The ABC’s of Hepatitis

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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
  – Incubation period
    • Averages 30 days (range 15 to 49 days)
Hepatitis A

• Clinical manifestations

  – Prodromal symptoms
    • Fatigue, malaise, nausea, vomiting, anorexia, fever, and right upper quadrant pain
  
  – Dark urine, acholic stools, jaundice, and pruritus

  [Missing bilirubin]

[not specific for Hep A - applicable to any hepatitis]
Hepatitis A

• Clinical manifestations
  – Exam
    • Hepatomegaly
    • Jaundice
    • Less common:
      – Splenomegaly
      – Lymphadenopathy
      – Rash
      – Arthritis
Hepatitis A

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

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

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

Wasley, A.
JAMA 2005

Vaccination works.

Before

After

Reported Cases per 100,000

1987-1997 Average Incidence

2003 Incidence
Hepatitis A

• Post-exposure prophylaxis
  – Hep A immunoglobulin
    • IM injection within 2 weeks after exposure greater than 85% effective
  – Add vaccination if high-risk group

He ate at the pizza hut, so they gave him Ig first

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 Hepviridae 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
• Most complications with chronic infection
• Risk of chronic infection
  – Perinatal transmission 30-90%
  – Childhood infection 20-50%
  – Adult infection <5%

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

prob closer to 90% - big problem for baby

Kids have a harder time dealing with this than adults
Hepatitis B

• Clinical Manifestations
• 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 +
  - Both may be negative at time of presentation if acute liver failure

- History important

Remember IgM spikes before IgG
Chronic Hepatitis B Serologies

- **Surface Antigen**
  - Core IgM
    - (+) Acute infection or reactivation
    - (-)
  - Core IgG +
    - (?) Prior infection or vaccinated
  - Surface antibody + ?
    - (+) Prior infection
      - (++) but now cleared
    - (-)

- **Core IgM**
  - (+)
  - (-)

- **Envelope (e) antigen**
  - (+)
  - (-)

- **HBV DNA > 2,000 copies/ml**
  - (+)
  - (-)

- **Low, non-replicative state “Carrier”**
  - (+)
  - (-)

- **Chronic infection**
- **Chronic infection e antigen negative**
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*+

**HBeAg Positive**

- **HBV DNA <20,000 IU/ml**
  - *No treatment*
  - *Monitor every 6–12 mo*
  - [Low risk for liver damage (still infectious!)]

- **HBV DNA ≥20,000 IU/mL**
  - **ALT Normal**
    - *Monitor every 3–12 mo (immunotolerant)*
    - *Consider biopsy, if age >35–40 y, and treat if significant disease*
  - **ALT Elevated***
    - *Treat*

*Elevation defined as:*
- >30 IU/L males
- >19 IU/L females

Lok A and McMahon A. AASLD Guideline 2007

Duke Clinical Research Institute
Approved HBV Therapies

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

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)
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

- **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

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

www.cdc.gov
HCV in the USA

Prevalence, %

- US: 1.6%
- 40-49 years: 4.3%
- Blacks 40-49: 9.4%
- Black men 40-49: 13.6% (1 in 7)

HIV & HCV

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

HIV
180 million

Hepatitis C
40 million

Staples CT. Clin Infect Dis 1999
Transmission

- Bloodborne
  - sharing drug-injection equipment
  - transfusion of unscreened blood or untreated clotting factors

- Infrequent
  - Sexual contact
  - Vertical transmission

Source: www.cdc.gov
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

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

from drug use years ago

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

1. Clean needle and syringe are used to draw medication.
2. When used on an HCV-infected patient, backflow from the injection or removal of the needle contaminates the syringe.
3. When again used to draw medication, a contaminated syringe contaminates the medication vial.
4. If a contaminated vial is subsequently used for other patients, they can become infected with HCV.

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

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
  - to avoid detecting maternal antibody, children should not be tested before age 18 months

CDC FAQs for Health Professionals. Last updated June 9, 2009.
Who Should be Tested for HCV Infection?

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

Acute Hepatitis C

Chronic Hepatitis 75-85 %

Cirrhosis 20 %

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

OPPOSITE OF HEP B! Most go into chronic infection!

20-50 years

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
Hepatocellular carcinoma

*Rates per 100,000

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

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

**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

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.
Diagnosis

- Genotype
  - 6 genotypes worldwide

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

Forns X & Bukh J. Clin Liver Dis 1999

Sucks for us - 1 is no fun
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
  - Ribavirin

Fried MW, *NEJM* 2002
Treatment

• 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

1. Viral entry
2. Endocytosis, cell entry
3. Release of positive strand RNA into cytoplasm
4. Translation of RNA into protein
5. Polyprotein processing
6. RNA replication
7. Viral packaging
8. Release of virus

what can we target?

Courtesy A. Jazwinski, MD
HCV genome

HCV RNA 9600 nucleotides

Translation

Core, E1, E2, NS2, NS3, NS4A, NS4B, NS5A, NS5B

Polyprotein Processing

Core

E1

E2

NS2

NS3

NS4A

NS5A

NS5B

Envelope glycoproteins

Protease-cleaves site between NS2 and NS3

Protease-catalyzes polyprotein cleavage at NS3/4A, NS4A/4B, NS4B/5A, NS5A/5B

RNA-dependent RNA polymerase (RdRp) for RNA replication

Cofactor for NS3 protease

Courtesy A. Jazwinski, MD
1\textsuperscript{st} generation protease inhibitors

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

winner!
Telaprevir + PEG/RBV

SVR, %

SOC 44
T8 69
T12 75

P<0.0001

Jacobson IM, AASLD 2010
Viral Hepatitis

• Hepatitis A
• Hepatitis B
• Hepatitis C
• **Hepatitis D**
• Hepatitis E

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

- 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

HEV Transmission

**Transmission during pregnancy**

- 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

Soon-to-be moms - avoid undercooked meats and oysters (water transmission of feces)
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
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
The ABC’s of Hepatitis

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