Viral Hepatitis

Marsha H. Kay, M.D.

Department of Pediatric Gastroenterology & Nutrition
Cleveland Clinic

Objectives- Viral Hepatitis

• 1. Understand the method of transmission of the various viral agents that cause hepatitis

• 2. Identify who is at risk in the pediatric age group for the various forms of viral hepatitis

• 3. Understand methods of prevention, treatment and prognosis indicators for viral hepatitis

Historical Perspective

• Epidemic jaundice described by Hippocrates > 2000 years ago (fever, anorexia, nausea, malaise, fatigue

• 1940’s differentiation Hepatitis A & B
  – 1960’s antigen tests to differentiate

• 1955 epidemic enteric viral hepatitis India
  – Hepatitis E
  – Second major outbreak 1980
  – 20% mortality pregnant women
Historical Perspective

- 1970 Dane et al identify viral particle assoc. with Hepatitis B
- 1972 Feinstone identify Hepatitis A
- 1989 immunoassay to detect antibody to Hepatitis C
- 1993 new research tests available for anti-HEV
  - Virus first described 1983
- Current new viruses; non-A,B,C,D,E, etc.

Disease Burden of Hepatitis in the U.S.-2006 (all ages)
Substantial shifts incidence and prevalence HAV & HBV after implementation of childhood vaccination strategies

- Estimated number of new infections/year
  - HAV: 32,000
  - HBV: 46,000
  - HCV: 19,000

- % ever infected
  - HAV: 33%
  - HBV: 4.9%
  - HCV: 1.6%

- HDV & HEV – surveillance data not available
  - CDC-MMWR 2008
  - HDV & HEV- not known
    - National Health and Nutrition Examination Survey

Third of the world infected with hepatitis:
WHO

- (Reuters) - Around one third of the global population, or 2 billion people, have been infected with one of the viruses that causes the liver disease hepatitis, which kills about a million victims annually, the World Health Organization said on Tuesday July 26, 2011.

- Although most of those carrying hepatitis do not know they have it, they can unknowingly transmit it to others and at any time in their lives it can develop to kill or disable them, the United Nations agency warned

- "This is a chronic disease across the whole world, but unfortunately there is very little awareness, even among health policy-makers, of its extent," WHO hepatitis specialist Steven Wiersma told a news conference.

- The conference marked the first U.N. World Hepatitis Day
Hepatitis A

- RNA virus
- Picornaviridae
- Pathological effects limited to liver
- Acute hepatitis only
- Likelihood of symptoms related to patient age
  - Often asymptomatic
  - 90% children < age 6 asymptomatic
- Most common in developing countries
  - Prevalence may approach 100%
  - Majority < age 5 at acquisition
- Cyclic occurrence in developed countries
  - Peak every 10-15 years
  » Source CDC 2008

Hepatitis A

- Approximately 30% adults in U.S. have positive serology
  - 1990 29,000 cases reported to CDC
    » 130,000-150,000 estimated
  - 2006 significant decrease in cases 3,579 (CDC)
    » 32,000 estimated new infections
  - 90% decline 1995-2006
  - Greatest among children and routine vaccination states
  » Source CDC 2008

Figure 2.1. Reported and adjusted* number of acute hepatitis A cases — United States, 1990–2009

*Adjusted for underreporting.
Source: National Notifiable Diseases Surveillance System (NNDSS)
Hepatitis A

- Incubation 28 days (mean) (r = 15-50 d)
- Transmission
  - Contagious two weeks before symptoms
  - Fecal-oral
  - Contaminated shellfish
  - Rare percutaneous
- Diagnosis elevated IgM
- 5 weeks post exposure at time of clinical symptoms
- Persists 3-4 months
- IgG positive after 4 months, may persist for years

Hepatitis A infection

![Diagram showing the phases of hepatitis A infection with timelines and markers for ALT, Anti-HAV (IgG), Anti-HAV (IgM), and-via excretion]

Hepatitis A- Clinical Features

- Children usually asymptomatic
  - Like viral URI
- Adults more symptomatic, may be severe
  - Fever, nausea, vomiting, diarrhea, fatigue, dark urine, appetite loss
- Fulminant hepatitis very rare
  - .01-2.0 %
  - May result in death
  - Increased risk age > 50 or chronic liver disease
- No chronic carrier state
- 2006 Rates in U.S.
  - Now similar in all age groups due to vaccination strategy
Hepatitis A- Prevention & Management: Immunoglobulin

- Prior to exposure: travel to endemic area
  - Risk is 4-30 cases/100,000 mos. stay for unimmunized traveler
  - Require q 4-6 month re-administration for ongoing exposure (i.e. military)
  - Mexico, Caribbean, S. America, Central America, Africa, Asia (not Japan)
- Passive immunity lasts < 12 weeks
- After exposure
  - Within 14 days of exposure
  - Household/intimate contact
  - Day care/ custodial care (diapers)
  - Common source outbreak

Hepatitis A: Vaccination

- 2 single antigen products available 1996
  - Havrix- Glaxo Smith Kline
  - Vaqta- Merck & Co.
- Inactivated whole cell virus vaccine
- IM administration
- Both require booster (initial dose & 6-18 months later)
- Consider for post exposure prophylaxis
  - Immunoglobulin modestly better vs. vaccine*
  - but infection rates in contacts < 5% for both*
- Combination HAV/HBV vaccine for patients \( \geq \) age 18
  - Twinrix- Glaxo Smith Kline
  - 0, 1, 6 months
  - *Victor JC et al. NEJM 2007: 357 (17)

Hepatitis A- Prevention & Management: Vaccination

- Travelers
  - international travel source of 25% cases of HAV
- high risk population
  - Children in communities with high hepatitis rates
  - Native Americans, Alaskans
  - IV drug use, Non injection drug use
  - lab workers, primate animal handlers
  - homosexual-bisexual men
  - patients with chronic liver disease/ disorder of clotting factor
  - child care/institutional staff
- +/- hospital personnel, food handlers, anyone >2
Hepatitis A: Vaccination

- **1996** initial vaccination children in high risk states/occupational or lifestyle risk factors
- **1999** CDC recommends expansion of childhood vaccination strategy to include children in communities w/ rates > national average
  - Significant decline in HAV infection rates in both pediatric patients & adults even in high risk states
  - Similar effect noted in Israel w/in 2 years of adoption universal vaccination
  - Herd immunity
- **2005** FDA approve use HAV vaccine starting @ 12 mos. age
- **2006** CDC recommend HAV for all children age 12 mos. regardless of state of residence
  - Coadministration w/ other vaccines not assoc. w/ decreased immunity
- **2007** AAP recommend universal vaccination all infants @ 1 year of age
  - 2 dose regimen
  - Catch up immunization programs for children 2-18 years should be maintained if present or considered
- Continue immunization high risk individuals as previously specified
- Immunocompromised state not a contraindication (inactivated)

Hepatitis B

- DNA Virus
- Hepadnaviridae
- 8 genotypes (A-H); two subtypes (Aa/Ae, Ba/Bj)
- Incubation 60-150 days (mean 90 d)
- Mortality rate 1.4%
- **2 Billion infected**
- High prevalence **300 million carriers** worldwide
- Endemic Areas: China, Sub-Saharan Africa, Southeast Asia, Mediterranean Basin, Alaskan Eskimo’s, adoptees from endemic areas
- **U.S. 0.5-0.7% carrier prevalence** (approx. 1.25 million)
- Annual rate US infection 46,000 (2006)
  - Decrease 81% since 1990
  - Most dramatic decrease children and adolescents due to vaccination
    - Incidence Source: CDC 2008
**Hepatitis B- Pediatric Risk Factors**

- HBsAg positive mother
  - Especially if HBeAg positive
  - Includes IV drug users
  - Perinatal vertical acquisition- largest group of new pediatric infections
  - Transmission from mother to infant may reach 90%
  - 30-60 % will remain carriers from birth until at least 30 years of age
- IV acquisition: drugs, blood products
- Institutionalized care

**Hepatitis B new cases: Adults**

- primarily high risk groups
  - IV drug use, homosexual men
  - Communities w/ large # immigrants from endemic areas
Hepatitis B new cases: Children

- International adoptees
  - 2-5% infection rate
  - Varies by geographic origin & other factors
  - CCHMC: 4% of 1282 adoptees HBV+ (1999-2006)
  - 1.1% infected, 2.9% recovered
  - Family members of adoptee should be vaccinated (pre-adoption)
- Children of immigrants- endemic areas*
  - Immigrants themselves
  - Vertical transmission
  - Horizontal transmission: household or enclave
  - CDC web site provides high and intermediate prevalence areas

Hepatitis B: Serology

- HBsAg
  - Almost all acquire
  - Increase coincident with symptom onset and increased LFT’s
    - 45 days post infection
  - May decrease prior to symptom resolution
  - Persistence = chronic carrier
- HBeAg
  - Marker for infectivity
  - Low molecular weight soluble protein assoc. w/core

Hepatitis B: Serology

- Anti-HBe
  - IgM then IgG
  - Increases shortly after symptom onset 1-4 weeks after appearance HBsAg
  - May persist many years
- Anti-HBe
  - Indicates reduced infectivity
Hepatitis B: Serology

- Anti-HBs
  - Immunity to infection
  - Acquired after effective vaccination
- HBV DNA
  - Measure of viral replication
  - Found in viral core
  - Selection of candidates for and follow response to antiviral therapy

Acute hepatitis B infection

- Incubation phase
- “Symptomatic” phase
- Convalescent phase

- ALT
- Anti-HBs
- Anti-HBc (IgM)
- Anti-HBe
- HBsAg
- HBcAg
- HBV DNA
- Jaundice

Hepatitis B: Clinical Features

- Higher % with clinical symptoms
  - Anorexia, malaise, nausea, vomiting, abdominal pain
- Higher % fulminant hepatitis
- Chronic Hepatitis
  - Adults: 6-10%
  - Children age 1-5: 25-50%
  - Perinatal acquisition: 90%
    - Large inoculum blood during birth or maternal secretions after birth
    - Immune tolerance to virus
    - Low rate spontaneous HBeAg seroconversion
    - Immunocompromised increased risk chronic disease
      - HIV, hemodialysis
Hepatitis B: Clinical Features

- Children characteristically have
  - Normal or minimal elevations of transaminases (<100 IU/L)
  - High levels of viral replication
  - Asymptomatic until cirrhosis
- Consequences of chronic active hepatitis
  - Inflammation
  - Necrosis
  - Cirrhosis
  - Hepatocellular carcinoma
    - Increased risk 200-500 vs. unaffected
    - More than 90 childhood cases (mean age 11 year)
    - Taiwan: 80% children HCC anti-HBe +
    - Chronic HBsAg positive- 25% lifetime risk HCC

Hepatitis B Prevention-HBV Vaccine

- Antibody response to HBsAg protein
- Plasma derived or recombinant
- 90-95% efficacy
  - Re-immunize non-responders
- Immune memory for 15 years
  - [Protective Ab] may be less in those vaccinated at birth vs. ≥ 6 months*
    - Antibody titers may continue to wane 13-15 years post vaccine
  - Vaccination at birth required to prevent vertical infection
    - Advisory Committee on Immunization Practices: MMWR December 23,2005 54
    - *Ped Infectious Dis J 10/08
Hepatitis B Vaccine

- Indications
  - Neonate HBsAg positive mother
  - Intimate contact acute HBV infection
  - Intimate/ household contact chronic HBV infection
  - HBsAg positive needlestick injury in HBsAg negative individual

Hepatitis B Vaccine

- Routine immunization of infants (1992)
- AAP universal vaccination by age 11 or 12 (1995)
- All injection drug users
- Patients with chronic liver disease
- Sexually active individual w > 1 partner/ 6 months or a history of STD
- Sexually active homosexual men
- Health care personnel
- Residents & staff of institutions for developmentally disabled patients

Hepatitis B Vaccine

- Hemodialysis patient
- Patient w/ bleeding disorder requiring clotting factor concentrates
- Traveler to HBV endemic area
- Inmates- juvenile detention or correctional facilities
- Booster for at risk population
  - Concentration < 10mIU/ml
  - Hemodialysis, immunocompromised, etc.
- Booster may ultimately be required for children vaccinated at birth
  - 5-20% protective Ab titer 13-15 years post vaccine vs. 60% vaccine at 6 months age
  - However vaccination at birth essential to prevent vertical transmission
Hepatitis B: Prevention

- **HBIG**
  - Used in conjunction with vaccine
  - Administer at birth to infant at risk in addition to vaccine
    - Synergistic 90% vs. 75-80% alone
  - Indications
    - Neonate HBsAg positive mother
    - Intimate contact acute HBV infection
    - Intimate/household contact chronic HBV infection
    - HBsAg positive needlestick injury in HBsAg negative individual

Hepatitis B Therapy- Alpha interferon

- Recombinant bacterial product
  - 5-10 MU s.q. 3x/week per sq. meter
  - 6 months or longer up to 10 MU/dose
- Predictors of a response
  - Increased ALT
  - Low HBV DNA
  - Horizontal acquisition
  - Short duration of infection
  - Younger age
  - Anti-HIV negative
  - Active liver histology
  - Genotype (B or A > C or D)

Alpha interferon goals of antiviral therapy

- Remove stimulus for ongoing inflammation by elimination of the virus
- Interrupt progression to fibrosis/cirrhosis
- Decrease risk of hepatocellular carcinoma
  - **Hepatitis B**: 200-500x risk
    - Mean age in childhood 11 years
  - **Hepatitis C**
    - 60-80% of hepatocellular carcinoma cases positive for HCV in Japan
Alpha interferon

- Naturally occurring protein produced by B-lymphocytes & monocytes
- Synthetic form produced by recombinant DNA techniques using E. coli
- Mediates its effects by inducing protein synthesis within the recipient’s cells
- Proteins act on various stages of viral replication cycle

Alpha interferon- actions

- **Interference in translation of the viral genome into virus specified proteins**
- Immunoregulatory actions
  - Alteration MHC expression
  - Alteration macrophage activation
  - Alteration cytokine induction
  - Alteration regulation of T-cell activity

Alpha interferon therapy- HBV

- Flare of ALT prior to response
- Side effects
  - Flu like symptoms
  - Anti-thyroid antibodies
  - Psychiatric disturbances
- Determinants of a response
  - Decreased ALT
  - Improvement in liver histology
  - Loss of HBsAg
  - Formation of anti-HBs
- Side effects
  - Flu like symptoms
  - Anti-thyroid antibodies
  - Psychiatric disturbances
- Determinants of a response
  - Decreased ALT
  - Improvement in liver histology
  - Loss of HBsAg
  - Formation of anti-HBs
Recommendations for Alpha interferon Rx-HBV

- Children ≥ age 2
- Consistently abnormal ALT
- 6 MU/m² 3x/ week x 24 weeks

- Increased ALT during therapy not indication for discontinuation if no signs of decompensation present
- Pegylated interferon α- 2a approved for HBV in adults
  - no pediatric data yet
  - Jonas M. JPGN 2006

Alternate therapies- HBV

- Ribavirin & other alternate therapies not shown to be efficacious currently
- Nucleoside analogues with activity against HBV- now approved
  - Lamivudine
  - Inhibits HBV DNA polymerase activity therefore inhibits viral replication
  - associated w/ emergence of resistant HBV

Alternate therapies- HBV

- Nucleoside analogues with activity against HBV
  - Entecavir (Baraclude)
    - in research phase for children
    - Act directly on viral replication rather than on patients immune system (interferon)
    - Oral administration, few adverse effects
    - Not associated with development of HBV mutations
      - Role in Lamivudine non-responders
Alternate therapies- HBV

- **Nucleoside analogues** with activity against HBV
  - **Adefovir** (Hepsera)
    - Oral reverse transcriptase inhibitor & inhibits DNA polymerase
    - in research phase for pediatrics
    - Delayed/ infrequent occurrence resistant strains vs. Lamivudine
      - Consider if long term Rx anticipated
    - Nephrotoxicity

Liver transplantation -HBV

- Patients with cirrhosis
- High recurrence in allograft if untreated
  - Higher recurrence if active viral replication pre-OLT
- Re-infection may result in graft loss
- Prophylaxis treatment at time of transplant
  - Pre- OLT antiviral
  - Post OLT: combination of nucleoside analogues (Lamivudine) & HBIG
  - 5-10 %+ recurrence risk 5 year
    - 75% w/o prophylaxis
  - Expensive repetitive infusions required
    - Research: alternative regimens low dose HBIG or withdrawal over time

Hepatitis Delta

- Defective RNA virus
- **Needs machinery of HBV to replicate**
- Components
  - RNA molecule and inner protein core
  - HDAg (core antigen)
  - Encapsulated by HBsAg
- Increased prevalence in Mediterranean basin
  - Intrafamilial/intimate contact
- Developed countries
  - Percutaneous transmission, immigration from endemic area
Hepatitis Delta

- Coinfection
  - Simultaneous infection
  - Perinatal coinfection rare
- Superinfection
  - Chronic HBV carrier
- Diagnosis
  - IgM Anti-HDV (persists w/ chronic infection)
  - Antigen staining on liver biopsy
  - HDV RNA
- Incubation 3-13 weeks

Hepatitis Delta- Manifestations

- Coinfection: acute hepatitis
- Superinfection: chronic or fulminant hepatitis
- HDV infection leads to direct liver damage
- Cirrhosis
  - More rapid progression than HBV
- Hepatocellular carcinoma
- Mortality rate 30%
Acute HDV-HBV coinfection that resolves

HDV infection

Hepatitis Delta- Prevention and Therapy

• Prevention: HBV prevention
• Therapy: Alpha Interferon
  – Longer duration therapy
  – ? Permanent Rx
  – No clear prognostic indicators
  – Requires clearance of Hepatitis B
  – May have better prognosis after liver transplant
Hepatitis C

- Single stranded RNA virus
- Causes approximately 85% of chronic non-A, non-B hepatitis
  - 90% of post transfusion hepatitis
- Primarily parenteral exposure
- Incubation varies widely
  - 2 weeks- 6 months (average 6-7 weeks)
  - Exposure to viremia 1-2 weeks
  - 90% Antibody positive at 3 months

Hepatitis C virus

- Antibody testing available 1989/1990
- Particle identified in 1994 by immuno-electron microscopic study in Japan
- RNA > 9400 nucleotides
- Single stranded
- Encode single polypeptide
  - Putative core, E1,E2/NS1,NS2,NS3,NS4,NS5 protein regions

Hepatitis C virus

- Classified into family Hepacivirus
- 55-65 nm spherical particles with fine surface like projections 6nm in length
- 3-35nm inner core
- Multiple genotypes (9) & subtypes (90)
- Replicates preferentially in hepatocytes with multiple mechanisms of injury
  - Results in persistent infection
Hepatitis C- Prevalence

- 1.6% general U.S. population (4.1 million)
  - 75-80% HCV RNA + (3.2 million in US-1.3%)
- 19,000 additional cases estimated each year (2006)
- 0.2% children < 12 years in U.S.
- 0.4% adolescents 12-19 years in U.S.
- Highest prevalence age 40-59 years
  - Majority infected 1970s-1980s @ time highest incidence
- Worldwide prevalence 3% (at least 180 million chronic)
  - Mediterranean, Brazil, Middle East, Indian subcontinent

![Figure 4.1. Reported and adjusted* number of acute hepatitis C cases — United States, 1992–2009](image)

* Adjusted for underreporting.
Source: National Notifiable Diseases Surveillance System (NNDSS)

Hepatitis C- Prevalence

- 60-90% people with large or repeated direct exposure to blood or blood products
- 15-50% homeless, incarcerated
- 10-20% hemodialysis patients
- 1-10% high risk sexual behavior group
- 1% health care providers
### Risk Factors for HCV in the U.S.

- **54% IV drug use**
  - Prevalence 90% IV drug users and treated hemophiliacs
  - 70% infected w/in 1st year
  - Decreased annual incidence in US due to decrease in this group
    - Most already infected
    - Decreased # new injection users, needle exchange
  - Cocaine snorting also risk factor
- **Sexual exposure**
  - 36% exposure to multiple partners during incubation period
  - 10% sexual contact w/known HCV infected individual
  - Transmission documented in men who have sex w/men
- **16% surgery**
  - Transfusion important factor in the past
- **1.5% occupational** (veteran esp. Vietnam, healthcare, 1st responder)
- **32% no known risk factor**
- Misc: dialysis patients, needle stick injury, household contact

### Pediatric Risk Factors for HCV in the U.S.

#### Perinatal-
- **Leading U.S. pediatric cause (7500/yr.)**
  - 0.75% pregnant women positive for Chronic HCV
  - Cause at least 60% of current infections in children
  - Transmission risk correlates w/ maternal viral load at delivery
    - 5-7% if HCV RNA positive at delivery
  - HIV infection important risk factor
    - 20%
  - Avoid fetal scalp monitoring & prolonged labor after rupture of membranes > 6 hours if possible
  - Elective C-section not protective
  - Ribavirin & interferon contraindicated during pregnancy

### Hepatitis C- Pediatric Risk Factors

- **Perinatal continued**
  - May develop or be detectable some months after birth, esp. if anti-HIV positive
  - More likely to be chronic
- **Chronic infection in recipients of blood products**
  - Hemophilia
  - Survivors childhood malignancy, leukemia
  - Cardiac surgery, etc.
  - Gammagard between 4/93 and 2/94
Hepatitis C Detection

- **PCR-**
  - within 1-2 weeks of exposure, weeks before LFT changes or positive anti HCV
  - May be intermittently negative in an infected pt
- **ELISA-IgG**
  - Screening: 98% sensitive, 97% specific
  - False negatives early in course of infection
  - 3rd generation tests positive w/in 6-8 weeks post acquisition
- **RIBA-IgG**
  - Confirmatory
- No IgM tests available at this time

Acute HCV infection

<table>
<thead>
<tr>
<th>Weeks postexposure</th>
<th>ALT</th>
<th>HCV-RNA</th>
<th>Anti-HCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>36</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HCV- Perinatal

- Testing for infants born to HCV positive mothers
  - HCV RNA at 2 & 6 months
    - 2 tests required for negative result
    - FU anti-HCV required
  - Anti- HCV after 15-18 months of age
- Breast feeding controversial, generally thought to be safe
Hepatitis C - disease manifestations

- Often mild
- May be more severe or fulminant than hepatitis A or B
- Associated with aplastic anemia or agranulocytosis
- 10-25% jaundice
- **80-85% develop chronic hepatitis**
- Mortality rate 1-2%
  - 2-5% mortality associated with cirrhosis annually
  - chronic HCV 8-10,000 deaths/year in US (CDC)
  - HCV mortality: triple next 10 yrs.
    - Peak expected on 2030 (HIV death decrease by 2/3 same period)
    - Leading cause liver transplantation
- 10-25% jaundice
- 80-85% develop chronic hepatitis
- Mortality rate 1-2%
  - 2-5% mortality associated with cirrhosis annually
  - chronic HCV 8-10,000 deaths/year in US (CDC)
  - HCV mortality: triple next 10 yrs.
    - Peak expected on 2030 (HIV death decrease by 2/3 same period)
    - Leading cause liver transplantation
- 0.1-0.2% mortality associated with cirrhosis annually
- chronic HCV 8-10,000 deaths/year in US (CDC)
- HCV mortality: triple next 10 yrs.
  - Peak expected on 2030 (HIV death decrease by 2/3 same period)
  - Leading cause liver transplantation
- 0.1-0.2% mortality associated with cirrhosis annually

Hepatitis C-Chronic Infection

- Fluctuating aminotransferases typical
  - 30% normal ALT, 40% ALT< 2x ULN
- RNA and antibody levels may also fluctuate
- **50% develop cirrhosis**
  - 25-40% of total infected
- Associated with hepatocellular carcinoma
  - In U.S. 1/3 cases HCC
  - In Japan 60-80% of hepatocellular carcinomas are anti-HCV positive
  - Increased risk w/ more severe disease, HBV, ETOH
  - 3-4% risk/ year HCC in patients w/ HCV & cirrhosis
- Often asymptomatic

**Hepatitis C: Chronic infection**

<table>
<thead>
<tr>
<th>Time postexposure</th>
<th>Months</th>
<th>Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Anti-HCV</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>

Jaundice, symptoms, HCV/RNA (PCR)
**Extrahepatic Manifestations**

**HCV**

- Symptoms/ syndromes- rheumatologic in origin
  - Keratoconjunctivitis sicca
  - Lichen planus
  - Membranoproliferative glomerulonephritis
    - (children and adults)
  - Lymphoma (adults)
  - Essential mixed cryoglobulinemia (adults)
  - Related to porphyria cutanea tarda
  - Psychological symptoms/ depression/ impaired QOL

---

**Hepatitis C**

- No prevention
- No vaccine (yet)
  - Genetic heterogeneity HCV
  - High mutation rate
- Risk following a needle stick injury estimated at 2%
- High recurrence in allograft following liver transplant
  - 5 year patient survival 72%
  - 5 year graft survival 55%

---

**Natural History HCV Infection**

- Approximately 80% of infected adults will become chronic carriers
- Frequency of ALT normalization in untreated adult controls 30-40%
  - Viral replication may be ongoing
- Frequency of ALT normalization in untreated children 3-10% with 1-6 years followup
- Highest reported pediatric rate spontaneous clearance HCV RNA 25% @ age 5
  - Decreased likelihood if RNA positive 1st year of life
- Rx with pegylated interferon & ribavirin patient with chronic HCV (FDA approved)
  - Sustained virological response (SVR) 20-50%
- IFN ± Ribavirin in patients w/ acute HCV
  - SVR to may be > 80%
Alpha interferon therapy for Chronic HCV

- Mechanism of viral injury – combination of effects cytopathic & immune mediated
- Interferon actions
  - Prevention of viral binding of HCV to hepatocyte plasma membrane
  - Inhibition of HCV entry into cell
  - Suppression of viral cell proliferation
  - Enhancement of macrophage phagocytic activity
  - Augmentation of cytotoxic activities of T lymphocytes

Alpha interferon-HCV
Predictors of a response
- Low HCV RNA levels
- Minimal elevation of ALT levels
- Mild inflammation on liver biopsy
- Absence of cirrhosis
- Non-immunocompromised (including HIV)
- Lack of iron overload - Hemophilia, thalassemia
- Shorter duration of infection
- Younger age
  - 5-12y better than ≥ 12 years
  - Horizontal acquisition
- Genotype - varies by country (non-1)
- Early response to therapy < 12 weeks

Determinants of response
Alpha interferon HCV
- Persistent loss of HCV RNA
- Persistent normalization of AST, ALT
- Anti-HCV will persist
- Improvement on liver biopsy
  - No stainable antigens
Newer therapies HCV

• **Ribavirin**
  - Non interferon inducing guanosine nucleotide analogue
  - p.o. administration
  - Combination therapy only
    - Doubled sustained virological response to 40%
  - Mechanism action not known
    - May have direct effect vs. viral replication & viral RNA synthesis
  - Hemolysis is potential complication
  - Other complications: teratogenicity, cough, dyspnea, rash, pruritus, insomnia, anorexia
  - Contraindication thalassemia patients

Newer therapies HCV- **Pegylated interferon**

• Prolonged half life
  - 40-77 hours elimination vs. 8 hours standard interferon
• Constant blood levels in the systemic circulation
  - Greater efficacy due to slower elimination
• Once weekly administration
• Products
  - Pegylated interferon alfa 2b (Peg-Interferon)
    • dose based on kg
  - Pegylated interferon alfa 2a (Pegasys)
    • fixed dose
• Can be part of combination therapy
• 2008 FDA approval for children: Peg -Interferon & Ribavirin combination therapy

Cleveland Clinic Foundation- Pediatric experience with Alpha interferon & Ribavirin

• Younger patients
• Longer duration of therapy
• High dosage
• Use of pegylated interferon
• Co-administration Ribavirin- HCV
  - initial non-responders
  - initial Rx in patients without hemolytic disease
Response to α-IFN on pediatric patients with chronic HCV

- UK HCV National Registry 1998-2005
- 246 patients age ≤ 16 years
  - 57% significant underlying medical condition
- 110 (45%) antiviral Rx
  - 47% response rate
    - 38% IFN mono Rx group
    - 51% IFN & Ribavirin combination group
    - 18% response rate in genotype 1 group
    - 79% response rate in non-genotype 1 group
  - Harris HE, Miele-Vergani et al. JPN 2007

Pegylated IFN & Ribavirin combination therapy children with chronic HCV

- 62 children
- open label uncontrolled pilot study- Germany
- Mean age at Rx = 10.6 years (r: 2-17 yr.)
- None w/ HBV or HIV coinfection
- 76% genotype 1, 21% genotype 2 or 3, 3% genotype 4
- PEG α-IFN 2b 1.5μg/kg/week sq + ribavirin 15 mg/kg/day
  bid p.o. x 48 weeks
- 59% (39/61) sustained viral response (SVR) @ 6 months
- SVR
  - 48% genotype 1
  - 100% genotype 2 or 3
  - 50% genotype 4
  - Wirth et al. Hepatology 2005

Recent FDA approvals HCV May 2011

- For adult patients ≥ age 18
- Boceprevir (Victrelis) and Telaprevir (Incivek)
- HCV genotype 1 w/ compensated liver disease
- Direct acting antiviral drugs- protease inhibitors
- Use in conjunction with Pegylated Interferon and Ribavirin only
- In treatment naïve adult patients may improve SVR to 80%
Hepatitis E

- Enteric & Epidemic form of NonA NonB hepatitis
- RNA virus, single stranded
  - 4 genotypes
- Unassigned genus “Hepatitis E like viruses”
- Detected by research techniques
  - Anti HEV IgM & HEV RNA by PCR
  - Commercial assays not yet approved by U.S. FDA
- High Prevalence
  - Indian Subcontinent
  - Middle East
  - Southeast & Central Asia
  - North, West & South Africa
  - Mexico

Hepatitis E prevalence - CDC

Geographic Distribution of Hepatitis E
Outbreaks or Confirmed Infection in > 20% of NonA NonB hepatitis

Hepatitis E

- Older patients than hepatitis A
  - Peak 15-34 years
- Incubation 2-9 weeks (mean 45 days)
- Abrupt onset of symptoms
- Fecal oral transmission
- Fecally contaminated drinking water
- Zoonotic infection - raw meat
  - Venison, boar, pork
- Mortality 1-2%
Hepatitis E

- High fatality rate pregnant women
  - 20% (third trimester)
  - Premature delivery
- Cause of acute hepatic failure
  - > 50% of cases in India/Nepal
- No chronic form
- Prevention
  - Pooled immunoglobulin from endemic areas
  - Vaccine(s) in initial development

Hepatitis E in the U.S.- Much more common than previously thought?

- CDC tested 82 samples 2002-2009
  - 11% (9/82) positive by reverse transcriptase pcr
    - 6 domestic, 3 travel
- 21% US residents positive for anti-HEV
  - NHANES survey 1988-1994
- Pathogenicity of genotype 3 HEV in US
  - not well understood
  - 21% Americans infected
  - No major outbreaks reported
- Suggest majority infections asymptomatic/ mild Sx
- Chronic & clinically severe infections reported in organ transplant recipients and other individuals
- Developed countries infection assoc. w/ swine consumption (wild or domestic), shellfish

Hepatitis F

- Enteric agent
- 1994 transmitted experimentally to primates
- Double stranded DNA
Hepatitis G

- RNA virus (Flaviviridae)
  - Like HCV, 9300 nucleotides
- Community acquired
- World wide distribution
- Acute and chronic forms
  - may result in fulminant hepatitis & cirrhosis
- Blood borne
  - Present within accepted U.S. Donor blood pool (1.5-1.7%)
  - Infected donor not identified by abnormal transaminases
  - 17% prevalence HGV infection after transfusion infected blood
  - Poly-transfusion associated w/ increased risk of acquisition
  - Long term persistence of viremia after infection
  - May not be associated with abnormal transaminases
- Antibody detection does not exclude viremia
- Absence of antibody and RNA does not exclude infection

Other Causes Hepatitis

- Viral
  - EBV, CMV
- Medication/Toxins
  - ETOH
  - Anticonvulsants
  - Acetaminophen, Isoniazid, PTU, Sulfonamides, etc.
  - Amanita Phalloides
- Metabolic
  - Wilson’s Disease
  - Alpha-1-antitrypsin deficiency
  - Autoimmune disease
  - IBD

ARS Question 1

- The most common form of viral hepatitis in children in the United States is?
  - A. Hepatitis A
  - B. Hepatitis B
  - C. Hepatitis C
  - D. Hepatitis D
  - E. Hepatitis E
ARS Question 1

- Answer: A
- The most common form of viral hepatitis in the United States is Hepatitis A

ARS Question 2

- All of the following are true of hepatitis B except:
- A. It is a DNA virus with a mean incubation period of 120 days
- B. A smaller viral inoculum is required for infection than HIV infection
- C. Parenteral and perinatal transmission are important routes of transmission
- D. HBeAg positivity is indicative of a chronic carrier state
- E. Chronic infection is associated with increased risk of hepatocellular carcinoma

ARS Question 2

- Answer D
- HBsAg positivity is indicative of a chronic carrier state
ARS Question 3

- Which of the following is true of Hepatitis C infection?
  - A. Patients may be asymptomatic
  - B. There is no chronic carrier state
  - C. Detection may be delayed because of a delay in antibody formation
  - D. Transmission is primarily by fecal oral spread

Option(s):
- E. A & C
- F. B & D

Answer:
E. A & C

A. Patients may be asymptomatic
C. Detection may be delayed because of a delay in antibody formation