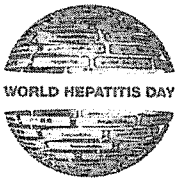
Hepatitis

- Review epidemiology of Hepatitis A, B, C
- Describe clinical and pathologic features
- Discuss the classic serologic findings
- Newer aspects of testing, including the impact of mutations

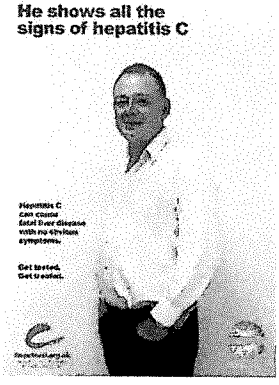


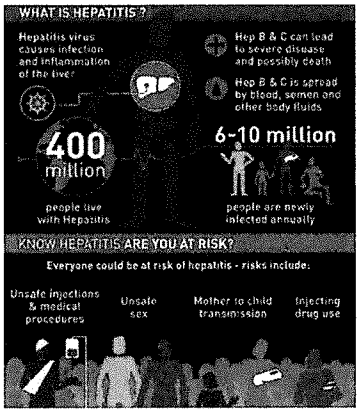


From the UK:

Hepatitis C can cause fatal liver disease with no obvious symptoms.

Get tested
Get treated





Hepatitis: Historical Perspective

- "jaundice" recognized in biblical times
- outbreaks of war (HAV until transfusions)
- 1885 idea of parenteral transmission
- 1908 viral origin suggested
- "Silver Age" 1940-1960
  - problem in WW II, yellow fever vaccines
  - hepatitis A & B
  - liver enzymes (1955)

Hepatitis: More History

- "Golden Age" 1965 - 74:
  - 1965 Blumberg Australia Antigen
  - Hepatitis B surface antigen (HBsAg)
  - 1970 Dane particle, 42 nm
  - early 1970's tests for HBsAg
  - 1972 Hepatitis B "e" antigen (HBeAg)
  - 1973 Hepatitis A virus identified
  - 1974 Non A, non B hepatitis

Hepatitis: 1977- 95

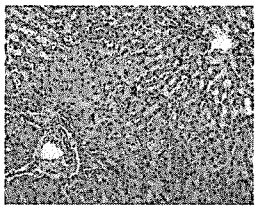
- 1977 hepatitis D (HDV) identified
- 1979 HBV cloned
- 1980 hepatitis E identified (HEV)
- 1983 - 1990 saw the cloning of HAV, HDV, HCV and HEV
- vaccines for HBV & HAV
- 1995 hepatitis G (GBV) reported

Hepatitis – Recent

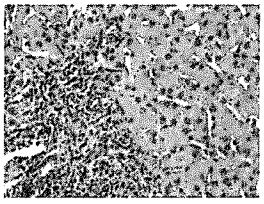
- Molecular testing for HBV, HCV viral loads
- Antiviral therapy development
- Resistance to antiviral therapy
- For HCV - Direct Acting Antivirals (DAA)

What is Hepatitis?

- Inflammation of the Liver



From Utah Med



From Gut 2007

Types of Hepatitis

- older terminology:
- type A: infectious hepatitis
- type B: serum hepatitis
- type C: transfusion associated, community acquired, Non A, Non B (NANB)
- type D: delta
- type E: enteric, waterborne, endemic

Causes of Hepatitis

- Viruses:
  - A,B,C,D,E,G
  - CMV (newborns, immunosuppressed)
  - EBV (mild)
  - Yellow fever
- Bacteria: S. typhi
- Parasites: tapeworms
- Drugs:
  - anticonvulsants
  - corticosteroids
- Alcohol
- Toxins: DDT
- Autoimmune responses

Hepatitis - Epidemiology

- Viral hepatitis is leading cause of liver cancer
- Most common reason for liver transplant
- Est 3.5-6.1 million chronic hepatitis in US
  - HBV 0.85-2.2 million
  - HCV 2.7-3.9 million
- ~ 59,000 acute infections per yr
  - HAV = 2,800, HBV = 21,900, HCV = 33,900
  - Adjusted for under reporting

Source: www.CDC.gov

Transfusion Associated Risks

- transfusion associated hepatitis (TAH)
- overall varies 0.1-10%
- HBV - 1 in 205,000
- HCV – 1 in 1-2 million

For comparison -

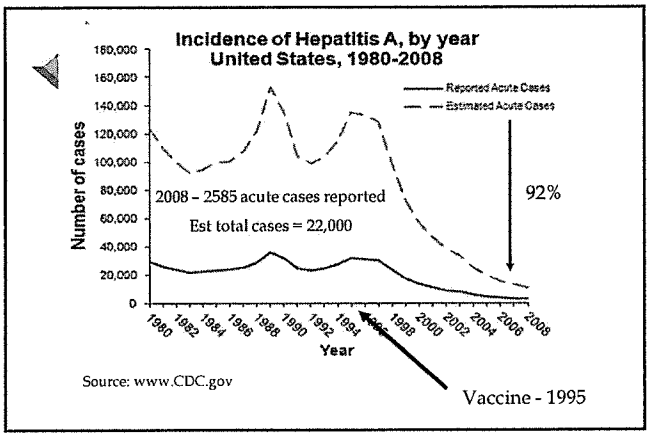
- HIV – 1 in 1.5 million

Symptoms of Hepatitis

- nonspecific
- fatigue, myalgias, nausea, vomiting, diarrhea, fever, appetite loss, chills, even weight loss
- mimics many diseases

Hepatitis A

- accounts for about 25-30% of cases/yr
- 1973 small (27 nm) RNA virus
  - Family Picornavirus, Genus Hepatovirus
- RNA codes for 4 structural nucleocapsid peptides
- response to infection is by cytotoxic CD 8 cells
- virus doesn't destroy liver, the immune response does


Incidence of Hepatitis A, by year
United States, 1980-2008
Reported Acute Cases
Estimated Acute Cases
Number of cases
180,000
160,000
140,000
120,000
100,000
80,000
60,000
40,000
20,000
0
2008 – 2585 acute cases reported
Est total cases = 22,000
92%
1980
1982
1984
1986
1988
1990
1992
1994
1996
1998
2000
2002
2004
2006
2008
Year
Source: www.CDC.gov
Vaccine - 1995

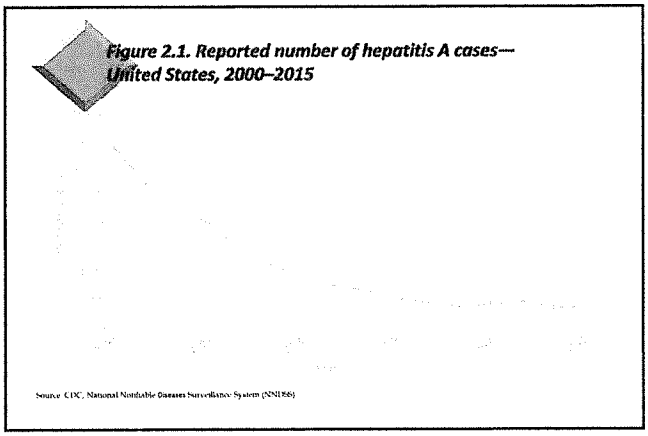


Figure 2.1. Reported number of hepatitis A cases—
United States, 2000–2015
Source: CDC, National Notifiable Diseases Surveillance System (NNDSS)

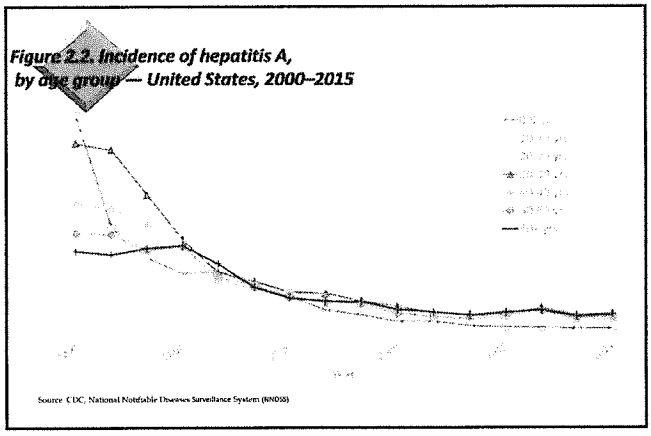


Figure 2.2. Incidence of hepatitis A,
by age group — United States, 2000–2015
Source: CDC, National Notifiable Diseases Surveillance System (NNDSS)

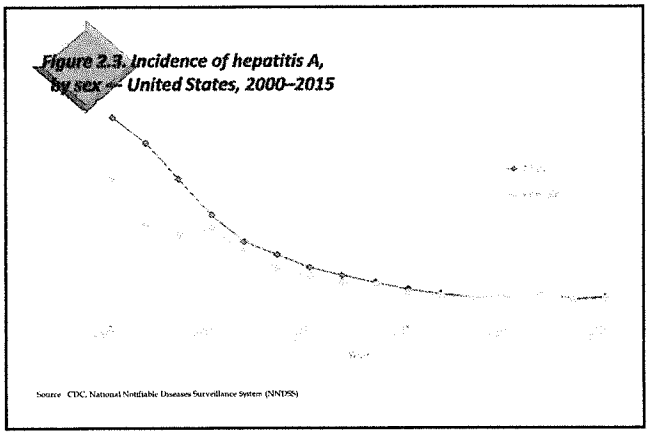
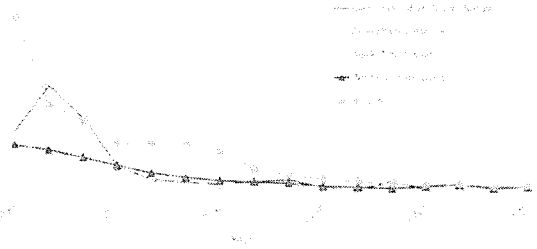


Figure 2.3. Incidence of hepatitis A,
by sex — United States, 2000–2015
Source: CDC, National Notifiable Diseases Surveillance System (NNDSS)

Figure 2.4. Incidence of hepatitis A, by race/ethnicity — United States, 2000–2015



Source: CDC, National Notifiable Diseases Surveillance System (NNDSS)

Hepatitis A Transmission

- fecal-oral route
- Person-to-person is most common in US
  - Institutional settings – schools, nurseries
  - poor personal hygiene, IV drug users
  - oral-anal sexual activity
  - sharing eating utensils
  - sharing toys that may be contaminated
- Outbreaks – contaminated food/water
- HAV transmission in blood is very rare
  - Viremia is transient

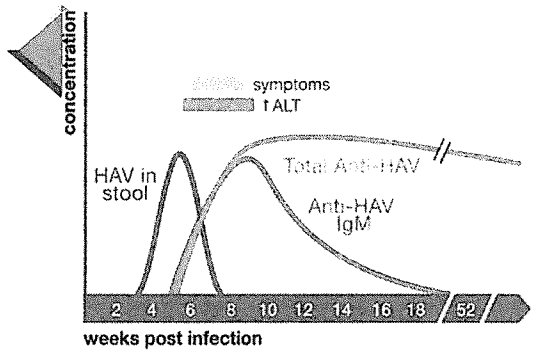
Who's at Risk for HAV Infection?

- Travelers to endemic countries
- Men who have sex with men (MSM)
- Drug use – both injection and non-injection
- Persons with clotting factor disorders (plasma products)
- Persons working with nonhuman primates

Source: www.CDC.gov

Clinical Features for Hepatitis A

- incubation period 15-50 days (avg 28 d)
- onset is usually abrupt
- symptoms in only 1/3
  - 70% of kids don't become jaundiced
  - 70% of adolescents and adults do
- no carrier state is known, chronicity is rare
  - "relapse" occurs in 3-20% 4-15 wks after initial symptoms
  - But persistent infection after 12 mo is very rare
- mortality is 0.1-0.2 % so fulminant disease is rare



Source – Bio-Rad

Laboratory Diagnosis of Hepatitis A

- HAV in stools 1-2 weeks before symptoms
- IgM to HAV is usually detectable by 4-6 weeks
  - will disappear in 3 to 12-18 months
- IgG to HAV appears within 2 weeks of symptoms = Ab levels persist for life
- HAV IgG is protective

Serology of Hepatitis A

- in the US: Ab's to HAV are:
- rare in young children (< 5%)
- in the < 20 yrs group (5-20%)
- in older adults (30-50%)
- in endemic countries: Ab's are found in nearly 90%

Prevention of Hepatitis A

- good hygiene, wear gloves
- don't share food/utensils
- vaccine available since 1995
- immune globulin for postexposure prophylaxis

How Stable is HAV?

- Depending on environment – HAV can survive outside the body for long periods (months)
- Heat kills – 185°F for 1 min
  - Proper food preparation
  - But – HAV will survive if food is contaminated after proper cooking
- Chlorine level in US water will kill HAV

Source: www.CDC.gov

HAV Vaccine

- All approved in US are inactivated virus
- Doses/schedules – see CDC or ACIP
- Postvaccination testing – not recommended
- If you're not sure if a pt is immune or has been vaccinated – does it hurt to give vaccine? NO
- How long does immunity last – expert panel
  - Adults at least 25 yrs
  - Kids 14-20 yrs

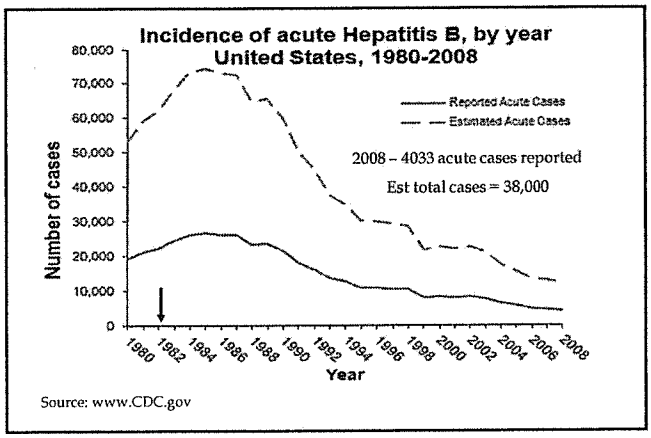
Source: www.CDC.gov

Hepatitis A Vaccines

- CDC recommends HAV vaccination for persons at increased risk:
  - persons traveling to endemic areas (Mexico, S. America, Africa, Asia)
  - children in high risk communities (> 2yrs age)
  - homosexual males, IV drug users
  - persons with chronic liver disease
  - persons with coagulation disorders

Hepatitis B

- accounts for 40-50% of cases/yr
- 42 nm DNA virus, Hepadenavirus
- the complete infectious virus called Dane particle
- outer lipid coat, inner core (nucleocapsid)
- HBsAg is part of the outer coat
  - has many antigenic epitopes, viral subtypes


Incidence of acute Hepatitis B, by year
United States, 1980-2008
Reported Acute Cases
Estimated Acute Cases
2008 – 4033 acute cases reported
Est total cases = 38,000
Number of cases
Year
Source: www.CDC.gov

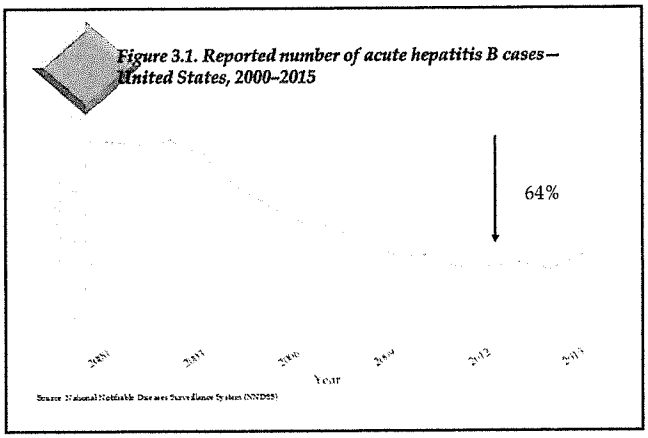
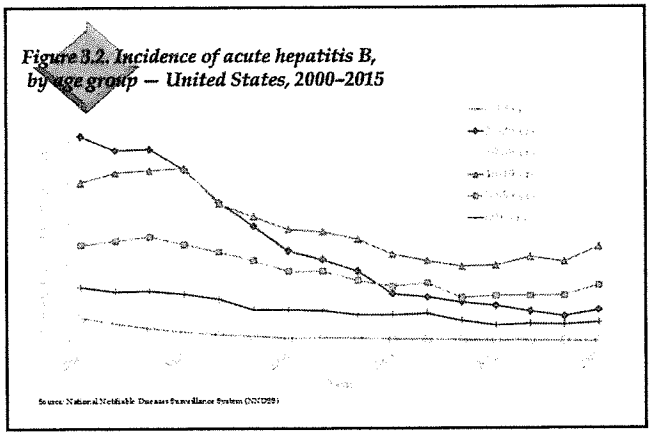


Figure 3.1. Reported number of acute hepatitis B cases—
United States, 2000–2015
64%
Year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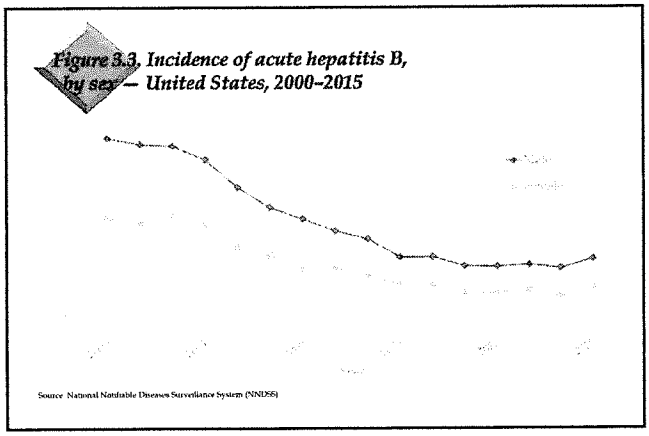
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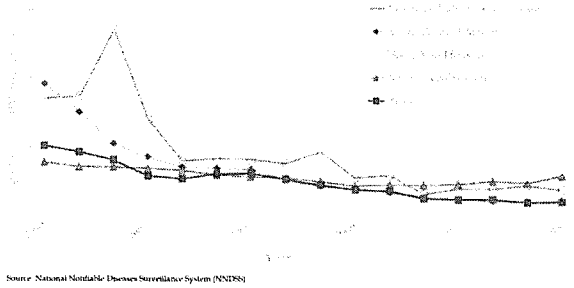
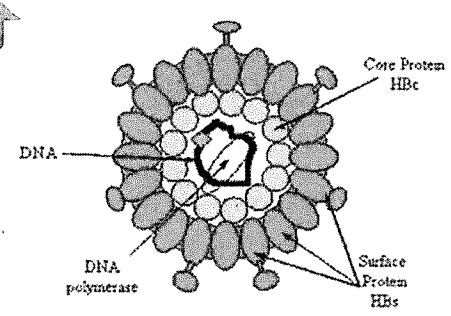


Source: National Notifiable Diseases Surveillance System (NNDSS)



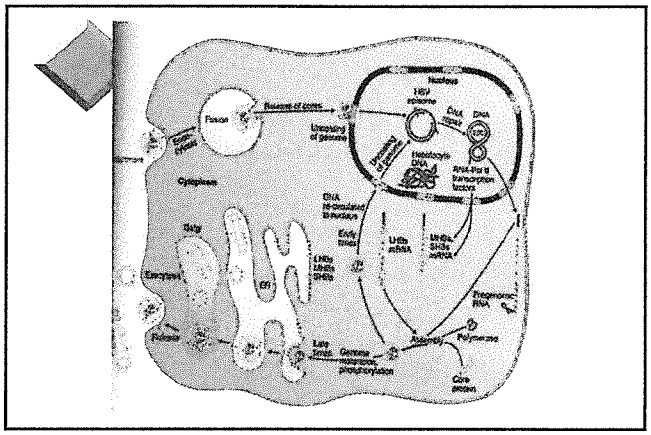
Source - Hepatitis B Health on Net Foundation

Hepatitis B virus

- 8 genotypes (A-H)
- HBV genome is a partially DS circular DNA
- Unique – DNA virus that replicates using an RNA transcript
- Relatively small gene – codes for 7 proteins
- HBsAg is produced in excess - released

Hepatitis B Genome codes for:

- Nucleocapsid core – core Ag - HBcAg
  - Longer polypeptide region - HBeAg
- Envelope glycoprotein – HBsAg
  - 3 components – large, medium, small
  - Main secretion – small HBsAg
- HBx protein – needed for replication, ?role in HCC
- DNA polymerase with RT activity
  - DNA ⟶ RNA ⟶ DNA



Hepatitis B Transmission

- parenteral: transfusion, dialysis, needle sticks, sharing needles, razors, toothbrushes
- non-parenteral: sexual contact, other body fluids
- perinatal: mother to fetus/baby
- unknown: 30-40% of cases in the US have no known risk factors

Hepatitis B is NOT Transmitted by:

- Food or water
- Sharing eating utensils (intact mucosa)
- Breastfeeding
- Hugging/kissing/holding hands
- Coughing, sneezing

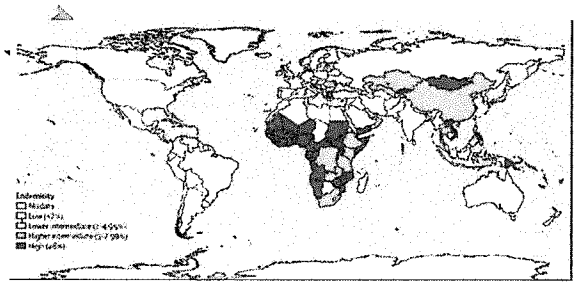
Source: www.CDC.gov

HBV Factoids

- Depending on environment – HBV may remain viable up to 7 days in a dried blood spot
- Use dilute hypochlorite solution (1:10) or other approved (EPA) disinfectant
- KEY – contact time
  - HIV-1 is killed in ~ 30 sec
  - HBV – recommendation is 10 MINUTES

Hepatitis B

- ~ 600,000 die each yr – acute or chronic HBV
- ~ 1 million carriers in the US
- ~ 2 billion people infected with HBV - world
- ~ 350 million have HBV chronic liver disease
  - if not tx'd – 15 - 40% progress to ESLD, cirrhosis, HCC or require transplant
- Humans are the only reservoir
- HBV is 50-100x more infectious than HIV



Worldwide HBsAg positivity

Source: www.CDC.gov

Clinical Features of Hepatitis B

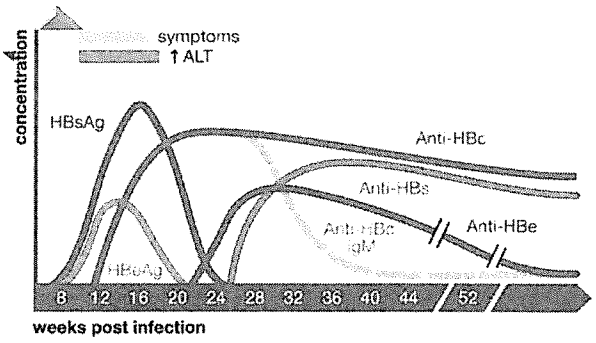
- incubation period 30-150 days, avg 90 d
- Range – asymptomatic/mild – rare fulminant
- symptoms in 1/2 of persons
  - Last several weeks, can persist for 6 months
- onset is insidious
- Disease is more severe in persons > 60
- mortality rate 0.5-1%

Clinical Features of Hepatitis B

- newborns unlikely to be symptomatic (< 5%)
- 30-50% of adults develop jaundice
- arthritis, glomerulonephritis occur in 10-20%
- chronicity in 5-10%
  - 90-95% adults recover completely
- But infants (90%), kid 1-5 yrs (25-50%) more likely to develop chronic HBV infection

Serology for Hepatitis B

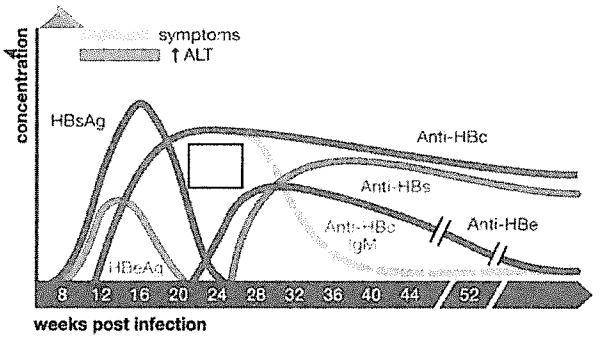
- HBsAg may be detected in 2-4 weeks, before sx's, peaks, declines in 3-6 mo's
- HBeAg signifies highly infectious period
  - Indicates high level of viral replication
- HBV DNA – similar timing as HBsAg
- Anti-HBc appear about the same time as symptoms
  - IgM anti-HBc is first (except in perinatal infections)



Source Bio-Rad

Serology for Hepatitis B

- Anti-HBs appears after disappearance of HBsAg – few wks to several months
- lag time called the "Core Window"
  - anti-HBc may be the only + serologic test
- Anti-HBs signals recovery and immunity
- titers rise for 6-12 months and persist for life
- Anti-HBe – is detected only after acute HBV
  - Titer declines after viral production ceases
  - It does not neutralize HBV



Source Bio-Rad

HBV – Molecular Testing

- Detectable HBV DNA is useful for
  - Dx some cases of acute HBV infection (infrequent)
  - Distinguish active from inactive infection
  - Monitoring response
- All assays have dynamic ranges from 20 copies/mL up to > 1 million copies/mL
- 2001 – WHO standard – IU/mL
  - 1 IU of HBV is eq to 5.4 genome eq's/copy
- To be consistent – use the same assay/lab

Risk Factors for Hepatocellular Ca

- Host Factors
  - Older than 50 yrs
  - Males
  - Cirrhosis (2-3%)
  - African or Asian
  - Obesity, DM
- Environmental - EtOH
- Viral Factors
  - ↑ HBV DNA
  - Genotype C > B
  - Core promoter variant
  - Coinfection w HCV or HDV

Chronic Hepatitis B

- Persistence of HBsAg > 6 months
- Immune Tolerant Phase –
  - HBeAg +, HBsAg+, high HBV DNA, ↑ ALT
  - Minimal histologic changes
  - Phase may last 20-40 yrs
  - Most likely result of clonal deletion T cells in fetus

Chronic Hepatitis B

- Immune Clearance Phase
  - HBeAg + with seroconversion to Anti-HBe
  - HBsAg and HBV DNA decrease
  - If persistently ↑'d – fibrosis and inflammation
  - ↑ ALT
  - Genotype C seroconverts more slowly
    - higher incidence of HCC

Chronic Hepatitis B

- Inactive Phase
  - Seroconversion HBeAg to Anti-HBeAg
    - Better prognosis if before age 30 yrs
  - ↓ HBsAg, HBV DNA, ALT
  - HBsAg clearance before age 50 – better Px also

Chronic Hepatitis B

- Reactivation Phase
  - 20-30% will reactivate
  - ↑ HBV DNA or ↑ ALT or both
  - HBeAg still negative
  - Precore or core promoter mutations or both
  - Risk for cirrhosis/HCC

HBV Mutants

- HBV kinetics – very proliferative virus
  - On the order of 10^8 to 10^{11} virions per day
  - large # variants generated every day – most not viable
- Some mutations provide virus with an advantage
- Variant HBsAg or HBeAg – may not be detected by current assays (rare, but possible)
- Serology results may not match clinical picture
  - HBV DNA testing helps to resolve
- Variant HBeAg assoc with poorer clinical outcome

Prevention of Hepatitis B

- Universal/standard precautions
- condoms, don't share needles, etc
- immune globulin (HBIG)
- Vaccine – 1982
  - 1991 – national program implemented
  - 164 countries have HBV vaccination programs
  - Protective > 95%, lasts <u>at least</u> 20 yrs maybe life
  - Postvaccine testing – at least 6 weeks after final dose
  - Follow CDC/ACIP guidelines
  - Allergy to yeast is contraindication to vaccine

Vaccine and HBV Mutants

- Reports of HBV infection in
  - persons who had been successfully vaccinated
  - neonates who had received HBIG
- Altered HBsAg – escapes vaccine-induced immunity
- HBV "Escape mutants"
- Estimates # of variants in chronic carriers may be 6-12%

HBsAg testing

- Majority of assays – monoclonal/monoclonal
  - Few – monoclonal/polyclonal
- All have different responsiveness to mutants
- HBsAg should NOT be the only test used to detect HBV infection
  - Anti-HBc IgM, Anti-HBc – total, Anti-HBs
  - HBV DNA, HBeAg

Treatment of Hepatitis B

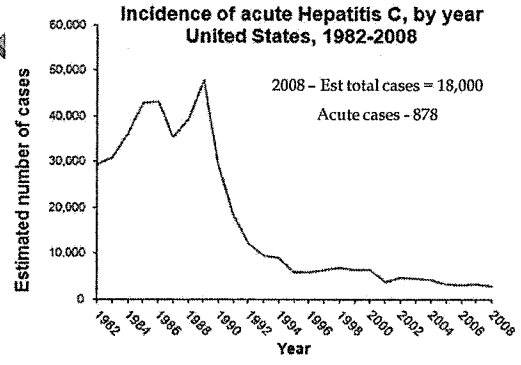
- Acute - supportive therapy
- Antiviral agents –
  - Protracted or severe acute disease
  - Chronic infection
- Assess HBV replication
- Screen for HIV, HCV, HDV
- Assess liver function, CBC
- Assess liver fibrosis/inflammation

Hepatitis C

- Global problem – est 150 million infected
- 2.7-3.9 million infected in the US
- 75-85% will develop chronic infection
- Cirrhosis, end-stage liver disease, HCC
- Newer direct-acting antiviral therapies
- Diagnostic algorithm changed in 2014

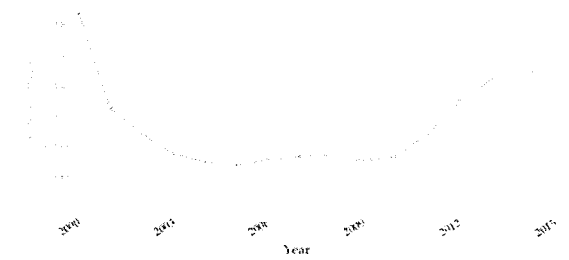
Hepatitis C

- single stranded RNA virus, 50 nm
- Flaviviridae
- prior to serologic assays HCV caused 90% of post-transfusion NANB hepatitis
- Ab's to HCV are found in 0.13-1.4% of blood donors – most common bloodborne infection in the US (CDC)



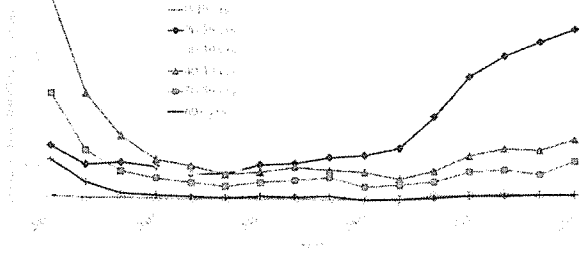
Source: www.CDC.gov

Figure 4.1. Reported number of acute hepatitis C cases — United States, 2000–2015



Source: CDC, National Notifiable Diseases Surveillance System (NNDSS)

Figure 4.2. Incidence of acute hepatitis C, by age group — United States, 2000–2015

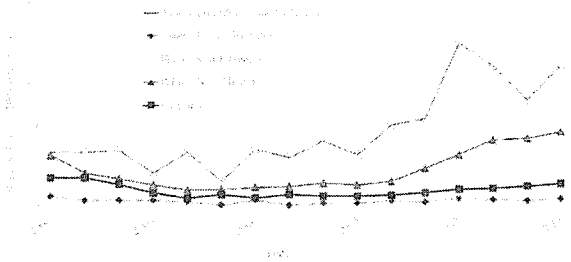


Source: CDC, National Notifiable Diseases Surveillance System (NNDSS)

Figure 4.3. Incidence of acute hepatitis C, by sex — United States, 2000–2015

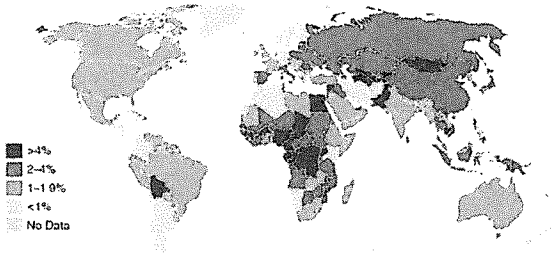
Source: CDC, National Notifiable Diseases Surveillance System (NNDSS)

Figure 4.4. Incidence of acute hepatitis C, by race/ethnicity — United States, 2000–2015



Source: CDC, National Notifiable Diseases Surveillance System (NNDSS)

Global Hepatitis C Prevalence



Source: Lavanchy, D. Evolving epidemiology of hepatitis C virus. Clin Microbiol Infect. 2011; 17:107–115.

Hepatitis C - Risk Factors (WHO)

- IVDU
- Intranasal drug use
- Transfusions (prior to 1992) or inadequate infection control practices
- Maternal to child transmission
- Sexual transmission
- people with HIV infection
- prisoners or previously incarcerated persons; and
- people who have had tattoos or piercings.

Hepatitis C in IVDUs (2008 est)

- In IVDUs 18-30 yrs old – 1/3 are HCV+
- In IVDUs > 30 yrs – 70-90% are HCV+

- IVDUs with HIV – 50-90% co-infected w HCV
- Overall persons w HIV – 15-30% co-infected with HCV

Sexual Transmission of Hepatitis C Virus Among HIV-Infected Men Who Have Sex with Men --- New York City, 2005-2010

MMWR
Morbidity and Mortality Weekly Report

July 22, 2011 / 60(28);945-950

CDC

Why is this important?

- Sexual transmission of HCV is considered inefficient – except in HIV infection
- Higher HCV viral burden increases infectiousness through sexual contact
- HIV also accelerates HCV liver disease
- ESLD and/or HCC are leading causes of nonAIDS deaths in HIV infection

MMWR July 22, 2011

- Oct 2005 – 2 HIV-infected men w HCV
- NO history of IV drug use
- Case control study Oct 2005 – Dec 2010
- Total of 74 cases
  - PCR & sequencing analysis of 47 cases - genotype 1a
  - 5 clusters of closely related HCV variants
- Risk factors – MSM, methamphetamine use
- Recent study in Europe (2002-2007) also showed increased HCV cases in HIV-infected MSM

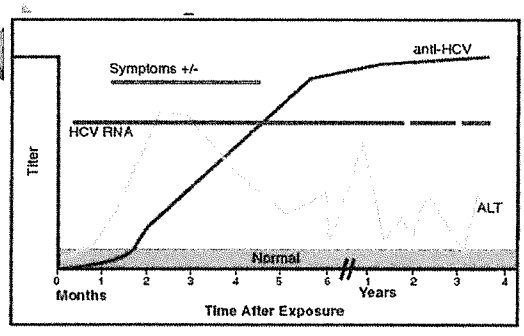
Hepatitis C by the numbers.....

Of every 100 persons with HCV infection

- 75-85 – will have chronic infection
- 60-70 – will develop chronic liver disease
- 5-20 – will develop cirrhosis in 20-30 yrs
- 1-5 will die of chronic infection (HCC, cirrhosis)
- 15-25% resolve HCV w/o Tx (not known why)

Clinical Features of Hepatitis C

- incubation period averages 4-12 weeks
  - range 2-26 wks
- viremia begins about 2 wks after exposure
- 20-30% are symptomatic (70-80% no sx's)
  - Abd pain, poor appetite, jaundice
- onset is insidious
- acute symptoms are rare



Source – Abbott Diagnostics

Hepatitis C Viral Testing

Seroconversion: 60-65% in acute phase (4-10 wks)

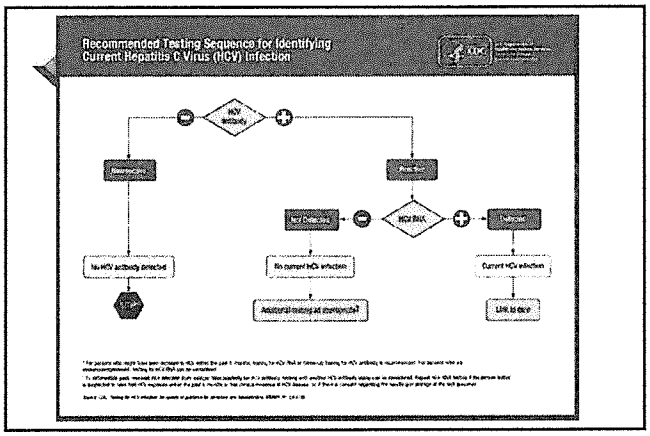
- 30-35% weeks to months later
- By 6 mo - > 97% have anti-HCV
- 5% never seroconvert

Confirmation:

Polymerase chain reaction (PCR)

- may be + within a few days after infection

- RIBA – not recommended



Anti-HCV + with HCV PCR ND

- What does this mean?
- False positive EIA
- Resolved HCV infection (15-25% resolve HCV)
- Assess the risk factors
- Alternative EIA may help

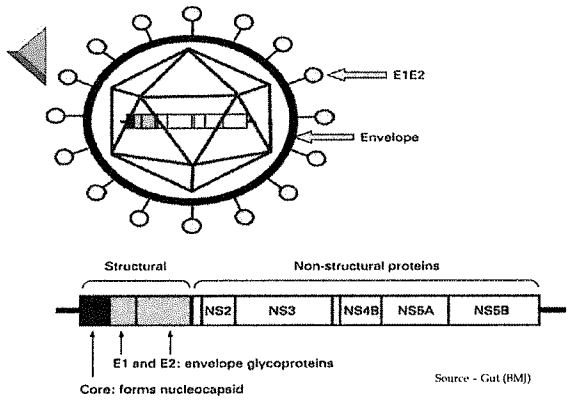
Screening Test Kit Name	Manufacturer	Assay Format	Signal-to-cut-off ratio predictive of a true positive ≥ 95% of the time
Ortho HCV Version 3.0 ELISA Test System	Ortho	EIA (Enzyme Immunoassay)	≥ 3.8
Abbott HCV EIA 2.0	Abbott	EIA (Enzyme Immunoassay)	≥ 3.8
VITROS Anti-HCV	Ortho	CIA (Chemiluminescent Immunoassay)	≥ 8.0
AxSYM Anti-HCV	Abbott	MEIA (Microparticle Immunoassay)	≥ 10.0
Architect Anti-HCV	Abbott	CMIA (Chemiluminescent Microparticle Immunoassay)	≥ 5.0
Advia Centaur HCV	Bayer	CIA (Chemiluminescent Immunoassay)	≥ 11.0

Source: www.CDC.gov

Hepatitis C Virus

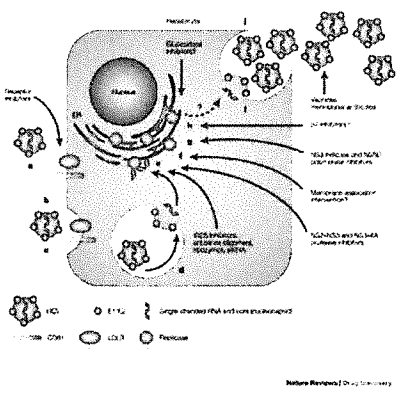
- heterogeneous genetic makeup
  - variations in antigens and proteins
- Six major genotypes (1-6)
  - Definition > 30% genomic sequence differences
- > 50 subtypes – 10-30% sequence differences
- in U.S the major isolate is type 1 (74%)
  - Genotype 2 (15%), 3 (7%)

Hepatology 2001



Hepatitis C Infection

- infects liver cells, lymphocytes, bone marrow cells
- mainly replicates in the liver
- studies suggest production & turnover rate is very high – 10^{12} virions/d
  - Kinetics similar to HIV or HBV
  - uptake linked to LDL receptor



HCV:

✓ genome encodes for a polyprotein

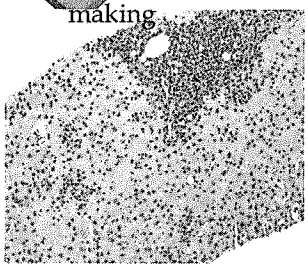
✓ does not integrate into nucleus

✓ replicates in cytoplasm using host machinery

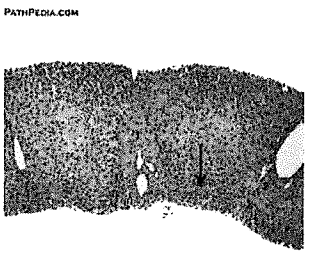
Immune Response to Hepatitis C

- mild lymphocytic inflammation
  - portal & parenchymal
- ballooning, focal hepatocyte necrosis
  - mostly a CD8 cell response
  - polyclonal CD4 cell activation also
- immune complexes may be formed

Liver Biopsy – gold standard for assessing fibrosis – prognostic decision making



Source - Modern Pathology Images

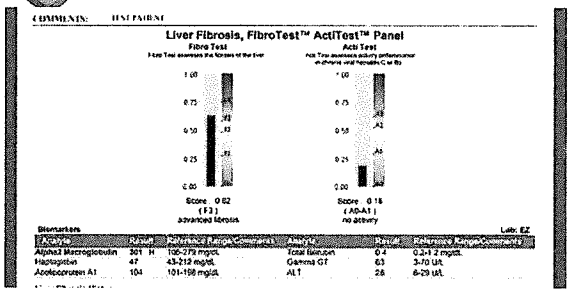


Source - Pathpedia.com

Laboratory Testing - Biomarkers

- Liver biopsy has known risks –
  - Invasive, bleeding, pneumothorax
  - Sampling error
- HCV FibroSURE™
- Haptoglobin, α2-macroglobulin, total bilirubin apolipoprotein A1, GGT, ALT, age, gender
- Algorithm calculation
- Fibrosis and necroinflammatory grades
- Baseline, post-treatment assessment of liver
  - 6 mo's after treatment

FibroTest/ActiTest Sample Report

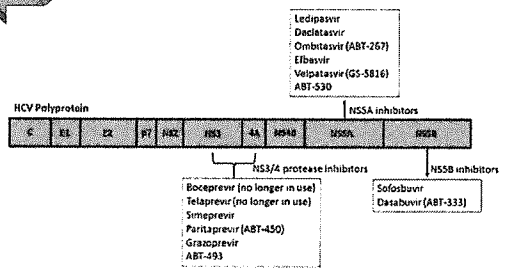


Hepatitis C – Progression to Cirrhosis

- Longer duration of infection
- Older age at time of exposure
- Male sex
- Co-infection with HBV or HIV
- Daily EtOH consumption > 50 g/d
  - 13.7 gm EtOH in 12 oz beer, 5 oz wine, 1.5 oz shot
  - Caffeinated alcohol – have 5-12% ↑'er EtOH than beer

Therapy for Hepatitis C

- Pegylated IFN α + ribavirin
- 40-50% response if TX for 48 mo's (genotype 1)
  - 70-80% response for genotypes 2 or 3
- Direct-acting antivirals – major advance
  - SVR's at 12 weeks of 93-99% (SOF/LDV)
  - Genotype 3 still difficult to treat
  - Special populations – ESRD, HIV/HCV co-infection



N Am J Med Sci Apr 2016

Viral Load Monitoring

- Limit of Detection – smallest amt the method can reliably detect presence or absence (but not quantify)
- Limit of Quantification – smallest amt can reliably measure – within precision goals
- Undetectable – below the LoD

HCV RNA IU/mL	# replicates	# positive	Positivity Rate
0.0	56	0	0%
2.5	57	30	53%
5.0	58	41	71%
7.5	59	45	76%
10.0	60	53	88%
15.0	58	58	100%
25.0	56	56	100%
50.0	57	57	100%

Roche - Cobas AmpliPrep/Cobas TaqMan HCV Test June 30 2011

Viral Load Monitoring

- HCV RNA - Target Not Detected
  - Below the LoD
- HCV RNA – detected, not quantifiable
  - Above LoD, but below LoQ
- HCV RNA – 43 – 69,000,000 IU/mL
- HCV RNA > 69,000,000 IU/mL

- HCV detected but not quantifiable is NOT the same as "Not Detected"!

Roche – Cobas June 30 2011

Hepatitis C Vaccine (?)

- will not be easy
- virus is very heterogeneous
- immune response is relatively weak
- research is ongoing

Thanks!

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