

The ABC's of Hepatitis

APPROVED

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Viral Hepatitis

- Avoid these myths
- Hepatitis viruses are part of the same family
 - Very little in common except that they infect the liver
 - Signs and symptoms similar
 - Mixture of RNA and DNA viruses
- All hepatitis viruses have a vaccine
 - Only hepatitis A & B available

Viral Hepatitis

- **Hepatitis A**
- Hepatitis B
- Hepatitis C
- Hepatitis D
- Hepatitis E



Hepatitis A

- RNA virus
- Hepadnavirus genus of the Picornaviridae

3 restaurants in Durham that
have had a hepatitis outbreak -
they didn't survive



Hepatitis A

- Fecal-oral transmission wash your hands!
- Settings
 - Contact with infected person
 - International travel i.e. digging latrines in a 3rd world country
 - Daycare centers
 - Outbreaks

Hepatitis A

- Clinical manifestations

- Vary with age

- Usually silent or subclinical in children
 - More severe in adults

why daycare
outbreaks are mild

- Incubation period

- Averages 30 days (range 15 to 49 days)

difficult to track

Hepatitis A

- Clinical manifestations not specific for Hep A - applicable to any hepatitis
 - Prodromal symptoms
 - Fatigue, malaise, nausea, vomiting, anorexia, fever, and right upper quadrant pain
 - Dark urine, acholic stools, jaundice, and pruritus

Missing bilirubin



Hepatitis A

- Clinical manifestations
 - Exam
 - Hepatomegaly
 - Jaundice
 - Less common:
 - Splenomegaly occasionally
 - Lymphadenopathy
 - Rash common
 - Arthritis

Hepatitis A

- Laboratory features
 - Liver tests
 - AST/ALT usually > 1000 Normal ≤ 20
 - ALT $>$ AST
 - Bili > 10
 - Diagnosis
 - Hepatitis A **IgM** shows infectivity
 - May remain positive 4-6 months
 - Hepatitis A IgG – remote infection

Hepatitis A

Only one person at
Duke who has ever
failed under this regimen

- Treatment
 - Supportive
 - Avoid dehydration if N/V
 - Discharge with supervision
 - Close follow-up

Hepatitis A

- Prognosis
 - Excellent
 - Acute liver failure rare
 - More common if **underlying liver disease**
 - Italian study
 - Prospective; 595 adults with HBV (163) or HCV (432)
 - Tested q4 months for antibodies to HAV
 - 27 acquired HAV superinfection
 - 10 with HBV
 - 1 marked cholestasis
 - 17 with HCV
 - **7 acute liver failure; 6/7 died**

Moral of the story: vaccinate people against HepA for those who have an underlying liver disease (i.e. Hep C)

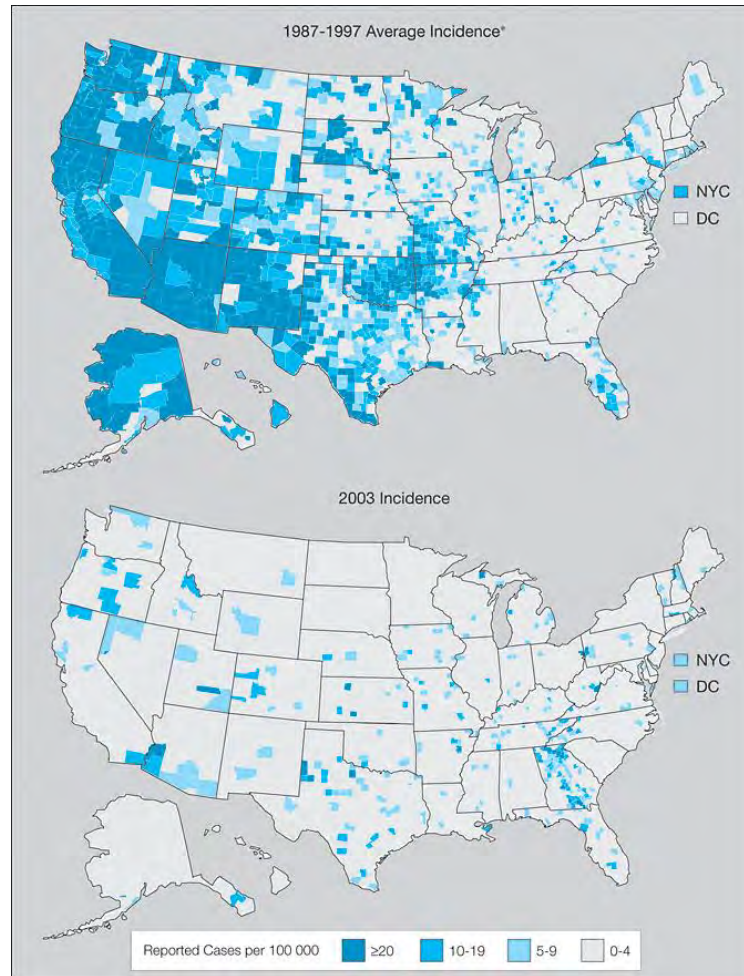
Vento S, NEJM 1998

Hepatitis A vaccination

- 1996: Hepatitis A vaccine recommended for
- international travelers
 - men who have sex with men (MSM)
 - injection- and noninjection-drug users
 - children in communities with high rates of disease
- 1999: the Advisory Committee on Immunization Practices (ACIP)
 - For children living in 11 states
 - > 20/100,000 population
 - Now for all children age 1 year

Hepatitis A

Vaccination works.



Before

After

Wasley, A.
JAMA 2005

Hepatitis A

- Post-exposure prophylaxis
 - Hep A immunoglobulin He ate at the pizza hut, so they gave him Ig first
 - IM injection within 2 weeks after exposure greater than 85% effective
 - Add vaccination if high-risk group later he got vaccinated

Acute Viral Hepatitis

- Hepatitis A
- **Hepatitis B**
- Hepatitis C
- Hepatitis D
- Hepatitis E

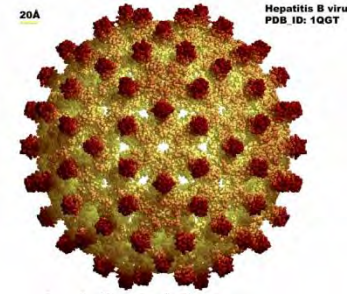


Hepatitis B

- Hepadnavirus family

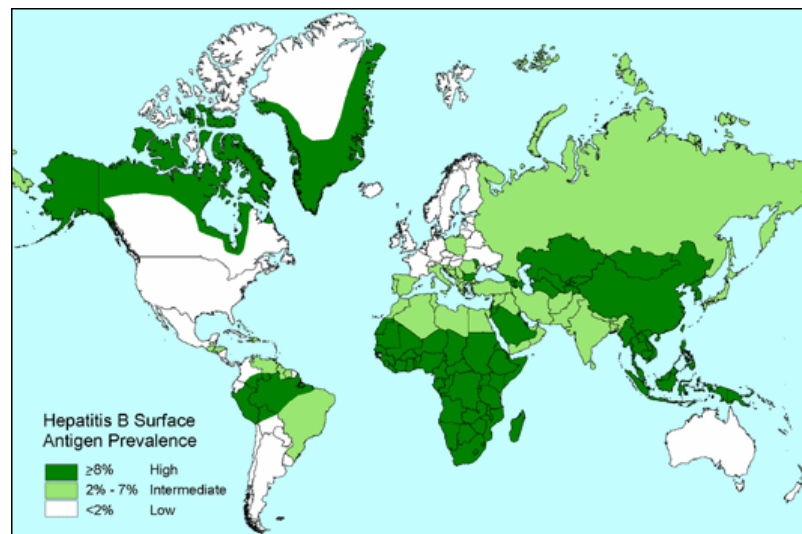
- DNA virus

Only one of the Hep
viridae that is DNA



Hepatitis B

- Epidemiology
- Worldwide > 400,000,000
 - 0.1 - 2% U.S., Europe, Australia
 - 3-5% Japan, central Asia, Middle East, South America
 - 10-20% Southeast Asia, China, subsaharan Africa
- > 1 million deaths annually



Hepatitis B

- Transmission
- Perinatal
 - in utero, at time of birth, after birth
 - no benefit to C-section
 - HBV DNA in colostrum but **no increased risk with breastfeeding**

Hepatitis B

- Transmission
- Perinatal
- Horizontal
- Transfusion (historical) not common these days
- Sexual the one to watch out for!
- Percutaneous esp. healthcare workers - has declined with vaccination

Hepatitis B

- Epidemiology

Only about 1% go fulminant - chronic is the big prob

- **Most complications with chronic infection**

- Risk of chronic infection

- Perinatal transmission 30-90% prob closer to 90% - big problem for baby

- Childhood infection 20-50%

Kids have a harder time dealing with this than adults

- Adult infection <5%

Hepatitis B

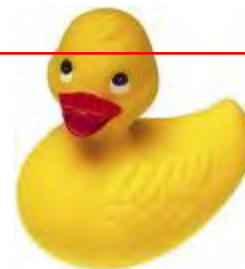
- Clinical Manifestations Just like Hep A presentation
- Acute hepatitis
 - 30% icteric (jaundiced)
 - 70% subclinical or anicteric
 - incubation period 1-4 months
 - AST/ALT typically 1000-2000 IU/L

Hepatitis B

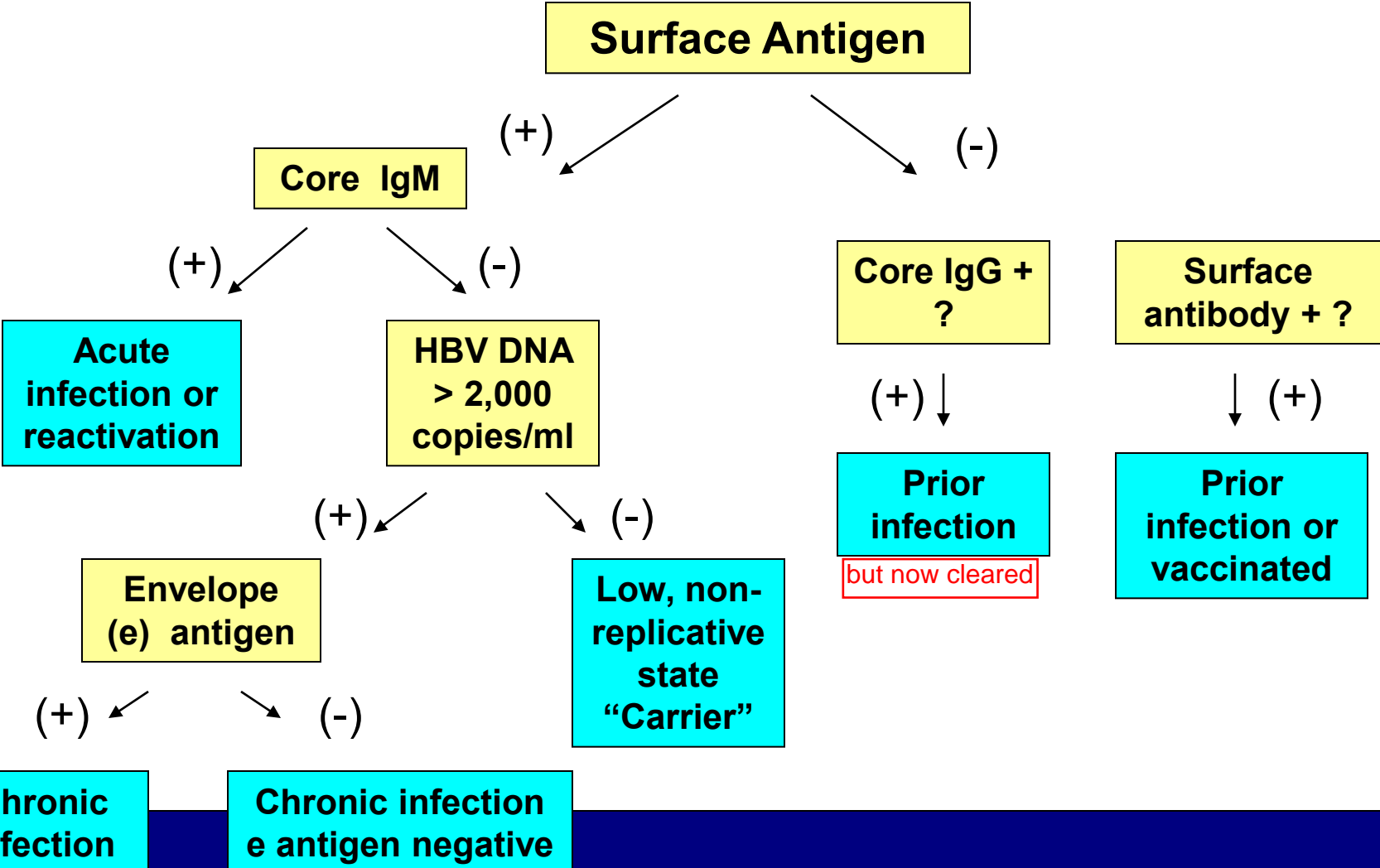
- Diagnosis
- The major proteins
- **Hepatitis B surface antigen (HBsAg)**
 - element of the outer surface of the virus
- Hepatitis B core antigen (HBcAg)
 - subunit proteins which form the genomic core of the virus
- Hepatitis B e antigen (HBeAg)
 - HBcAg and HBeAg are different forms of the same polyprotein
 - HBeAg is a truncated form thought to play a role in signaling for viral replication

Hepatitis B

- Diagnosis
- Acute infection
 - HBV surface antigen +
 - HBV core antibody IgM + Remember IgM spikes before IgG
 - Both may be negative at time of presentation if acute liver failure
 - History important



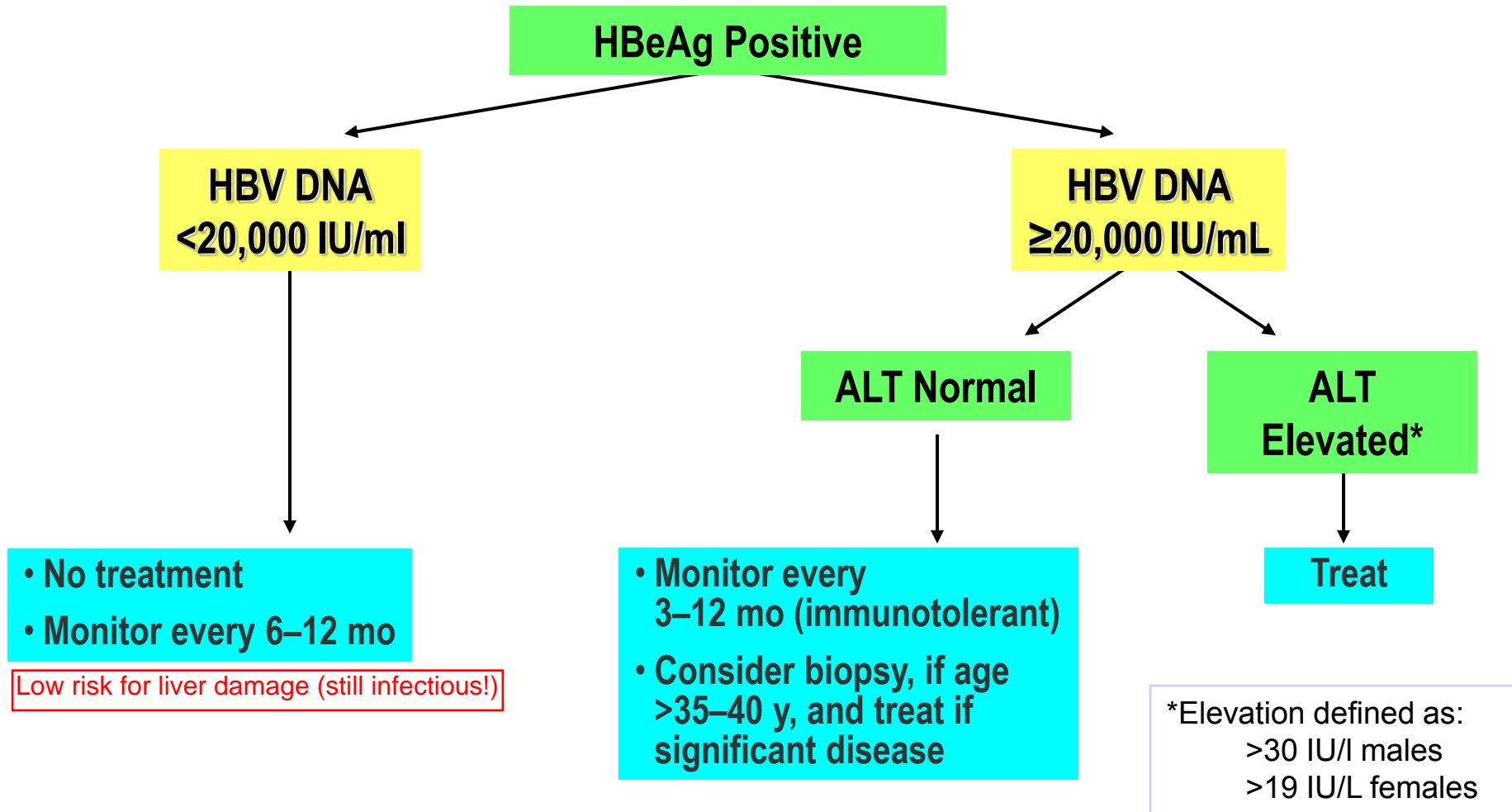
Chronic Hepatitis B Serologies



Goals of Chronic HBV Therapy

- **Not cure** just weather the storm
 - Decrease hepatic inflammation
 - Decrease rate of progression to fibrosis
 - Decrease incidence of long-term sequelae (cirrhosis, end-stage liver disease, hepatocellular carcinoma)

US Treatment Algorithm Update *HBeAg+*



Difficult to stop these drugs - once you start it's probably gonna be a lifelong regimen (you don't actually eliminate these buggers, you just suppress them)

Approved HBV Therapies

- Interferon (Intron-A[®], Pegasys[®])
- Lamivudine (Epivir[®])
- Adefovir dipivoxil (Hepsera[®])
- Entecavir (Baraclude[®])
- Telbivudine (Tyzeka[®])
- Tenofovir (Viread[®])



Chronic HBV and Pregnancy

- Vertical transmission important mode of transmission
 - HBIG and HBV vaccination of newborns has significantly reduced the risk
 - failure rate <5% if vaccine series completed)
- SE Asia study
 - HBeAg+, high viremia mothers
 - Protection rates of only 68% despite prophylaxis
- Lamivudine 100 mg daily last trimester
 - reduces risk of vertical transmission in high viremia mothers
 - 13% in treated moms versus 28% in historical controls

Hepatitis B

Don't have to memorize these regimens, just to get you familiar

- Postexposure prophylaxis
- Nonvaccinated
 - first dose of vaccine should be given within 12 hours
 - Doses 2 and 3 at regular interval
 - If source HBsAg positive, HBIG at same time in another site
- Vaccinated
 - Vaccinated with documented response → no post-exposure prophylaxis required
 - No post-vaccination testing → second course of vaccine unless anti-HBs is detectable at the time of exposure
 - Non-responders to vaccine → HBIG x 2 one month apart

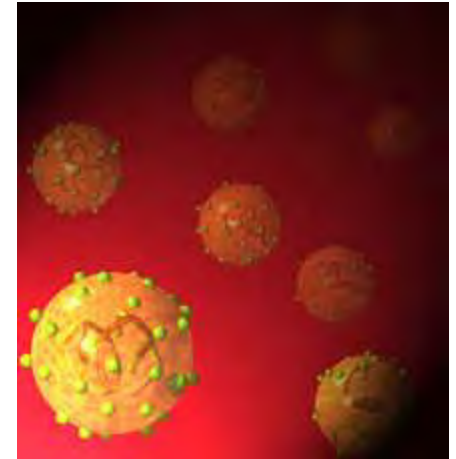
Viral Hepatitis

- Hepatitis A
- Hepatitis B
- **Hepatitis C**
- Hepatitis D
- Hepatitis E



HCV Virology

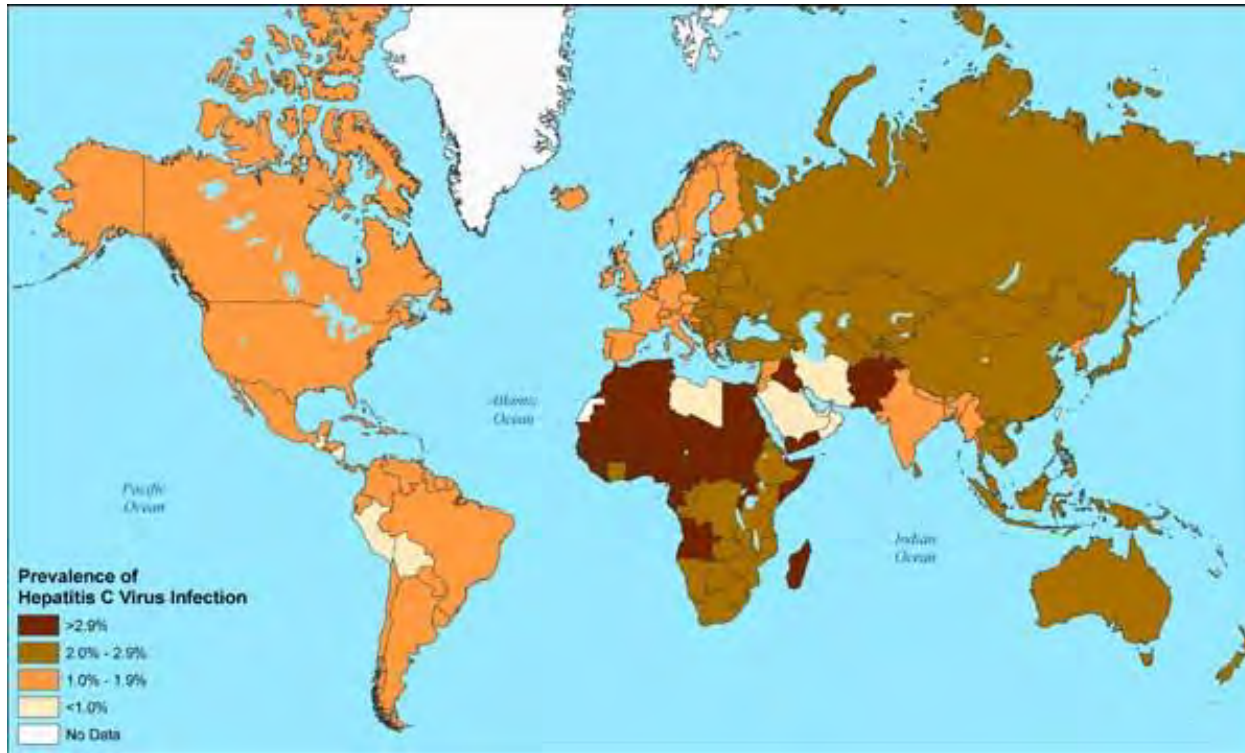
- RNA virus
- *Hepacivirus* genus of the *Flaviviridae* family



Hepatitis C

- 8 - 13,000 deaths per year
- 40 - 60% chronic liver disease
- #1 indication for liver transplant

Worldwide



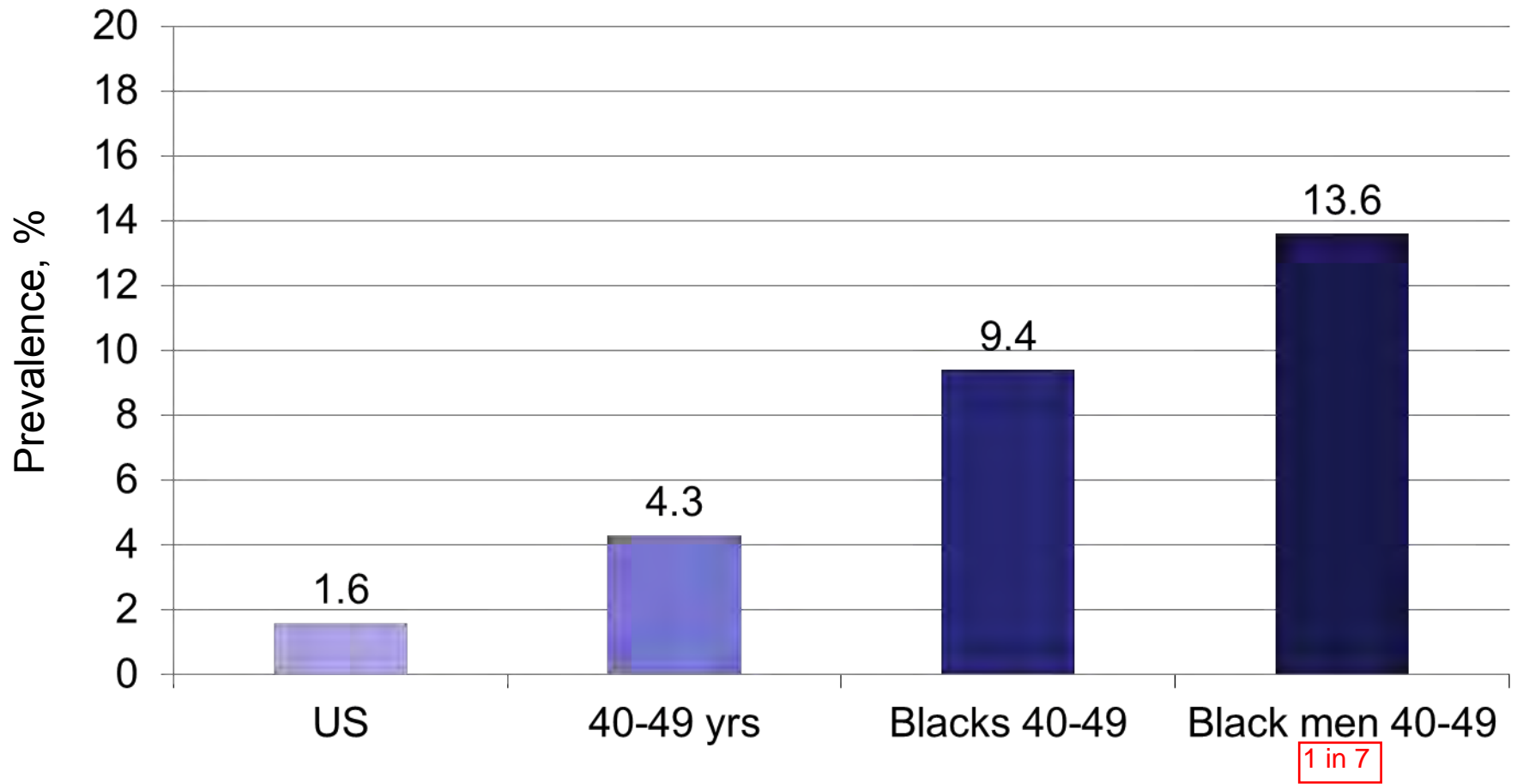
- 180 million infected
- Highest Asia & Africa
- Egypt > 15%
- USA 1.6%
 - 3-4 million infected

Flawed vaccination program that re-used needles

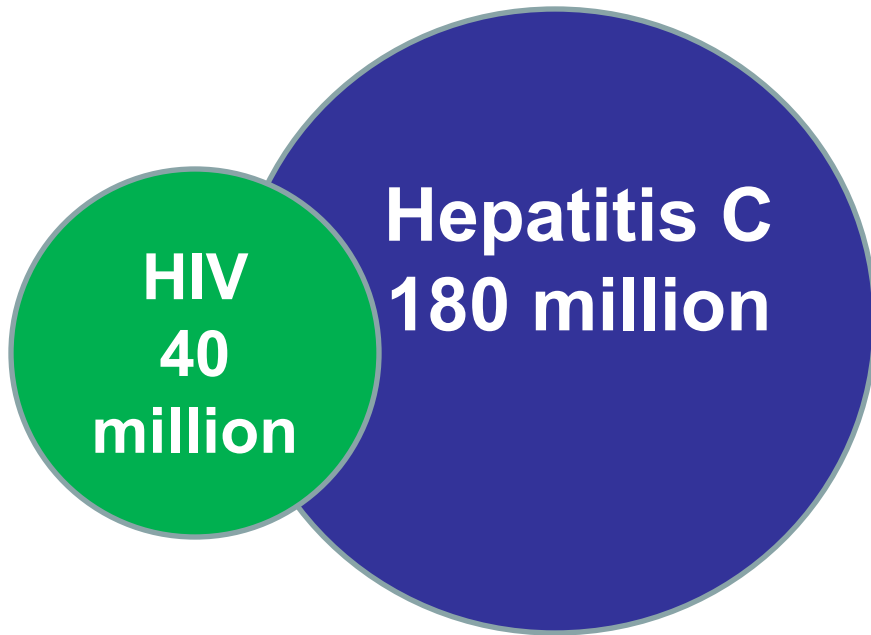
B greatest worldwide
C greatest USA

www.cdc.gov

HCV in the USA



HIV & HCV



Look how much more Hep C than HIV. Some overlap.

- 10 million people worldwide
- 30% of US patients with HIV have HCV

Staples CT. *Clin Infect Dis* 1999

Transmission

- Bloodborne
 - sharing drug-injection equipment most common route
 - transfusion of unscreened blood or untreated clotting factors
- Infrequent
 - Sexual contact
 - Vertical transmission Not routinely screened in pregnant women

Transmission

- Injection drug use, NHANES
 - 48.4% history IDU
 - 83.3% use remote
 - Needle exchange programs
 - Not legal NC
 - Insufficient evidence of reduced transmission of HCV

from drug use years ago

Q) What happens to the other 51.6%
A) Mixed causes - transfusions, sexual. These are patient reported, so the actual causation #s attributed to HepC are probably higher. Sex or STDs - use protection. Monogamous vaginal intercourse - low risk



Armstrong GL. *Ann Intern Med* 2006

Palmateer N. *Addiction* 2009

Transmission

- Tattoos
- Piercings
 - Uncommon modes of transmission



Hwang LY, Hepatology 2006

Transmission

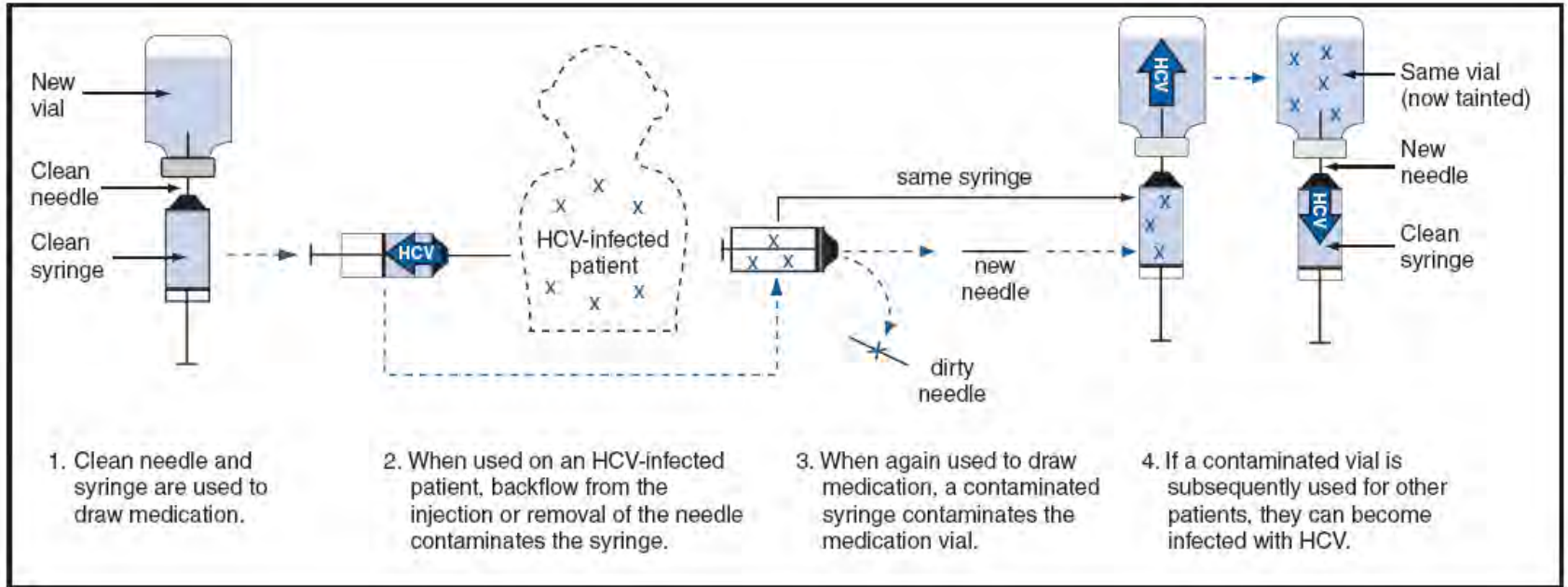
- Transmission to patients
 - New York endoscopy center
 - Oklahoma pain clinic
 - Nebraska Oncology treatment center
 - Las Vegas ambulatory surgical center 2008
 - North Carolina cardiology clinic 2008
 - VA hospitals in Miami and TN 2009



MMWR 2001, 2008

Transmission

It all comes down to poor needle technique - contaminated syringes and/or needles being used in a common vial



www.cdc.gov

Who Should be Tested for HCV Infection?

- Persons who have ever injected illegal drugs, including those who injected only once many years ago
- Recipients of clotting factor concentrates made before 1987 like hemophiliacs
- Recipients of blood transfusions or solid organ transplants before July 1992
- Patients who have ever received long-term hemodialysis treatment

CDC FAQs for Health Professionals. Last updated June 9, 2009.
Available at <http://www.cdc.gov/hepatitis/HCV/HCVfaq.htm>. Accessed 07/29/10.

Who Should be Tested for HCV Infection?

- Persons with known exposures to HCV, such as
 - Healthcare workers after needlesticks involving HCV-positive blood
 - Recipients of blood or organs from a donor who later tested HCV-positive
- All persons with HIV infection
- Patients with signs or symptoms of liver disease
 - (e.g., abnormal liver enzyme tests)
- Children born to HCV-positive mothers only after age 18 mos.
 - to avoid detecting maternal antibody, children should not be tested before age 18 months

CDC FAQs for Health Professionals. Last updated June 9, 2009.

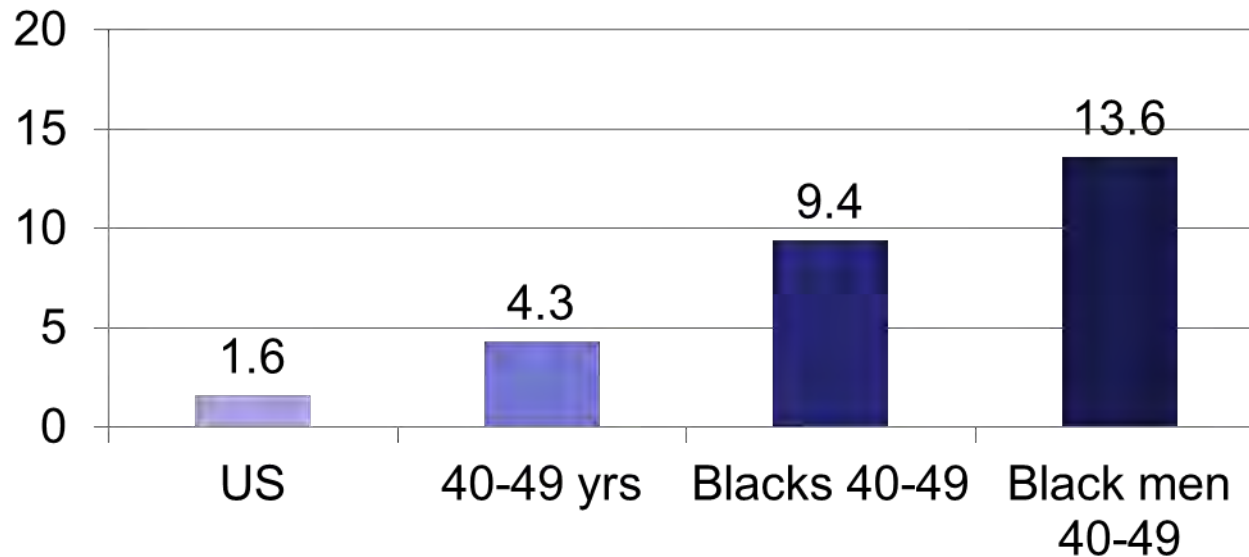
Available at <http://www.cdc.gov/hepatitis/HCV/HCVfaq.htm>. Accessed 07/29/10

What maternal antibody crosses the placenta?

What maternal antibody is in breast milk?

Who Should be Tested for HCV Infection?

- Baby boomers?
 - CDC pilot study in progress
 - Remove the stigma?



Natural History

OPPOSITE OF HEP B! Most go into chronic infection!

Acute Hepatitis C

**Chronic Hepatitis
75-85 %**

Cirrhosis 20 %

20-50 years

Faster progression

- older age at infection
- alcohol
- HIV infection
- post-transplant

Booze is bad for Hep +s

Cirrhosis

- Decompensated cirrhosis

- Ascites

- spontaneous bacterial peritonitis (SBP) **1 in 3 mortality**
 - Hepatic hydrothorax

- Bleeding varices **1 in 3 mortality**

- Hepatic encephalopathy

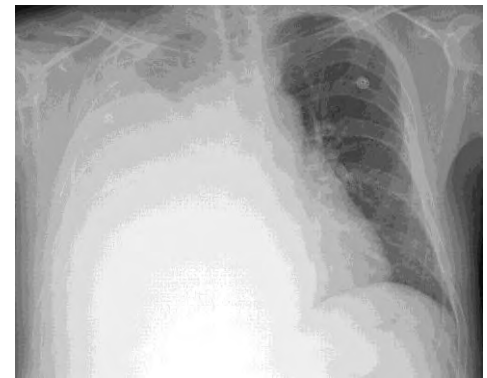
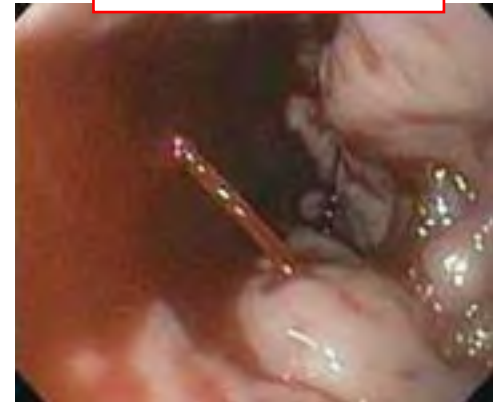
- Hepatorenal syndrome

- Not HCV treatment candidates

Must transplant

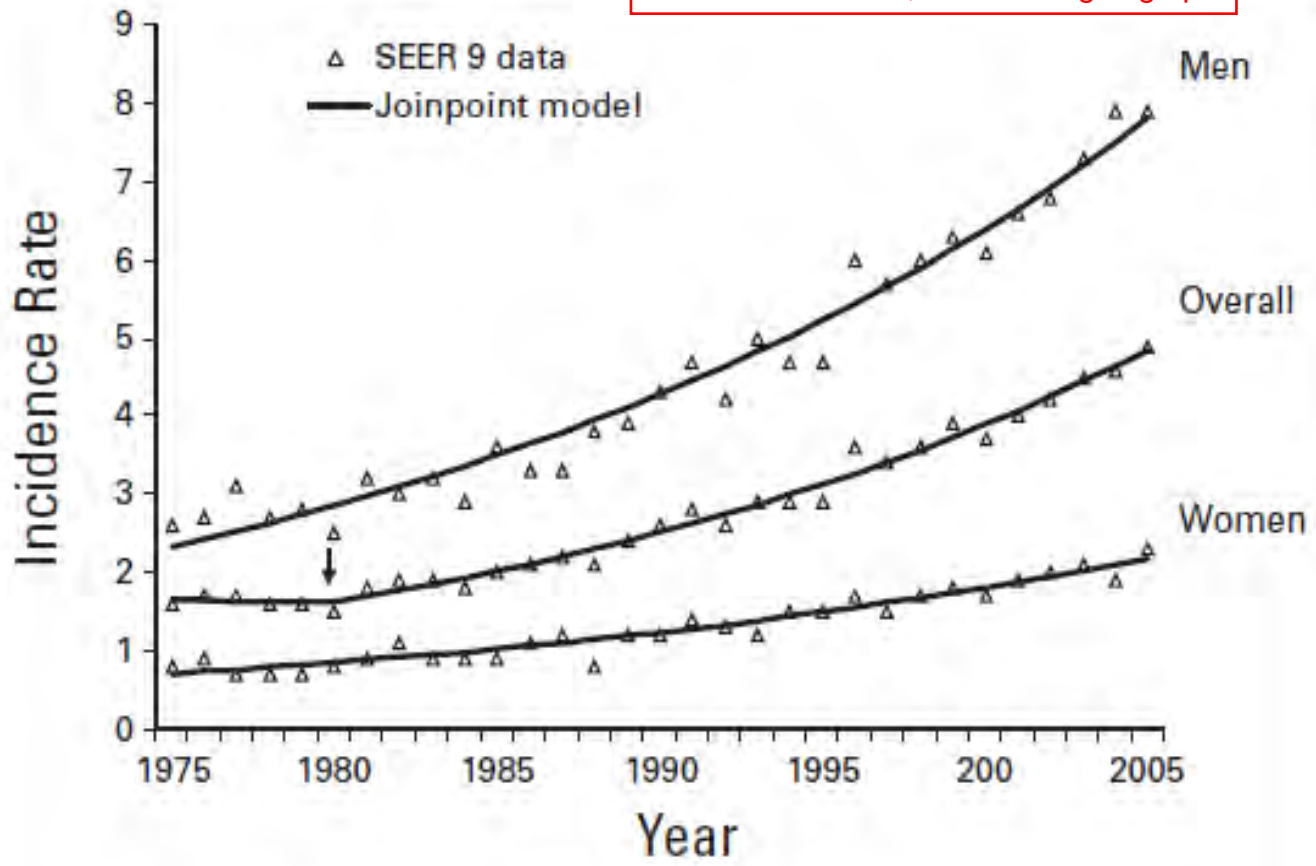


Esophageal varices



Hepatocellular carcinoma

Whereas we're getting better at reducing most other cancers, this one is going up



*Rates per 100,000

Diagnosis

Q about recurrent infection in transplant - Common across the Hep infections - use Ig treatment before transplant and therapy after. Avg. transplant effectiveness = 8-12 yrs.

Screening

Antibody tests

- ELISA
- positive 8-10 weeks
- Used in screening programs
- Could mean 3 things
 - Currently infected
 - Previously infected but cured
 - False positive test

Confirmation

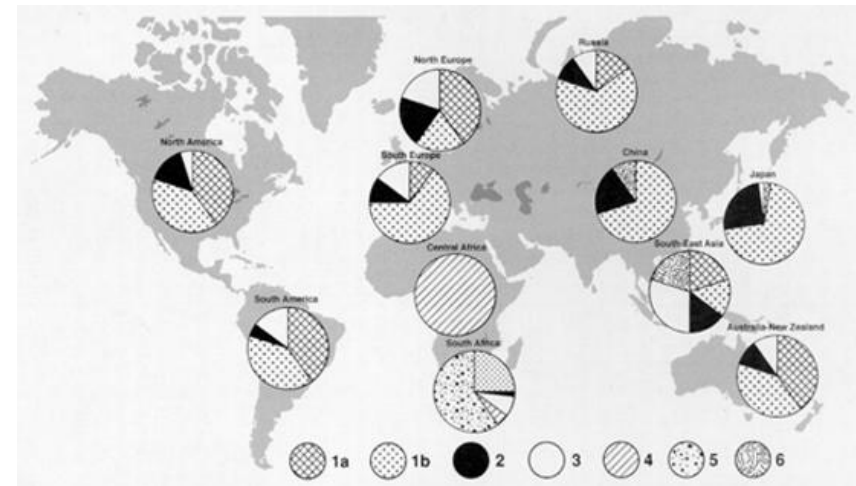
HCV RNA

- PCR
- Documents viremia and establishes infection
- Does not predict degree of liver injury
- Followed for response to treatment
- No role for serial measurements of treatment

Diagnosis

- Genotype
 - 6 genotypes worldwide
- Genotype 1
 - Most common USA
 - Lowest response rates
 - Longest treatment duration

Sucks for us - 1 is no fun



Forns X & Bukh J. Clin Liver Dis 1999

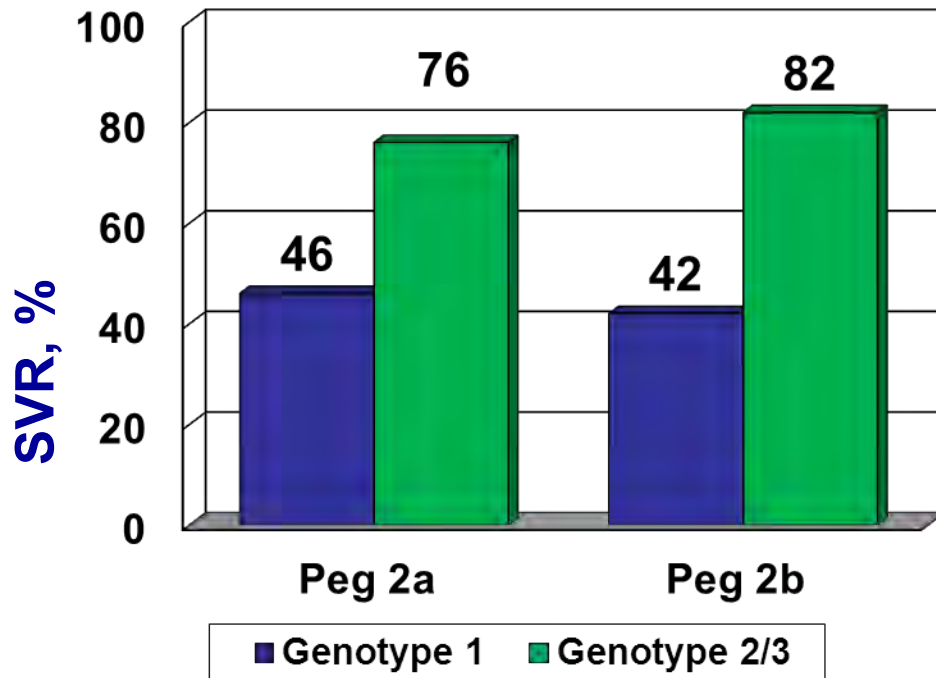
Treatment

- Goal of treatment:
 - Clinical trial definition
 - Sustained virologic response
 - HCV RNA negative 6 months after end of treatment
 - What we tell patients...

Cure!

Remember to tell patients - we can cure these

Chronic HCV



- Standard of care
 - Peginterferon alfa old Gold Standard
 - Ribavirin improves response rates - don't ask him about mechanism

Fried MW, *NEJM* 2002
Manns MP, *Lancet* 2001

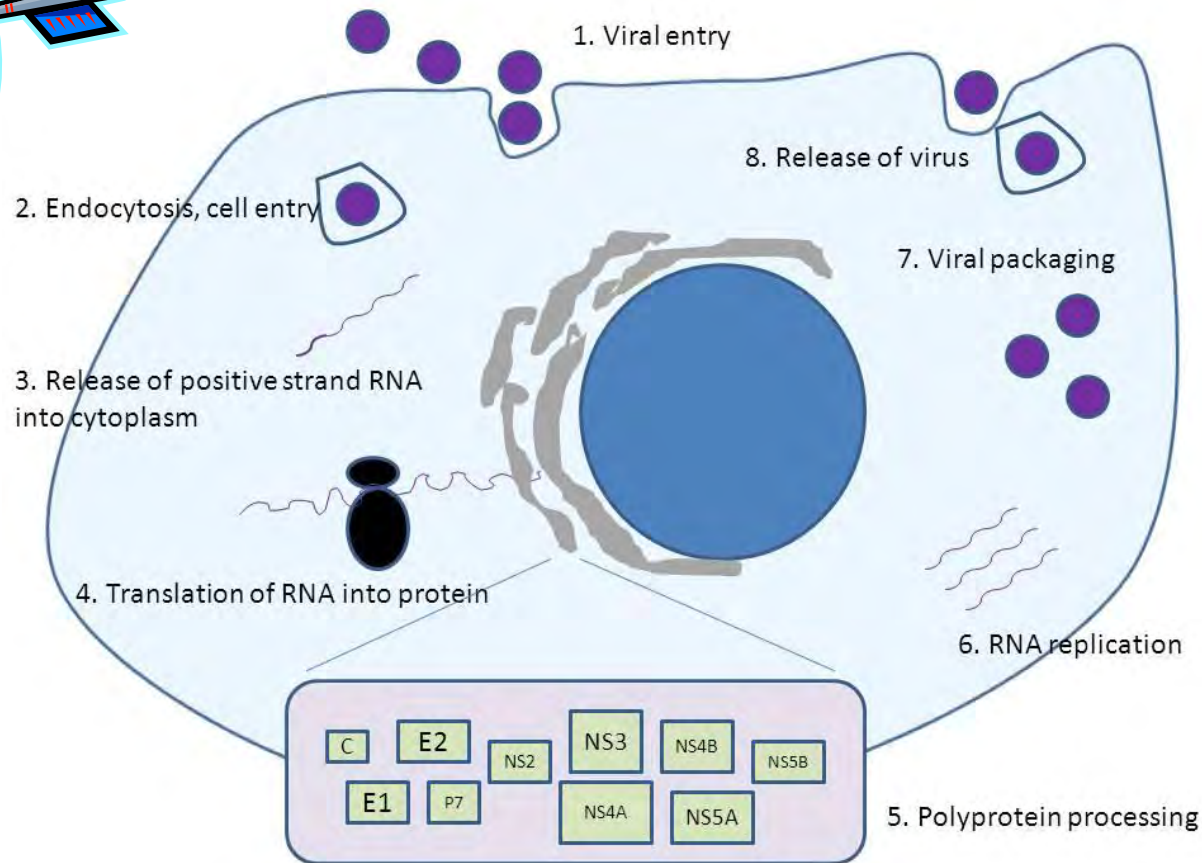
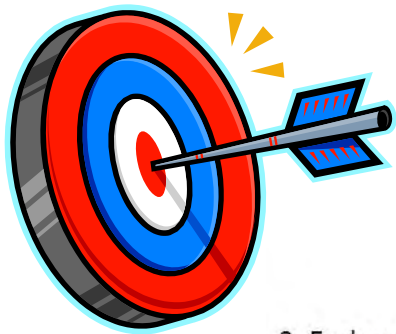
Treatment

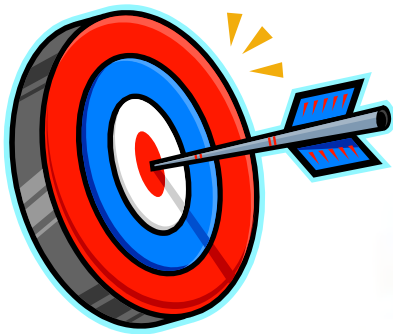
A lot of challenges

- **Contraindications**
 - Decompensated cirrhosis
 - Leukopenia, thrombocytopenia
 - Uncontrolled depression
 - Severe mental illness
 - Autoimmune conditions
 - Comorbidities
 - Advanced CHF, COPD
- **Ribavirin contraindications**
 - Pregnancy
 - Chronic kidney disease (stage 3-5)

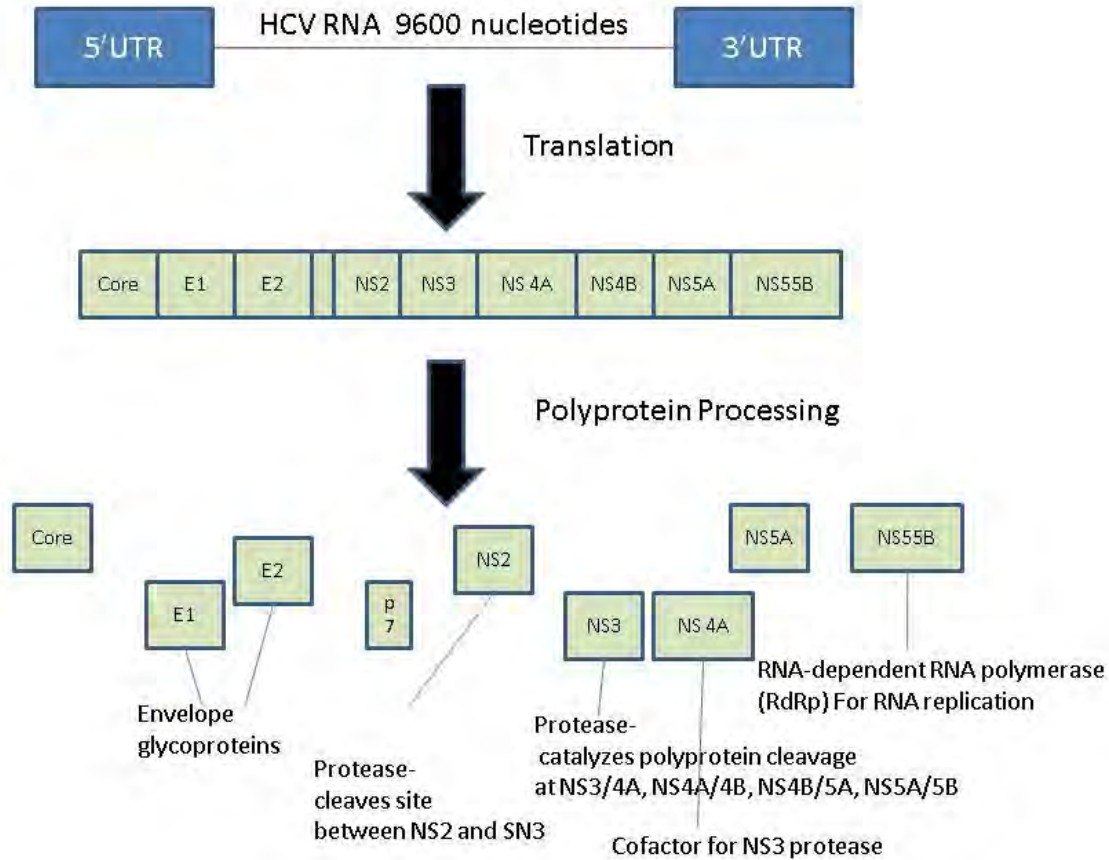
HCV life cycle

what can we target?





HCV genome

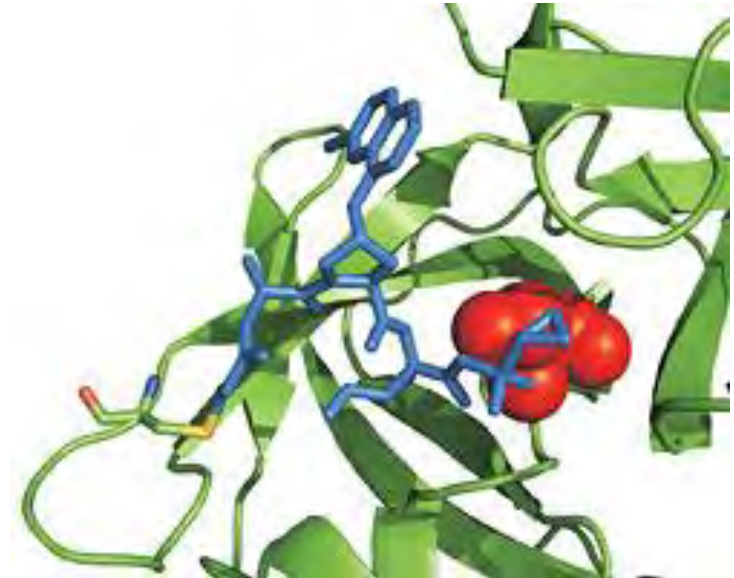


winner!

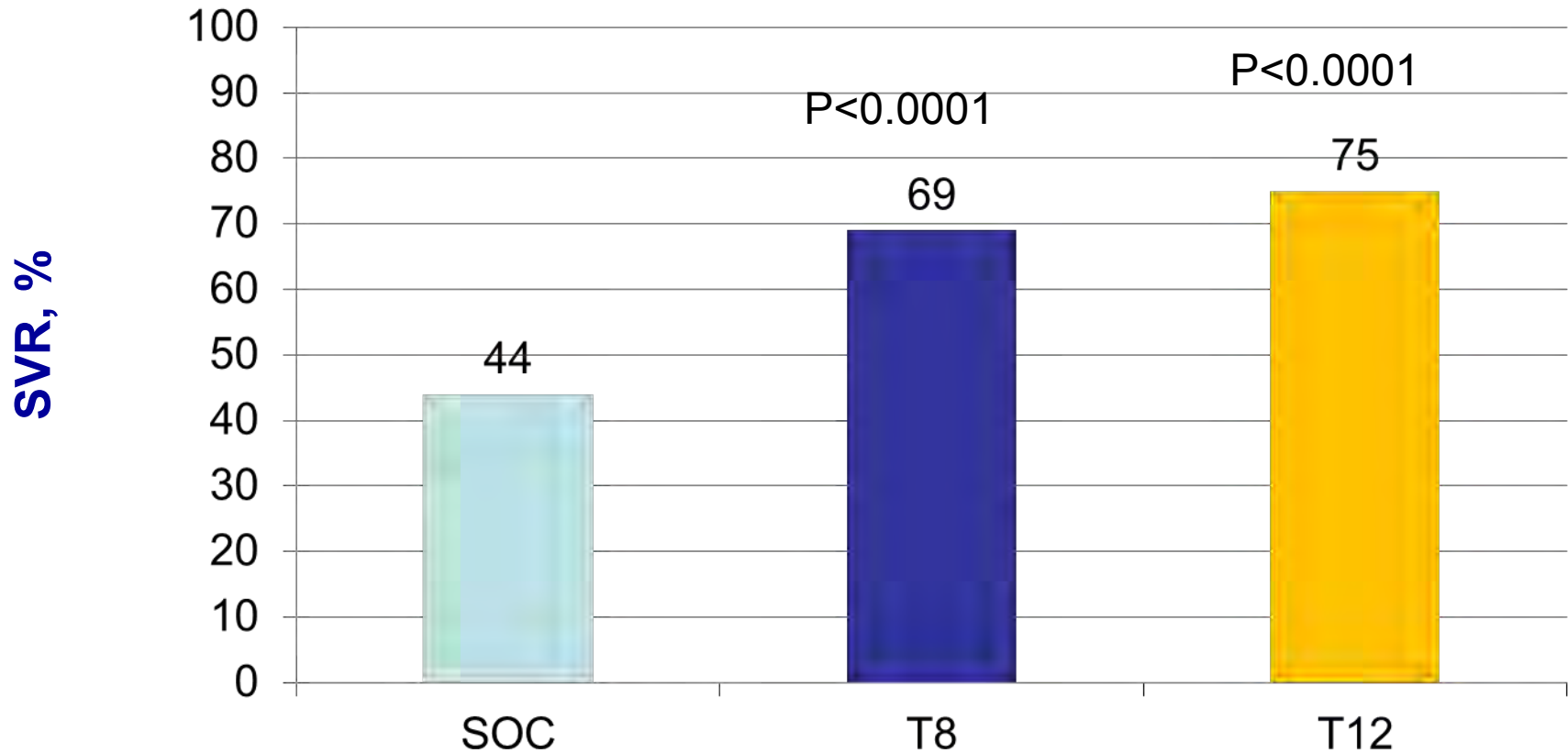
1st generation protease inhibitors

- NS3*4A protease inhibitors
- Boceprevir & Telaprevir
 - In combination with PEG/RBV 75-80% response rate
 - ↑ resistance with monotherapy

Must be given in combination!



Telaprevir + PEG/RBV



Viral Hepatitis

The key for D is you must be
coinfected with Hep B in order
to get it!

- Hepatitis A
- Hepatitis B
- Hepatitis C
- **Hepatitis D**
- Hepatitis E



Hepatitis D

- Small RNA virus
 - Genome 1700 nucleotides Hepatitis D virus (HDV) is replication defective RNA virus.
- **Requires co-infection with HBV** to complete assembly of new HDV viral particles

Hepatitis D

- Diagnostic testing
 - Anti-HDV

Hepatitis D

- Therapy
 - No specific therapy for HDV
 - Therapy targets HBV infection
 - no HBV = no HDV

Viral Hepatitis

Kinda like Hep A -
fecal->oral
transmission

- Hepatitis A
- Hepatitis B
- Hepatitis C
- Hepatitis D
- **Hepatitis E**



Hepatitis E

- Infection first documented in 1955 during outbreak in New Delhi, India

Purcell, RH. J Hep 2008

Hepatitis E

- **Epidemiology**

- Highest incidence in Asia, Africa, Middle East, and Central America
- > 100,000 individuals in the Xinjiang region of China between 1986 and 1988
- Large outbreaks in refugee camps in Darfur, Sudan and Chad

Purcell, RH. J Hep 2008

Hepatitis E

- Transmission
 - Fecally contaminated water in endemic areas
 - Person-to-person transmission uncommon
 - Possible by blood transfusion
 - Reports with transplantation
- Western countries reports limited to travellers to endemic areas
 - Reports of infection in pigs
 - Undercooked deer meat, wild boar meat, rodents

Purcell, RH. J Hep 2008

Hepatitis E

- **Diagnosis**
 - HEV RNA in serum or feces by PCR
 - HEV IgM antibodies
 - In the United States, testing for HEV available only in research laboratories

Purcell, RH. *Journal of Hepatology* 2008; 48(3):494-503.

HEV Transmission

- **Transmission during pregnancy**

Soon-to-be moms - avoid undercooked meats and oysters (water transmission of feces)

- Case series: 8 babies born to mothers infected with hepatitis E in the third trimester
- All 8 mothers had vaginal deliveries
- IgG anti-HEV detected in all 8 and HEV RNA detected in 5
- 6 (75%) infants had clinical, serologic, or virologic evidence of HEV infection
- Two infants died within 24 hours of birth, one with massive hepatic necrosis at autopsy

Khuroo, MS. Lancet 1995

HEV Transmission

- Design: Observational cohort.
- Setting: Tertiary care hospital, New Delhi, India.
- Patients: 220 consecutive pregnant women presenting with jaundice caused by acute viral hepatitis.

Patra S. *Ann Intern Med.* 2007

HEV Transmission

- HEV caused acute viral hepatitis in 60% of included women.
- Comparing HEV-infected women to non-HEV-infected women, increases were noted in:
 - Fulminant hepatic failure (RR 2.7 [1.7 to 4.2]; P = 0.001)
 - Maternal mortality (RR 6.0 [CI, 2.7 to 13.3]; P < 0.001)
 - Obstetric complications
 - antepartum hemorrhage (RR 4.1 [1.7 to 10.2]; P < 0.001)
 - intrauterine fetal death (RR 1.9 [CI, 1.3 to 2.7]; P < 0.001)
 - Poor fetal outcomes
 - preterm delivery (RR 1.2 [CI, 1.0 to 1.4]; P = 0.005)
 - stillbirth (RR 1.8 [CI, 1.2 to 2.5]; P = 0.026)

Patra S. Ann Intern Med. 2007

Hepatitis E

- Prevention
 - Vaccines in development
 - Phase 2 trial: vaccine 96% effective in preventing infection in a high-risk setting
- Treatment of infection remains supportive.

Viral Hepatitis

- Avoid these myths
- Hepatitis viruses are related
- All hepatitis viruses have a vaccine
 - Only hepatitis A & B available E is in the works

Viral Hepatitis

- Remember
- **Prevention is key**
 - Water-borne outbreaks of hepatitis A & E
 - Sex education for hepatitis B (and C)
 - Substance abuse programs for hepatitis B, C & D
 - Vaccinations for hepatitis A & B
- **Identify patients with chronic hepatitis**
 - Most asymptomatic
 - Screen for HBV and HCV if risk factors

APPROVED

The ABC's of Hepatitis



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