Common Causes
Acute and Chronic Hepatitis

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Nov 2011
Acute Hepatitis
Hepatitis A

- Hepatovirus from Picornavirus family.
- 27-32 nm, linear, (+) sense, simple stranded RNA.
- Reservoir: human only
- Acquisition: fecal-oral; concentrated in oysters.
  Contaminated water or food, men having sex with men, blood during short viremic phase.
- Non-cytopatic; immune mediated injury by lymphocytes
Hepatitis A
Sero-Prevalence

- **Poor sanitation countries:**
  - near 100 % by age 5.

- **Good sanitation countries (USA):**
  - 10 % by age 14;
  - 37 % in adults.
Acute Hepatitis A
Clinical Features

- **Incubation**: 2-4 (up to 6) weeks

- **Clinical Presentation**:
  - Children < 2 year: 80% anicteric & asymptomatic
  - Children > 2 y and adults: 80% icteric & symptomatic

- **Symptoms**:
  - Fatigue (90%),
  - jaundice (80%),
  - low fever (65%),
  - abdominal pain and
  - anorexia (85%),
  - nausea (75%),
  - headache,
  - myalgias.

- **Duration**: usually < 8 weeks
Acute Hepatitis A
Atypical Manifestations

- **Relapsing hepatitis**: less than 10%; 2 or more bouts of elevated enzymes.
- **Cholestatic hepatitis**: Severe and prolonged jaundice > 10 weeks. Is rare.
- **Fulminant Hepatitis**: very rare but lethal in 50%.
- **Extrahepatic Disease**:
  - renal failure, - red blood cell aplasia,
  - hemolysis,   - pancreatitis,
  - neurologic disease.
- **Mortality**: Not increased by pregnancy.
  - a) younger than 49 = 0.3%;
  - b) older than 49 = 1.8%.
Acute Hepatitis A

HEPATITIS A

Symptoms

ALT

Billirubin

Fecal HAV

IgG Anti-HAV

IgM Anti-HAV

Months after Exposure

1  2  3  4  5  6  7  8  9  10  11  12
Hepatitis A Vaccination Recommendation

- Children in areas with rate >20/100000
- High risk:
  - traveler to endemic area,
  - men having sex with men,
  - illegal drug users,
  - person with clotting factor disorder,
  - researcher working with HAV.
- Chronic liver disease: HBV, HCV
- During community outbreaks.
- **Immunogenicity:**
  - > 70% within 2-4 weeks after 1st dose, and
  - 94-99% after second dose.
Hepatitis A

Post-Exposure Management

• Post-exposure prophylaxis can be done:
  – with Intramuscular “Immune Serum Globulin” (ISG) within 14 days from exposure at 0.06 mL/kg (69-89% effective and lasting 12-20 weeks) or
  – with Inactivated Vaccine given also within 14 days post-exposure.
  – Response to vaccine is less robust and ISG is preferred:
    » before age 1 (due to circulating maternal antibodies), and
    » after age 40.

• Inactivated Vaccine is the preferred approach from age 1 to 40.

• Immune serum globulin is contraindicated in IgA deficiency or hypersensitivity to ISG.

• Active immunization with Hepatitis A vaccine can be given at the same time of ISG.
Hepatitis E

- 27-30 nm non-enveloped, single-stranded, positive-sense RNA Hepevirus.
- There are 4 (maybe 6) genotypes.
  - 1: India, China, Pakistan;
  - 2: Mexico;
  - 3: USA, France, Japan.
  - 4: China, Japan
- There is an avian and a rat HEV variant.
- Acquisition:
  - Waterborne, fecal-oral, by organ meat ingestion, or by contact with animals. In USA swine is a common source.
  - Rare person-person (1.5% intra-familial).
  - Increased risk in homosexual men.
Hepatitis E

- **Types:**
  - **Sporadic:** traveler to endemic areas, pet owners, organ meat eaters, male homosexuals, military service (Midwest USA).
  - **Epidemic:** after heavy rain and flooding in areas with poor sanitation (India, China, Latin America, Africa)
  - **Endemic:** In areas where asymptomatic infection occurs at early age, like in Egypt
  - **Chronic hepatitis:** in immunosuppressed patients, with progressive liver damage and cirrhosis (worse with Tacrolimus than with CSA).

- **Reservoir:** human, pig, sheep, cattle, rat,…

- **Prevention:** there is an experimental recombinant vaccine.
Hepatitis E

- **Incubation**: 2-10 weeks.
- **Prodrome**: 2 weeks of malaise, mild chills & fever, transitory macular rash.
- **Symptoms & Signs**: jaundice, nausea, vomiting, anorexia, aversion to food & smoking, abdominal pain, clay-color stool. Hepatomegaly in 65-80%; symptoms usually for 4 weeks.
- **Mortality**:
  - 0.1-0.6%; 15-25% during pregnancy in the epidemic form in India.
  - Mortality in pregnancy is low in Egypt and other endemic areas.
- **Diagnosis**:
  - Anti HEV-IgM last only 3 months, and is not always present in acute infection;
  - Anti-HEV IgG lasts for years;
  - HEV can be found by PCR in stool, serum, and bile.
- **Treatment**:
  - Support.
  - Peg-IFN and Ribavirin have effect in chronic HEV.
Acute Hepatitis E

Sequence of Events

- Fecal HEV
- ↑ ALT
- Symptoms
- HEV RNA
- IgM Anti-HEV
- IgG Anti-HEV

Days
Hepatitis B

- 42 nm, partially double-stranded circular DNA virus.
- 350 million carriers world-wide; causes 250,000 deaths a year.
- 1.25 million carriers in USA (0.5%); > 8% in Alaskan Eskimos.
- New infections: 260K/y in 1980’s; now 73,000/y
- **Transmission**: In most of USA predominantly sexual and percutaneous during adult age. In Alaska predominantly perinatal.
Hepatitis B Transmission

- **Sexual**: heterosexual in 41% of acute cases. Men having sex with men have 10% risk.
- **Percutaneous** (mostly illicit drug use): 15% of acute HBV cases
- **Perinatal**: 10% of acute cases (mother-child)
- **Transfusion**: 1/63000 transfusions.
- **Other**: organ transplant, tattoo, piercing, acupuncture, …
Hepatitis B

High-Risk Groups

- Born in high prevalence area
- Active homosexual men
- Promiscuous heterosexuals
- Healthcare & Public Safety workers
- Attendant/family of institutionalized mentally handicapped
- Intravenous drug abuser
- Person requiring frequent transfusions
- Inmate in long-term correctional facility
- Hemodialysis patient
- Traveler > 6 months to endemic area
- Sexual partner of HBsAg(+) person
Hepatitis B Vaccination

- All children and adolescents
- If not previously vaccinated: All high-risk groups
- Post-Vaccination testing:
  - Healthcare & Public-Safety workers
  - Infants from HBsAg(+) mother
  - Hemodialysis patients
  - Sexual partner of HBsAg(+) persons
Acute Hepatitis B

- **Incubation**: 1-4 months
- **Prodrome**: arthralgia, arthritis, skin rash
- **Symptoms & Signs**:  
  - malaise, anorexia, jaundice, nausea, fatigue, low-grade fever, myalgia, change in taste and smell.  
  - tender hepatomegaly in most patients; splenomegaly in 5-15%.  
- **Infrequently**: confusion, edema, coagulopathy, coma (Fulminant Failure in 0.5%)
Acute Hepatitis B

- **Diagnosis**: anti-HBc IgM antibody; frequently HBsAg(+) in early phase and anti-HBs(+) in late phase.

- **Evolution to Chronicity**:
  - a) Infants: 90%,
  - b) Children 1-5: 25-50%,
  - c) Adults & older children: 5%

- **Treatment**: Supportive; Anti-virals in “protracted hepatitis”, or failure to regenerate/sub-massive necrosis.
Acute Hepatitis B

- **Post-Exposure Prophylaxis:**
  Hyperimmune globulin HB + Immediate vaccination.

- **Neonate from HBsAg(+) mother:**
  Hyperimmune globulin HB 0.5 ml IM within 12 h from birth + Immediate vaccination @ 0, 1, 2, & 12 months
Acute Hepatitis B

ACUTE HBV INFECTION

Sequence of Events

<table>
<thead>
<tr>
<th></th>
<th>Jaundice</th>
<th>Symptoms</th>
<th>↑ ALT</th>
<th>HBeAg</th>
<th>Anti-HBe</th>
</tr>
</thead>
</table>

Titer

- HBsAg
- Anti-HBc
- Anti-HBc (IgM)
- Anti-HBs

Weeks after Exposure

- 4
- 8
- 12
- 16
- 20
- 24
- 28
- 32
- 36
- 40
- 52
## Acute Hepatitis D

- **Defective RNA virus** - needs HBV
- **Coinfection with HBV:** severe hepatitis
- **Superinfection of HBV:** frequent fulminant or chronic HDV

- **Parenteral, sexual, perinatal**
- **Diagnosis:** Transitory HDAg(+) or IgM anti-HD(+) \*strong anti-HD in superinfection
- **HBV vaccine is protective**
Hepatitis C

- 50 nm enveloped, positive-sense, single-stranded RNA hepacivirus. Six genotypes and > 100 subtypes.
- 170 million infected worldwide; 4-7 million in USA (1.8%); 38,000 new infections/year.

Risk of Transmission:
- a) Needle stick: 1.8%
- b) Sexual intercourse: 1/95 patient-year (2.2%),
- c) Perinatal:
  » HIV(-) mother: 5%;
  » HIV(+): 14%
<table>
<thead>
<tr>
<th>GROUP</th>
<th>%</th>
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</thead>
<tbody>
<tr>
<td>Hemophilia &lt;’87</td>
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<td>IVDA</td>
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<td>Hemodialysis</td>
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<tr>
<td>Transfusion &lt; ’90</td>
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<tr>
<td>Person w STD</td>
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</table>

<table>
<thead>
<tr>
<th>GROUP</th>
<th>%</th>
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</thead>
<tbody>
<tr>
<td>Infant of RNA(+) mother</td>
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<tr>
<td>Homosexual men</td>
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<tr>
<td>Monogamous partner</td>
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<tr>
<td>General population</td>
<td>1.8</td>
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<tr>
<td>Volunteer blood donor</td>
<td>0.16</td>
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</table>
Risk of HCV in IVDU (% infected)

- Year 1: 78%
- Year 5: 83%
- Year 10: 94%
<table>
<thead>
<tr>
<th>Country</th>
<th>General (%)</th>
<th>HD (%)</th>
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<tbody>
<tr>
<td>Egypt</td>
<td>18.1%</td>
<td>80%</td>
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<tr>
<td>Moldavia</td>
<td>4.9%</td>
<td>75%</td>
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<tr>
<td>Bulgaria</td>
<td>1.1%</td>
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<td>Saudi Arabia</td>
<td>1.8%</td>
<td>57%</td>
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<td>Turkey</td>
<td>1.5%</td>
<td>31%</td>
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<tr>
<td>Italy</td>
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<tr>
<td>France</td>
<td>1.1%</td>
<td>16%</td>
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<tr>
<td>Belgium</td>
<td>0.9%</td>
<td>9%</td>
</tr>
<tr>
<td><strong>USA</strong></td>
<td><strong>1.8%</strong></td>
<td><strong>9%</strong></td>
</tr>
<tr>
<td>Netherlands</td>
<td>0.1%</td>
<td>3%</td>
</tr>
</tbody>
</table>
Acute HCV

- **Incubation**: 2-26 weeks (usually 7-8)
- **Symptoms**:  
  - occur in < 30%, usually mild & lasts < 1 month.
  - anorexia, arthralgia, myalgia, fatigue;
  - rarely jaundice, fever or skin rash.
  - very rare FHF.
- **DX**:  
  - HCV-RNA (+) days to weeks after acquisition;
  - anti-HCV (+) in 6 weeks.
- **Spontaneous HCV clearance**:  
  - Children < 2 y.o. & young women = 45%;
  - Others = 23%
Acute HCV
Acute HCV Treatment

- If HCV-RNA(+) 3 months after inoculation, spontaneous clearance is rare.

- Best regimen is unknown: starting 3 months after inoculation,
  - IFN 5 MU QD x 4 wks + 3 MU TIW x 20 wks gave 98% clearance; the mildest & shortest effective therapy is unknown.
  - Pegasys 180 mcg/week +/- RBV x 12 weeks

- Patients should be abstinent from alcohol and drugs (anti-HCV is not protective).
Treatment of Acute HCV @ 8, 12, & 20 wks, Pegasys vs Rebetron x 12 wks
Kamal et al Abst # 37 AASLD, 2004

- 68 pts with Acute hepatitis C;
  7 had spontaneous clearance.

- Treatment started at:
  - A) Wk 8 (21),
  - B) Wk 12 (20),
  - C) Wk 20 (20)

- Rebetron vs Pegasys x 12 wks; if HCV-RNA (+) at wk 12, treated 12 more wks.
RESULTS
Abstr # 37

Start Wk 8 PEG
Start Wk 12 PEG
Start Wk 20 PEG

Rpx12 Wks  Rpx24 Wks  SVR

90 100 100
80 90 90
0 10 20 30 40 50 60 70 80 90 100
Starting therapy at week 12 gave best results.

Pegasys monotherapy x 12 weeks, was superior to Rebetron treatment x 12 weeks, in all groups.
Practical Approach to Treat Acute HCV

- Wait for 12 weeks from time of acquisition to see if spontaneous clearance occurs.

- Spontaneous clearance is more likely if patient is:
  - IL28B (rs12979860) CC regardless of symptoms or jaundice, or
  - IL28B CT and jaundiced.

- In absence of spontaneous clearance, treat with Peg-IFN + RBV (may improve outcome) for:
  - 3 months if HCV-RNA (-) at 4 weeks;
  - otherwise treat longer.
Auto-Immune Hepatitis
- Acute Presentation

- 30% present acutely, like viral hepatitis
- Extrahepatic manifestations are common:
  - arthralgia  - skin rash  - chronic diarrhea
  - pleuro-pericarditis  - thyroiditis
  - ulcerative colitis  - glomerulonephritis
  - vitiligo  - neuropathy
- Dx:
  - 1) Autoantibodies (+): ANA, ASMA, Anti-LKM₁, anti-SLA, anti-LP, ANCA, increased gammaglobulins (IgG), AND
  - 2) Compatible Liver Biopsy; frequently has centrilobular zone 3 necrosis with plasmacytic infiltrate and bile duct injury.
Auto-Immune Hepatitis - Acute Presentation

- **Treatment**: Prednisone ± Azathioprine
- **Prognosis**: failure to improve bilirubin, or marker of inflammation within 2 weeks strongly suggests that liver transplantation may be needed.
- **Patients who present with MELD >/= 12 are likely to fail corticosteroid therapy** (Sens = 97%, Specif = 68%)
Chronic Hepatitis
Chronic Hepatitis

- **Dx:** Persistent or Intermittent elevation of liver enzymes for $\geq 6$ months* **PLUS** consistent liver biopsy

*Some disorders are always chronic and do not need to be documented for 6 month: AIH, Wilson’s, Hemochromatosis, $\alpha_1$-antitrypsin, overlap syndrome
Chronic HCV

- Most common chronic viral hepatitis in USA.
- Most are asymptomatic; 6% symptomatic before diagnosis.
- **Symptoms**: fatigue, RUQ discomfort, anorexia, nausea, itching, arthralgia, myalgia.
- **Extrahepatic**:
  - mixed cryoglobulinemia, - purpura,
  - mononeuritis multiplex, - PCT,
  - xerostomy, - low-grade B-cell lymphoma,
  - corneal ulcers, - idiopathic pulmonary fibrosis,
  - lichen planus,
  - membrano-proliferative glomerulonephritis,
Chronic HCV

- **Diagnosis:**
  - Persistent HCV-RNA (+);
  - Most patients are anti-HCV(+).
  - Liver Bx useful to assess severity of disease.

- **False (-) anti-HCV: 0.45% in HIV & hemodialysis.**

- **False (+) are common & antibody remains (+) many years after clearance of infection.**

- **“Cut-off” for “high” vs. “low” viral load: 400,000 IU/mL**
Pattern of ALT Elevation in Chronic HCV

Pattern of ALT Elevation

- Normal ALT: 15
- ALT < 2X-ULN: 31
- ALT 2-3X-ULN: 12
- ALT > 3X-ULN: 42
Degree of Fibrosis in Chronic HCV

Degree of Fibrosis

- None: 16
- Stage 1: 19
- Stage 2: 22
- Bridging: 19
- Cirrhosis: 24
Chronic HCV

HEPATITIS C VIRUS

Chronic Hepatitis

HCV RNA in Serum

Anti-HCV

Second generation

Serum ALT

Normal

Months

Years

0 2 4 6 8 10 12 14 16 2 4 6
Genotype and Viral Load in US Patients

- Genotype 1 HVL: 49.5%
- Genotype 1 LVL: 24.5%
- Genotype 2,3 Low: 14.7%
- Genotype 2,3 Low HVL: 7.3%
- Genotype 4,5,6 Low: 1.3%
- Genotype 4,5,6 High: 2.7%

Outcome of HCV
25-30 year Follow-up

- Resolves @ acute hepatitis
- Chronic / No-cirrhosis
- Compensated Cirrhosis
- Decompensated Cirrhosis
- Death/ Decompensated
- Death/ HCC
Factors Associated With Disease Progression

<table>
<thead>
<tr>
<th>Associated with disease progression(^1)</th>
<th>Not Associated with disease progression(^1)</th>
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</thead>
<tbody>
<tr>
<td>Alcohol consumption</td>
<td>Alanine aminotransferase level</td>
</tr>
<tr>
<td>30 g/day for males</td>
<td>Viral load</td>
</tr>
<tr>
<td>~2 drinks/day</td>
<td>Transmission mode</td>
</tr>
<tr>
<td>20 g/day for females</td>
<td>Genotype</td>
</tr>
<tr>
<td>Disease acquisition at &gt;40 years</td>
<td></td>
</tr>
<tr>
<td>Male gender</td>
<td></td>
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<tr>
<td>Coinfection: HIV or HBV(^2)</td>
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</tr>
<tr>
<td>Immunosuppression(^2)</td>
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</tr>
</tbody>
</table>

## Histological Scoring of Fibrosis

<table>
<thead>
<tr>
<th>Description</th>
<th>Modified HAI (Ishak)</th>
<th>HAI (Knodell)</th>
<th>Batts-Ludwig, Scheuer, or IASL</th>
<th>META VIR</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mild: Portal fibrosis (some p. areas)</td>
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<td>1</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Moderate: Periportal Fibrosis (most p. areas, or occasional portal-portal septa)</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Severe: Bridging fibrosis (few / occasional bridges, any portal-central)</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Severe: Bridging fibrosis (many portal-central bridges)</td>
<td>4</td>
<td>3</td>
<td>3</td>
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</tr>
<tr>
<td>Incomplete cirrhosis</td>
<td>5</td>
<td>4</td>
<td>4</td>
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</tr>
<tr>
<td>Cirrhosis</td>
<td>6</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

Treat META VIR => 2, or Ishak/Batts-Ludwig/Scheuer/Knodell => 3
Treatment of Chronic HCV

- **Genotype 1:** Peg-Interferon weekly + Ribavirin 1000-1200 mg/d + Boceprevir or Telaprevir x 24 to 48 weeks (response guided)
  - SVR: 66-75%

- **Genotypes 2 and 3:** Peg-Interferon weekly + RBV 800 mg/d x 24 weeks
  - SVR: 78-80%

- **Genotypes 4, 5, or 6:** Peg-Interferon weekly + Ribavirin 1000-1200 mg/d x 48 weeks
  - SVR: 55-60%
Predicting SVR by HCV-RNA fall Peg-IFN alpha 2a + RBV

PEGASYS + Ribavirin
Sustained Virologic Response

Chronic Hepatitis B

- In low prevalence areas (USA) 30-50% history of acute hepatitis (rare in high prevalence)

- **Symptoms:**
  - frequently asymptomatic;
  - sometimes RUQ or epigastric pain or acute-like hepatitis episodes.

- **Extrahepatic:**
  - serum-sickness, - polyarteritis nodosa,
  - mixed cryoglobulinemia, - IgA nephropathy,
  - membranous- or membranoproliferative-
    glomerulonephritis, - papular acrodermatitis.
Chronic HBV

Sequence of Events

- **HBV DNA in Liver**: Nonintegrated (free) vs. Integrated
- **HBV DNA in Serum**
- **HBeAg in Serum**: Anti-HBe

![Graph showing the timeline of HBV viral markers over weeks and years](image)

**Titer**

- HBsAg
- Anti-HBc
- IgM Anti-HBc
- Heterotypic Anti-HBs

**Time after Exposure**

- Weeks
- Years
HBeAg-positive vs HBeAg-negative
Chronic Hepatitis B

HBeAg (+)
- High HBV DNA
- HBeAg produced
- Less difficult to treat
- Slower rate of progression to liver disease
- Natural resolution over time (8-10%)
- Clinical outcome measures: HBV DNA, ALT, “e” & “s” seroconversion

HBeAg (-)
- Lower HBV DNA
- No HBeAg produced
- Difficult to treat
- Fast rate of progression to liver disease
- No natural resolution over time
- Clinical outcome measures: HBV DNA, ALT normalization

Diagnosis:
- \textit{HBsAg} (+) & HBV-DNA (+) for > 6 months, with anti-HBc IgM (-) but anti-HBc total (+) [excludes incubation]
States of Chronic Hepatitis B

Inactive Carrier
Immunotolerant
Immunopositive
Occult HBV
Chronic Hepatitis B states

- **Inactive Carrier state**
  - **Normal ALT** (normal male < 30 U/L, normal female < 19 U/L) and
    - **Wild-HBe(+) or Wild-HBe(-):**
      - HBV-DNA < 20000 IU/mL,
    - **Mutant-HBe(-):**
      - HBV-DNA < 2000 IU/mL,

  (in HBe(-): if HBV-DNA > 2000 IU/mL but < 20000 IU/mL, needs testing for PreCore or Core-promoter mutation to classify, but management will not change)
Chronic Hepatitis B states

**Follow-up of Inactive Carrier state**

- Repeat ALT every 3 months x 1 year; then every 6-12 months. After age 40, add HBV-DNA every year.
- If ALT elevates > ULN and HBV-DNA remains low: investigate cause & consider liver Bx
- If ALT elevates > ULN & HBV-DNA increases to > 20000 IU/mL: treat
- If ALT remains normal but HBV-DNA elevates > 2000 IU/mL: Liver Bx if older than 40; otherwise observe (immunotolerant state).
Chronic Hepatitis B states

- **Immunotolerant state**
  - Normal ALT (normal male < 30 U/L, normal female < 19 U/L) and
    - Wild-HBe(+) or Wild-HBe(-):
      - HBV-DNA > 20000 IU/mL
    - Mutant-HBe(-):
      - HBV-DNA > 2000 IU/mL

- **NOTE:** Consider Liver Bx in older than 40 years & HBV-DNA > 2000 IU/mL (10^4 copies/mL), (May be immunoactive)
Chronic Hepatitis B states

- **Follow-up of Immunotolerant state**
  - ALT every 3-6 months
  - If ALT elevates > ULN & HBV-DNA still > 20000 IU/mL: consider liver Bx and/or treat
  - If person is or reaches age =/> 40: consider liver Bx to decide about treatment
Chronic Hepatitis B states

- **Immunoactive state**
  - Elevated ALT (male > 30 U/L, female > 19 U/L)
    - Wild-HBe(+) or Wild-HBe(-):
      - HBV-DNA > 20000 IU/mL
    - Mutant-HBe(-):
      - HBV-DNA > 2000 IU/mL
  - Treat
## Prognostic Factors For Progression To Cirrhosis

<table>
<thead>
<tr>
<th>Factors</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Older age</td>
<td>.0001</td>
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<tr>
<td>HBV-DNA persistence</td>
<td>.0001</td>
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<tr>
<td>Virus genotype C</td>
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<td>Recurrent acute flares</td>
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<td>Histologic Staging</td>
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<td>Alcohol consumption</td>
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<td>HCV, HDV co-infection</td>
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<tr>
<td>HIV co-infection</td>
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</table>

Chronic Hepatitis B

Treatment Candidates

- HBsAg(+) > 6 months, and:
  a) HBV-DNA > 20,000 IU/mL in HBe(+), or
  b) HBV-DNA > 2,000/mL in mutant HBe(-)
    - with ALT > ULN, or
    - with moderate or severe activity in liver biopsy
  c) Cirrhotic with HBV-DNA > 2000 IU/mL
     (independently of ALT value)
Chronic Hepatitis B
Treatment Options

- **Interferon**: if non-cirrhotic, and ALT > 2 x ULN, and HBV-DNA < 12 x 10^6 IU/mL

- **Peg-IFN**: if non-cirrhotic, and HBV-DNA < 3.6 x 10^9 IU/mL, with any abnormal ALT

- **Entecavir or Tenofovir**: if not candidate for interferon or not interested on interferon, but candidate for treatment.

- **In Patients with HIV co-infection**: Only use Peg-IFN, or Adefovir, unless the anti-HBV drug is being use as part of HAART.

- **In Pregnancy**: in the following order
  - Tenofovir (category B & conditionally safe for lactation depending on dose or patient-group).
  - Telbivudine (category B & possibly unsafe for lactation).
  - Lamivudine (category C & unsafe for lactation)
Chronic HBV

Goals of Therapy

• **Ideal:**
  - Clear HBsAg and cure disease; (infrequently reached).
Chronic HBV
Goals of Therapy

- **Practical:**
  - **HBe(+)**: Convert to “inactive carrier state” with:
    - HBV-DNA < 20,000 IU/mL and
    - sero-conversion to HBe(-)/anti-HBe(+);
    - ideally < 60 IU/mL (complete response)
  - **Mutant-HBe(-)**: Convert to “inactive carrier state” with:
    - HBV-DNA < 2,000 IU/mL
    - ideally < 60 IU/mL (complete response)
  - **Cirrhotic**: Convert to:
    - HBV-DNA < 2,000 IU/mL
    - ideally < 60 IU/mL (complete response)
Chronic HBV Therapy

Points to Keep in Mind

- Sustained loss of HBeAg requires to continue Adefovir, Entecavir, or Tenofovir for at least 6 months after loss of HBeAg.

- Long therapy with oral agents increases frequency of drug-resistance.

- If patients were HBe(-) pre-treatment, therapy will be life-long.
Definitions & Management for Treatment with Oral Antivirals

- **Primary non-response**: drop of HBV-DNA < 1 log after 12 wks of therapy
  - Check for viral resistance (INNO-Lipa HBV DR v2). May be compliance issue, or host pharmacologic effect.
  - Change or add second drug without cross-resistance.

- **Partial Response**: HBV-DNA > 2000 IU/mL after 24 weeks of therapy.
  - Predicts high risk for resistance. (Resistance risk is low if HBV-DNA is < 200 IU/mL).
  - Change or add second drug without cross-resistance.
Definitions for Treatment with Oral Antivirals

- **Breakthrough:**
  a) Increase of HBV-DNA > 1 log from nadir, at any time,
  b) Reappearance of HBV-DNA(+) after 2 negative HBV-DNA, at least 1 month apart.
  - Check for viral resistance (INNO-Lipa HBV DR v2). May be compliance problem.
  - Change or **add second drug without cross-resistance.**

- **Complete Response:**
  - HBV-DNA < 60 IU/mL

- **Commercial Test for Drug Resistance:**
  - Inno-LiPA HBV DR v2 (Lamivudine, Telbuvidine, Emtricitabine and Adefovir)
# Drug Cross-Resistance Profile

(Reverse transcriptase mutations)


<table>
<thead>
<tr>
<th>Mutation/Mutation</th>
<th>Lamivudine</th>
<th>Telbivudine</th>
<th>Entecavir</th>
<th>Adefovir</th>
<th>Tenofovir</th>
</tr>
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<tbody>
<tr>
<td>Wild</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>M204I</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>L180M + M204V</td>
<td>R</td>
<td>R</td>
<td>I</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>A181T/V</td>
<td>I</td>
<td>S</td>
<td>S</td>
<td>R</td>
<td>S</td>
</tr>
<tr>
<td>N236T</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>R</td>
<td>I</td>
</tr>
<tr>
<td>I169T + V173L + M250V</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>T184G + S202I/G</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>I233V</td>
<td></td>
<td></td>
<td>Resistance?</td>
<td></td>
<td>Resistance?</td>
</tr>
<tr>
<td>A194T</td>
<td></td>
<td></td>
<td>Resistance?</td>
<td></td>
<td>Resistance?</td>
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## Treatment Options for Antiviral Resistance

<table>
<thead>
<tr>
<th>Resistance to</th>
<th>Rescue Therapy</th>
</tr>
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<tbody>
<tr>
<td>Lamivudine or Telbivudine</td>
<td><strong>Add:</strong> Adefovir, or Tenofovir, or</td>
</tr>
<tr>
<td></td>
<td><strong>Switch to:</strong> Tenofovir + Emtricitabine (Truvada)</td>
</tr>
<tr>
<td>Adefovir</td>
<td><strong>Add:</strong> Lamivudine, or Entecavir, or</td>
</tr>
<tr>
<td></td>
<td><strong>Switch to:</strong> Tenofovir + Emtricitabine (Truvada)</td>
</tr>
<tr>
<td>Entecavir</td>
<td><strong>Add:</strong> Adefovir, or Tenofovir</td>
</tr>
<tr>
<td>Multidrug</td>
<td>?</td>
</tr>
</tbody>
</table>
Reactivation of HBV by Immunosuppression

- **Groups at Risk:** HBsAg(+) or anti-HBc(+)

- **Common Causes:** Rituximab, Alemtuzumab, Infliximab, liver transplant, hematological malignancies, HIV infection, stem cell transplantation, chemotherapy, kidney or heart transplantation.

- **Recommendation:** Test all patients for HBsAg & anti-HBc before immunosuppression.
Prevention of HBV Reactivation by Immunosuppression

- **Management:** treat until 12 months after end of immunosuppression.
  - If HBsAg(+) has 40% risk of reactivation: Test for HBV-DNA
    - If HBV-DNA is (+): treat with Entecavir or Tenofovir.
    - If HBV-DNA is (-): Any oral anti-HBV antiviral can be an option.
  - If only anti-HBc(+), has 4% risk of reactivation: Test HBV-DNA
    - If HBV-DNA is positive, treat with Entecavir or Tenofovir.
    - If HBV-DNA is (-):
      A) Start pre-immunosuppression prophylaxis with Lamivudine or other anti-HBV drug and continue antiviral until 12 months after end of therapy, or
      - B) monitor while on immunosuppressive therapy for reappearance of HBsAg or HBV-DNA; If HBV reactivates, treat.
Hepatocellular Carcinoma
Recommended Surveillance Groups
(Risk > 1.5% / year)

- **Hepatitis B**
  - All HBV cirrhotics
  - Africans > 20 y.o.
  - 1<sup>st</sup> degree w HCC & > 20 y.o.
  - Asian males > 40 y.o.
  - Asian females > 50 y.o.
  - Caucasians w. high HBV-DNA / activity & > 40 y.o.

- **Other Cirrhosis**
  - Hepatitis C (F3 ?)
  - Alcoholic
  - Genetic Hemochromatosis
  - Primary Biliary Cirrhosis
  - +/- Alpha-1 antitrypsin
  - +/- NASH
  - +/- Autoimmune hepatitis
**SEROLOGY**
- **AFP should be used only if U/S is not available**
- AFP > 20 ng/mL: sens=60%, PPV=41%
- AFP > 200 ng/mL: sens=22%, PPV=60%
- Des-gamma-carboxy prothrombin (PIVKA II), AFP L3 fraction, Alpha fucosidase, Glypican 3

**ULTRASOUND**
- **Method of choice.**
  - Sensitivity: 65-80%
  - Specificity > 90%
- False (+) Rate:
  - U/S=2.9%;
  - AFP=5%;
  - AFP+U/S=7.5%
- Classic is hypoechoic; can be isoechoic w halo, hyperechoic, or mixed.
- **Interval:** 6-12 months
- **Positive Result:** nodule > 1 cm
Chronic Hepatitis B+D

- Uncommon in USA
- \([\text{HBsAg}(+) \& \text{increased liver enzymes} > 6 \text{ months}] + [\text{anti-HDV}(+) \text{high titers or HDAg}(+) \text{in liver biopsy}]\)
- More aggressive than chronic HBV
- INF\(\alpha\) 3-18 MU qd x 1 year (poor success)
- Hepatocellular Ca is uncommon (early death)
Alcoholic Hepatitis

- Alcohol for > 5 years
  - > 40-60 g/d in men,
  - > 20-40 g/d in women

- (12 oz beer = 1.5 oz liquor = 5 oz wine = 13.3 g)

- Suspect in AST/ALT >1 and AST <280

- Prognosis by Discriminant Function = 4.6(PT sec) + T. Bili mg/dL

  - Mortality at 3 months:
    » DF <55 = 4%,
    » DF 55-89 = 20%,
    » DF >90 = 66%
# Glasgow Alcoholic Hepatitis Score

**GUT 2005;54:1174-1179**

Minimum = 5; Maximum = 12 points

<table>
<thead>
<tr>
<th>POINTS</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&lt; 50</td>
<td>&gt; 50</td>
<td></td>
</tr>
<tr>
<td>WBC count</td>
<td>&lt; 15</td>
<td>&gt; 15</td>
<td></td>
</tr>
<tr>
<td>BUN</td>
<td>&lt; 14</td>
<td>&gt; 14</td>
<td></td>
</tr>
<tr>
<td>INR</td>
<td>&lt; 1.5</td>
<td>1.5 - 2</td>
<td>&gt; 2</td>
</tr>
<tr>
<td>T. Bili</td>
<td>&lt; 7.35</td>
<td>7.35 – 14.7</td>
<td>&gt; 14.7</td>
</tr>
</tbody>
</table>
Prediction of 90-day mortality in patients with AH based on MELD. The curve demonstrates probability of 90-day mortality in AH for given MELD (black line) with confidence intervals (gray shading).

MELD was calculated using the following formula:
MELD = 9.57 \times \log_{e}(\text{Cr mg/dL}) + 3.78 \times \log_{e}(\text{bili mg/dL}) + 11.20 \times \log_{e}(\text{INR}) + 6.43.16

HEPATOLOGY 2005;41:353-358
http://www.mayoclinic.org/meld/mayomodel7.html
Alcoholic Hepatitis

**Diagnosis:** Clinical picture & history, or Liver Bx.
- Acetaminophen therapeutic misadventure - Hepatic necrosis with regular doses (2-4 gm/d)

**Treatment:**
- 1) Abstinence,
- 2) Aggressive nutrition (35-40 kcal/kg and 1.2 to 1.5 g/kg of protein (>2100 k-cal/d) po, or tube feed)
- 3) Pentoxyphilline 400 mg TID (decreases HRS)
- 4) For DF > 90 + encephalopathy: Prednisolone x 30 d (without infection nor GI bleed) +/- NAC, or Pentoxyphilline.
Non-Alcoholic Steato-Hepatitis

- **Prevalence**: 2.1-3%

- **Demographics**: - mean age 50-55,
  - female/male:2/1,
  - obesity 66%,
  - diabetes 66%,
  - hyperlipidemia 55%
  - BMI: USA (F:25, M:30); Asia (F:23, M:25)
  - Waist Circumference (cm): USA (F:88, M:102); Asia (F:80, M:90)

- **Predictors of progression** (2 or more of):
  - Obesity,
  - Type II DM,
  - Age > 45,
  - Elevated ALT, with AST > ALT
Non-Alcoholic Steato-Hepatitis

- **Symptoms:**
  - usually asymptomatic;
  - may have RUQ discomfort, fatigue, hepatomegaly, elevated ALT $> \text{AST}$.

- **Diagnosis:**
  - Bx with [steatosis + ballooning], or [steatosis + fibrosis] or [Mallory bodies]

- **Mortality:**
  - 11% at 10 years.
  - Elevated risk of HCC.

- **Treatment:**
  - weight control, and “tight control” of DM and hyperlipidemia.
  - Vitamin E 800 IU/d
  - Pentoxyphilline 400 mg po TID
Auto-Immune Hepatitis

- **Diagnosis:**
  - Compatible liver biopsy +
  - autoantibody (ANA, ASMA, anti-LKM$_1$, LC$_1$, pANCA (pANNA), anti-SLA, anti-ASGPR, anti-LKM$_3$, anti-LKM$_2$, anti-LM) positive or hypergammaglobulinemia (IgG dominant) +
  - No other cause

- **More common in women (3.6/1); incidence 1-2/100,000; point prevalence 11-17/100,000**

- **Frequent auto-immune disorders**

- **Type I:** ANA/ASMA(+). Most common (80%).
  - Females 10-20 or 45-70 yo.
  - Acute onset in 40%. Cirrhosis in 25% at Dx.
  - Common assoc: UC, autoimmune thyroiditis, synovitis, & RA.
  - Very steroid responsive
Auto-Immune Hepatitis (contd.)

- **Type II**: anti-LKM1(+) or anti-LC1(+); 4% of AIH; Girls 2-14 yo;
  - Common associations: IDDM, thyroid disease, vitiligo, APECED
    » Autoimmune PolyEndocrinopathy-Candidiasis-Ectodermal Dystrophy: is anti-LM(+) with mutation in chrom 21q22.3
  - Steroid responsive +/-

- **Prognostic Ab & HLA:**
  - a) Relapse: anti-SLA, anti-chromatin.
  - b) Severity: anti-actin, anti-LC₁, HLA-DR3

- **Concurrent PSC**: should be investigated by MRCP in:
  - Adults with no-response or poor response to therapy.
  - All adults with AIH + IBD
  - All children with AIH
### Revised AIH Score (1 of 2)

<table>
<thead>
<tr>
<th>Category</th>
<th>Value 1</th>
<th>Value 2</th>
<th>Value 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Female</td>
<td>+3</td>
<td></td>
</tr>
<tr>
<td>Alk Ph/AST ratio</td>
<td>&gt;3</td>
<td>-2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt; 1.5</td>
<td>+2</td>
<td></td>
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<tr>
<td>IgG or gamma-glob above Normal</td>
<td>&gt; 2</td>
<td>+3</td>
<td></td>
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<tr>
<td></td>
<td>1.5-2</td>
<td>+3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1-1.5</td>
<td>+1</td>
<td></td>
</tr>
<tr>
<td>ANA, ASMA, or anti-LKM1 titer</td>
<td>&gt; 1:80</td>
<td>+3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1:80</td>
<td>+2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1:40</td>
<td>+1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt; 1:40</td>
<td>0</td>
<td></td>
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<tr>
<td>AMA</td>
<td>Positive</td>
<td>-4</td>
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<tr>
<td>Viral markers</td>
<td>Positive</td>
<td>-3</td>
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<tr>
<td></td>
<td>Negative</td>
<td>+3</td>
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<tr>
<td>Drugs</td>
<td>Yes</td>
<td>-4</td>
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<tr>
<td></td>
<td>No</td>
<td>+1</td>
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<tr>
<td>Alcohol</td>
<td>&lt; 25 g/day</td>
<td>+2</td>
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<td>&gt; 60 g/day</td>
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## Revised AIH Score (2 of 2)

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<tr>
<th>Category</th>
<th>Description</th>
<th>Score</th>
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<tr>
<td><strong>HLA</strong></td>
<td>DR3 or DR4</td>
<td>+1</td>
</tr>
<tr>
<td><strong>Immune disease</strong></td>
<td>Thyroiditis, colitis, other</td>
<td>+2</td>
</tr>
<tr>
<td><strong>Other auto-Ab</strong></td>
<td>Anti-SLA, anti-actin, anti-LC1, pANCA</td>
<td>+2</td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td>Interface hepatitis</td>
<td>+3</td>
</tr>
<tr>
<td></td>
<td>Plasmacytic infiltrate</td>
<td>+1</td>
</tr>
<tr>
<td></td>
<td>Rosettes</td>
<td>+1</td>
</tr>
<tr>
<td></td>
<td>None of above</td>
<td>-5</td>
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<tr>
<td></td>
<td>Biliary changes</td>
<td>-3</td>
</tr>
<tr>
<td></td>
<td>Other feature</td>
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<tr>
<td><strong>Treatment response</strong></td>
<td>Complete</td>
<td>+2</td>
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<tr>
<td></td>
<td>Relapse</td>
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<tr>
<td><strong>Pre-Treatment Aggregate Score</strong></td>
<td>&gt; 15</td>
<td>Definite Diagnosis</td>
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<td>10-15</td>
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<tr>
<td><strong>Post-Treatment Aggregate Score</strong></td>
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<td>Definite Diagnosis</td>
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<td>12-17</td>
<td>Probable diagnosis</td>
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### Auto-Immune Hepatitis Simplified Scoring

<table>
<thead>
<tr>
<th>Variable</th>
<th>Result</th>
<th>Points</th>
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</thead>
<tbody>
<tr>
<td>ANA or ASMA</td>
<td>&gt;= 1:40</td>
<td>+1*</td>
</tr>
<tr>
<td></td>
<td>&gt;= 1:80</td>
<td>+2*</td>
</tr>
<tr>
<td>Anti-LKM1</td>
<td>&gt;= 1:40</td>
<td>+2*</td>
</tr>
<tr>
<td>Anti-SLA</td>
<td>+</td>
<td>+2*</td>
</tr>
<tr>
<td>Immunoglobulins level</td>
<td>&gt; ULN</td>
<td>+1</td>
</tr>
<tr>
<td></td>
<td>&gt; 1.1 ULN</td>
<td>+2</td>
</tr>
<tr>
<td>Histology</td>
<td>Compatible</td>
<td>+1</td>
</tr>
<tr>
<td></td>
<td>Typical</td>
<td>+2</td>
</tr>
<tr>
<td>Viral hepatitis markers</td>
<td>Absent</td>
<td>+2</td>
</tr>
<tr>
<td><strong>DEFINITIVE AIH</strong></td>
<td>&gt;= 7</td>
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</tr>
<tr>
<td><strong>PROBABLE AIH</strong></td>
<td>6</td>
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</tr>
</tbody>
</table>

* Maximal 2 Points Total from auto-antibodies
Auto-Immune Hepatitis (contd.)

- **Treatment**: Prednisone ± Azathioprine, or Budosenide + Azathioprine for years or life
  
  Prolongs survival. With “excellent control”, fibrosis may decrease over time.

- **Drug Schedule**: 
  - Vaccinate against Hep A&B; check TPMT activity
  - Wk 1: Pred 60, or Imuran 50 (1-2/kg) + Pred 30
  - Wk 2: Pred 40, or Imuran 50 (1-5/kg) + Pred 20
  - Wk 3: Pred 30, or Imuran 50 (1-2/kg) + Pred 15
  - Wk 4: Pred 30, or Imuran 50 (1-2/kg) + Pred 15
  - Maintenance: Pred <= 20, or Imuran 50 (1-2/kg) + Pred <= 10
  - Consider termination of therapy after 2 years of normal ALT, normal IgG, and no inflammation in biopsy.
Auto-Immune Hepatitis

Special Groups

- **Asymptomatic mild AIH**
  - Has better outcome but is not “benign”; cirrhosis in 49% after 15 y
  - 10 y survival 67% without treatment vs 98% with treatment
  - Spontaneous resolution without therapy 12% vs 63% with therapy
  - 26-70% develop symptoms
  - Respond to therapy better than classic AIH.

- **AIH with atypical serology**
  - 13% of AIH in Caucasians lack ANA, ASMA, and anti-LKM₁
  - Some have anti-SLA, anti-pANCA (atypical).
  - AMA(+) in 8-35% but without bile duct injury (no overlap)
  - They behave and respond to therapy as classic AIH
Auto-Immune Hepatitis
Special Groups

- **AIH with cholangiographic changes**
  - MRCP resembling PSC in 8% of adults; true PSC in only 2%.
  - Those with PSC like changes without IBD behave like classic AIH.
  - Those with IBD may have true PSC and are frequently steroid refractory.

- **AIH in males**
  - Have less concurrent immune diseases.
  - Have better survival.
  - Management is the same.
Auto-Immune Hepatitis
Special Groups

- **AIH in non-Caucasians**
  - Blacks have more cirrhosis at Dx (85% vs 38%)
  - South Americans are younger, with severe hepatitis.
  - Japanese have milder disease with late onset.
  - Alaskans have more acute icteric disease and severe fibrosis.
  - Native Americans have more cholestasis, advanced fibrosis, and autoimmune disorders.
  - Africans, Asians and Arabs have more bile damage in liver biopsy.
  - Management is the same.
Hemochromatosis

- Autosomic recessive.
- High intestinal Fe absorption.
- Fasting morning transf sat >45% & high ferritin
- Metocarpophalangeal arthritis, male impotence, DM, cardiomyopathy/ arrhythmia, bronze skin

**Diagnosis:**

1. Hepatic Iron Index (µmol/g ÷ age) ≥ 1.9
2. Phlebotomy 1 unit q 1 week for ≥ 20 g Fe after age 40, or ≥ 10 gm for age 20-40, before Fe deficiency (250 mg Fe / phlebotomy unit)
3. HFE C282Y homozygote; C282Y/H63D + (1) or (2)
Hemochromatosis

- **Liver Bx needed:**
  - a) Age > 39,
  - b) Ferritin > 1000 ng/mL,
  - c) Elevated ALT or AST

- **Treatment:** phlebotomy 1 unit q 1 week until Fe deficient (ferritin < 50); avoid vit C
Non-HFE HEMOCHROMATOSIS

- **TRANSFERRIN RECEPTOR-2 Mutation (TfR2)**
  - Autosomal recessive.
  - TfR2 is regulator of Hepcidin. Low hepcidin causes increased Fe influx.
  - High Transferrin sat in 2\textsuperscript{nd}-3\textsuperscript{rd} decade.
  - Onset 1-2 decade before HHC (2\textsuperscript{nd} to 4\textsuperscript{th}).
  - Mild to severe Liver Fe overload (periportal hepatocytes). Hypochromic anemia.
  - May cause cirrhosis.
Non-HFE HEMOCHROMATOSIS

- **HEPCIDIN ANTIMICROBIAL PEPTIDE (HAMP/19q13.1) Mutation & HEMOJUVELIN (HJV) Mutation**
  - Autosomal recessive.
  - HJV is regulator of Hepcidin. Very low hepcidin causes massive Fe influx.
  - High Ferritin & Transferrin sat in 1st decade.
  - Hypogonadism before end of 2nd decade, cardiac disease & abdominal pain.
  - Cirrhosis is later occurrence (massive hepatocyte Fe).
  - Death on 3rd decade from heart failure.
Non-HFE Hemochromatosis & Other Primary Fe-Overload

● FERROPORTIN DISEASE
  – Autosomal dominant. Worldwide distribution.
  – Decreased Fe efflux.
  – High Ferritin in 1st decade.
  – Fe deposit in RES with very high Ferritin but low or normal transferrin saturation; high saturation late in life.
  – Mild hypochromic anemia.
  – Mild liver injury with sinusoidal fibrosis.
  – Treatment: Phlebotomy q 2-3 weeks (not weekly)
Non-HFE Hemochromatosis & Other Primary Fe-Overload

- **ACERULOPLASMINEMIA**
  - Autosomal recessive.
  - Decreased Fe efflux.
  - Lack of ceruloplasmin, who has ferroxidase activity needed to release Fe from cells, causes deposit in:
    » basal ganglia & dentate nucleus giving ataxia and dementia; in
    » pancreas, causing diabetes, and in
    » RES giving hypochromic microcytic anemia.
  - Liver disease is mild.
  - **Treatment**: Chelation, Exjade® (deferasirox) & desferoxamine
Non-HFE Hemochromatosis & Other Primary Fe-Overload

- **ATRANSFERRINEMIA/HYPOTRANSFERRINEMIA**
  - Autosomal recessive.
  - Increased Fe influx.
  - Severe anemia
  - Onset in 1\textsuperscript{st} & 2\textsuperscript{nd} decade

- **H-FERRITIN ASSOCIATED HEREDITARY Fe-Overload**
  - Autosomal dominant.
  - Increased Fe influx.
  - Liver Fe overload in 4\textsuperscript{th}-5\textsuperscript{th} decade
\( \alpha_1 \)-antitrypsin Storage Disease

- Phenotype Pi ZZ (Mmalton, Mduarte, MZ, SZ, and MS may worsen other types of liver disease).
- Low serum \( \alpha_1 \) antitrypsin (low normal in acute illness)
- Hx: neonatal or childhood hepatitis/jaundice
- Family hx emphysema at < 40 years in smokers, and at age < 60 without tobacco.

**Treatment:**
- liver transplant for end stage liver disease
- Carbamazepine ? (increases autophagy)
Wilson’s Disease

- Autosomal recessive.
- Mutation in ATP7B (chr 13) or WND gene
  - encodes metal-transporting P-type ATPase in hepatocytes, causing decreased hepatocyte excretion of Cu in bile, causing systemic Cu accumulation.
- Prevalence: 30 per million.
- Presentations:
  - Neuro-psychiatric disorder + increased liver enzymes (any age)
  - Increased liver enzymes in < 55 years of age, or
  - Coombs(-) hemolysis in < 55 years of age
Wilson’s Disease

- **Liver** (42%): Hepatomegaly, Splenomegaly, elevated ALT or AST, fatty liver, acute hepatitis, AI-like hepatitis, cirrhosis, FHF
- **Neuro** (34%): movement disorder, dysarthria, dystonia, pseudobulbar palsy, seizures, migraine, drooling, dysautonomia, insomnia
- **Psych** (10%): depression, neuroses, personality change, psychosis.
- **Other** (14%): Fanconi S., kidney stones, hemolysis, osteoporosis, cardiomyopathy, dysrhythmia, pancreatitis, hypoparathyroidism, menstrual irregularity, miscarriages, infertility, lunulae ceruleae.
Wilson’s Disease

- Most have low or low-normal ceruloplasmin and increased 24 h urine copper; low alkaline phosphatase & uric acid.
  - Low ceruloplasmin due to failure to incorporate Cu into ceruloplasmin, forming apoceruloplasmin which has a reduced half-life.
- Ceruloplasmin is elevated by acute inflammation and estrogens. Normal ceruloplasmin do not exclude WD.
- **Ceruloplasmin < 5 mg/dL strongly suggest WD.**
- Tests: ceruloplasmin, MRI of brain (basal ganglia hyperintensity in T2), slit-lamp exam for K-F rings, 24 h urine for copper; Liver Bx with Cu quant.
Wilson’s Disease

**Diagnosis:** consider diagnosis in ages 3 to 55.

- 1) Low ceruloplasmin + K-F Rings;
- 2) Hepatic copper > 250 µg/g dry weight (1-2 cm core) in absence of chronic cholestasis + consistent histology
- 3) 24 hour urine Cu > 40 mcg/day
- 4) Direct mutation analysis (whole-gene sequencing), or studies based in “proband” mutant, for ATP7B mutation.
Algorithm for Diagnosis of Wilson disease:
Unexplained Liver Disease

Unexplained liver disease

Serum ceruloplasmin (CPN); 24-h urinary Cu; slit lamp examination

KF rings present
CPN <20 mg/dL
24-h urine Cu >40 mcg
Liver biopsy for histology and Cu quantification

KF rings present
CPN ≥20 mg/dL
24-h urine Cu >40 mcg

KF rings absent
CPN <20 mg/dL
24-h urine Cu ≤40 mcg*
Liver biopsy for Cu quantification

KF rings absent
CPN <20 mg/dL
24-h urine Cu >40 mcg

< 50 mcg/g dry wt
> 250 mcg/g dry wt
≤ 250 mcg/g dry wt

Other diagnosis

Molecular testing

Diagnosis of WD established

Hepatology
Volume 47, Issue 6, pages 2089-2111, 4 FEB 2008 DOI: 10.1002/hep.22261
http://onlinelibrary.wiley.com/doi/10.1002/hep.22261/full#fig1
Algorithm for Diagnosis of Wilson disease: Neuropsychiatric Disorder +/- Liver Disease

Scrum ceruloplasmin (CPN); 24-h urinary Cu; slit lamp examination

- KF rings present
  - CPN ≥20 mg/dL
  - 24-h urine Cu >40 mcg
  - Molecular testing
  - If indeterminate, liver biopsy for Cu quantification and histology
  - Diagnosis of WD established
- KF rings present
  - CPN <20 mg/dL
  - 24-h urine Cu >40 mcg
  - Liver biopsy for Cu quantification and histology
  - >250 mcg/g dry wgt
  - Diagnosis of WD established
  - <50 mcg/g dry wgt
  - 50-250 mcg/g dry wgt
  - Diagnosis of WD excluded: Consider other diagnosis
- KF rings absent
  - CPN <20 mg/dL
  - 24-h urine Cu >40 mcg
  - >50 mcg/g dry wgt
- KF rings absent
  - CPN ≥20 mg/dL
  - 24-h urine Cu ≤40 mcg
  - <50 mcg/g dry wgt
  - 50-250 mcg/g dry wgt
  - Diagnosis of WD excluded: Consider other diagnosis

Hepatology
Volume 47, Issue 6, pages 2089-2111, 4 FEB 2008 DOI: 10.1002/hep.22261
Wilson’s Disease

**Treatment:**
- penicillamine 250 mg/ x 4d, then BID x 4 d, then 500 mg BID 1 hour before meals + Pyridoxine 50 mg /d or
- *Trientine* 500 mg BID 1 hour before meals;
- Zn (elemental) 50 mg TID (5 h away from chelators: 6am: Zn, 7am: BF, 11 am: chelator, noon: lunch, 5 pm: Zn, 6pm: dinner, 9 pm chelator));
- Tetrathiomolibdate.

**In pregnancy, decrease chelator by 50% in 3rd trimester.**
No breastfeed if on penicillamine.

**Follow 24 h urine Cu (should be 200-500 mcg/d) and “free serum Cu” (> 15 mcg/dL = poor compliance; < 5 mcg/dL = overtreatment). In Zn therapy, 24h urine Cu < 75 mcg/d.**

**“Fulminant Hemolytic Wilson’s” needs urgent liver transplant**
Drug-Induced Hepatitis

- **Definitive**: alpha-methyldopa, nitrofurantoin, Dantrolene sodium, oxyphenisatin
- **Probable**: Isoniazid
- **Rare**: Clometacine, Acetaminophen, Halothane, aspirin, propylthiouracil, sulfonamides, etretinate, benzarone, papaverine; (almost any drug)
- **Treatment**: discontinue drug. Sometimes need steroids
Questions ?
Overlap Syndrome

- AIH/PBC, AIH/PSC
- A) Bx of chronic hepatitis ANA/ASMA(−) & AMA (+); B) Bx of PBC AMA(−) with ANA or ASMA(+); C) AIH with PSC on cholangiogram
- Look for: anti-piruvate dehydrogenase-E2, dominant immunoglobulin (IgG vs IgM), response to corticosteroids with repeat liver bx at 3-6 months
Ascites

- Physical exam unreliable - U/S
- Edema and hydrothorax are common
- Serum-ascites albumin gradient (SAAG)
  - SAAG>1.1 g/dl - portal hypertension
  - SAAG<1.1 g/dl - peritoneal disease (TB, Ca, pancreatitis, etc.)
- DX paracentesis: new onset, every admission, post- GI bleed, change in condition (pain, fever, encephalopathy, etc.)
Ascites (contd.)

- **Needed tests:** cell count + diff, T. protein, albumin, LDH, glucose, culture in “blood culture” bottle

- **Optional tests:** T. bili, amylase, triglycerides, cytology, AFB/fungus stain and culture

- **Treatment:**
  - Na restriction + diuretics (monitor spot urine Na/K pre-diuretic)
  - Single large volume paracentesis (LVP)
  - Serial LVP + albumin
  - Total paracentesis + albumin
  - TIPSS or portocaval shunt
Spontaneous Bacterial Peritonitis

- PMN $\geq 250/\text{mm}^3$ in low protein fluid (<1.5 g)
- Frequently asymptomatic. Sometimes pain, fever, encephalopathy
- Usually enterobacteria: E.coli, Klebsiella
- High mortality and frequent recurrence
- High LDH, high protein, low glucose or multiple micro-organisms suggest secondary peritonitis
- Treatment: Cefotaxime 2 g IV q8h x 5 days + albumin IV @ Dx & 72h later; repeat paracentesis 48 h after initiation of therapy (>50% decrease in PMN)
**SBP & HRS**

(Sort et al NEJM 1999;341:403-409)

- **POOR PROGNOSIS**
  - Creatinine $> 2.1$ mg/dl
  - **HRS**
  - Albumin $< 2.5$ mg/dl
  - Bilirubin $> 8$ mg/dl
  - PSE
  - UGI bleed

- **ALBUMIN in SBP**
  - Prosp.& Random
  - SBP: $>250$ PMN/mm³
  - Creatinine $< 3$ mg/dl
  - 63 Pts.: Cefotaxime
  - 63 Pts.: Cefotaxime + Albumin 1.5gm/kg & 1 gm/kg 3 days later
• Renal impairment:
  a) >50% incr. BUN or Cr if base Cr >1.5
  b) >50% incr. to Cr>1.5 or BUN>30 if base Cr <1.5
Variceal Bleeding

- First bleeding decreased by β blockers. No mortality change
- Acute bleeding controlled with banding. Adjuvant Octreotide + Quinolone x 7 days.
- Rebleeding decreased by β blockers or chronic sclerotherapy/banding. No change in mortality
- Liver Transplant
Risk Factors

Failure to Control Acute Hemorrhage

- Spurting varix
- Child-Pugh C
- Portal vein thrombosis
- Infection
- HVPG > 20 mm Hg

Gastroenterology 1999;117(3):626-31
Risk Factors
Rebleeding in < 6 weeks

• Age > 60
• Ascites
• Active bleeding at Endoscopy
• Red-color signs
• Platelet plug on varix
• Renal Failure
• Severe Initial Bleed (Hb < 8 g/dL)
• HVPG > 20 mm Hg
Risk Factors
Rebleeding in > 6 weeks

- Severity of Liver Failure
- Ascites
- Hepatoma
- Red-color signs
- Active Alcohol abuse
Effect of Antibiotic Prophylaxis on Rebleeding rate after Endoscopic treatment of Variceal bleed (283)

- Prospective, randomized.
- 91 cirrhotic patients with variceal bleed receiving endoscopic treatment
- Outcome: rate of rebleeding and infection
- Intervention: Ofloxacin 200mg BIDx 7d vs antibiotic for infection (46 vs 45)
- No difference on: age, sex, etiology, endoscopic finding, time to EGD, hepatoma, severity of bleed.
Results (%)

- **CONCLUSION**
  - Prophylactic antibiotics in variceal bleed decrease rebleeding rate and transfusion needs (0.7 vs 2.7 Units)
Risk of Infection

Cirrhotic with Gastrointestinal Hemorrhage

- Risk of Infection: 60%
- Acquisition time:
  - A) 20% before or at time of admission,
  - B) 40% after hospital admission.
- Types of Infection:
  - UTI (20-25%),
  - Respiratory (8%),
  - SBP (15-20%),
  - Bacteremia (8%).
Risk of Infection
Cirrhotic with Gastrointestinal Hemorrhage

- **Prophylactic antibiotics:**
  - Decreases mortality by 25% (RR 0.75),
  - Reduces infection risk by 60% (RR 0.4)
  - Decrease rebleeding rate by 56% (RR 0.44)
  - Decreases Transfusion needs (2.7 vs 0.7 units)

- **Regimens:** 7 to 10 days of
  - A) Ofloxacin 200 mg BID,
  - B) Norfloxacin 400 mg BID,
  - C) Ciprofloxacin 500 mg BID
  - D) Ceftriaxone 1 g/d