Common Causes Acute and Chronic Hepatitis

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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.

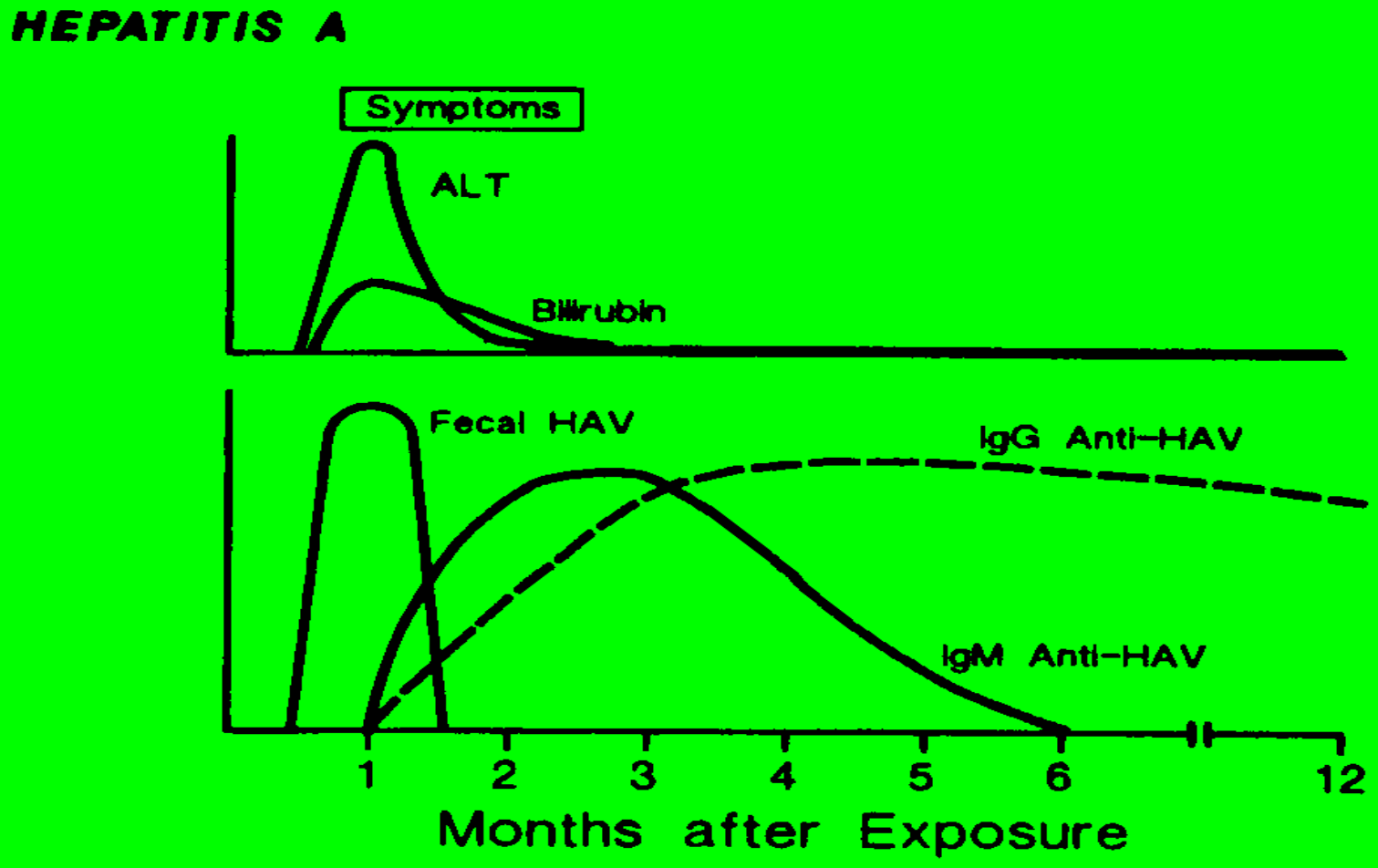
Acute Hepatitis A Clinical Features

- **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%), - anorexia (85%),
  - jaundice (80%), - nausea (75%),
  - low fever (65%), - headache,
  - abdominal pain and - 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,
  - hemolysis,
  - neurologic disease.
  - red blood cell aplasia,
  - pancreatitis,
- **Mortality**: Not increased by pregnancy.
  - a) younger than 49 = 0.3%;
  - b) older than 49 = 1.8%.

Acute Hepatitis A



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

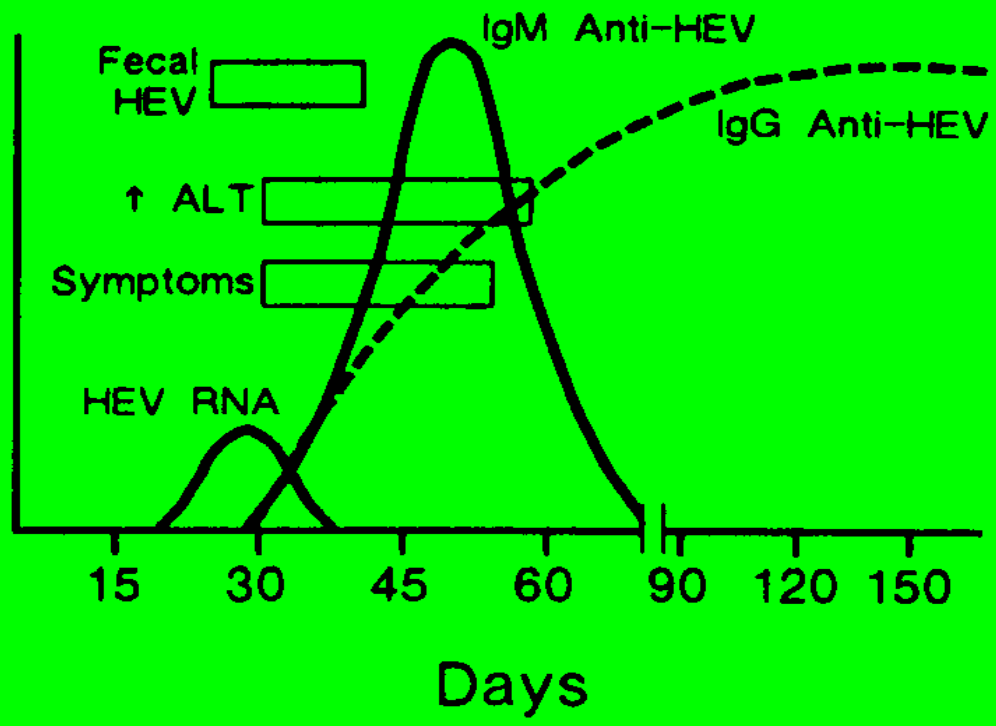
- **Types:**
  - **Sporadic:** traveler to endemic areas, pet owners, organ meat eaters, male homosexuals, military service (Midwest USA).
  - **Epidemic:** after heavy rain and flooding in areas with poor sanitation (India, China, Latin America, Africa)
  - **Endemic:** In areas were asymptomatic infection 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



Hepatitis B

- 42 nm, partially double-stranded circular DNA virus.
- 350 million carriers world-wide; causes 250000 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%)

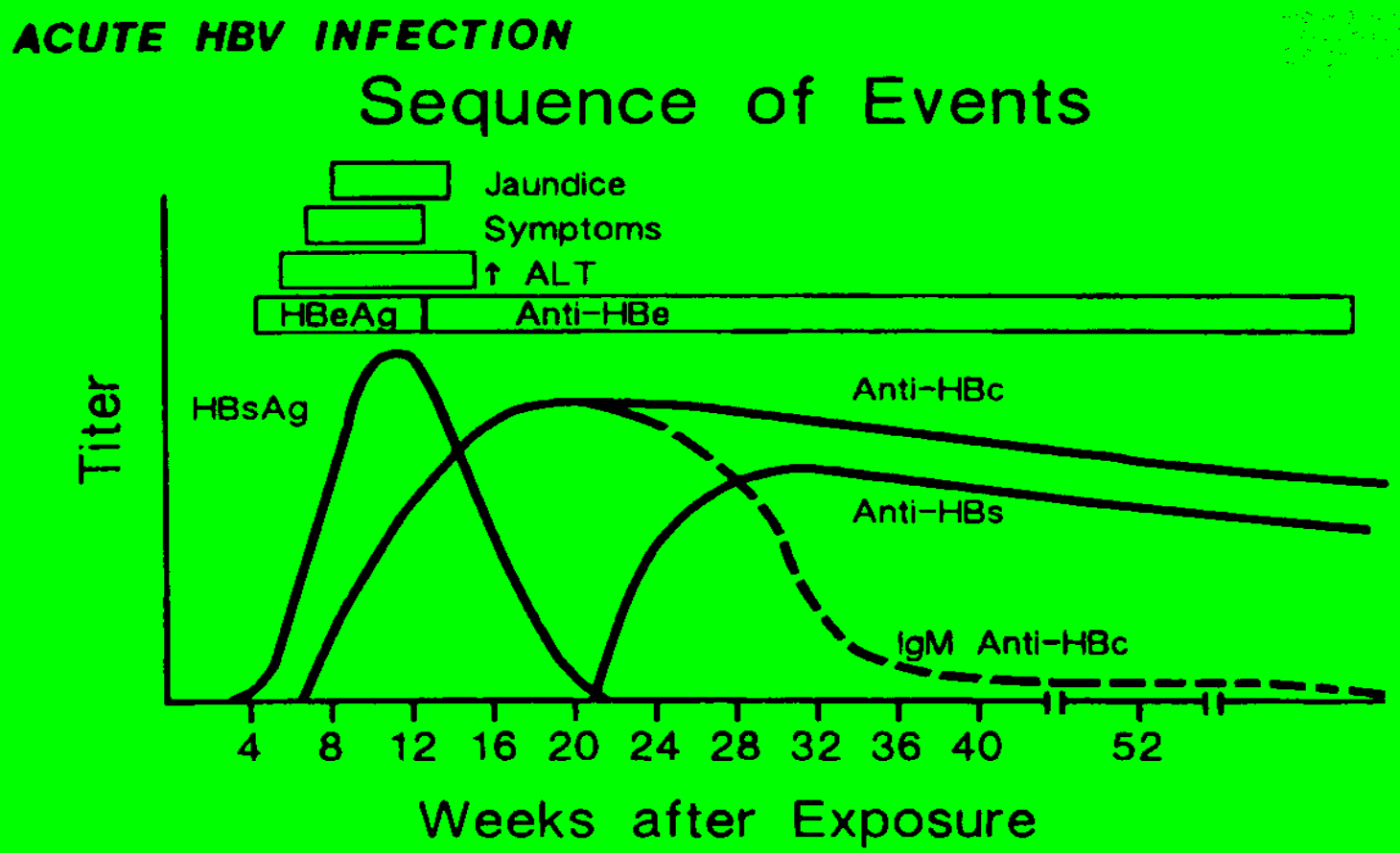
Acute Hepatitis B

- **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 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

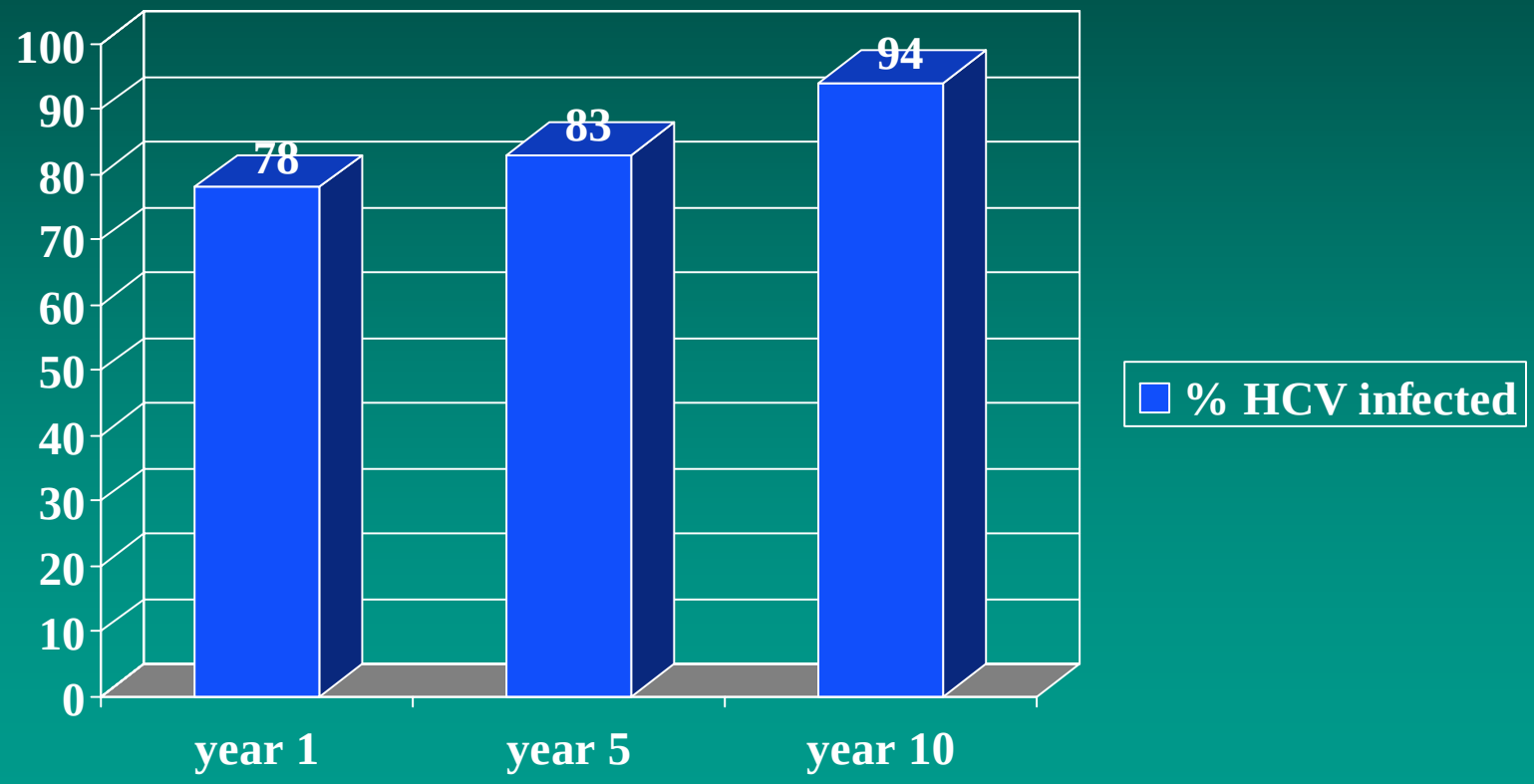
- 50 nm enveloped, positive-sense, single-stranded RNA hepacivirus. Six genotypes and > 100 subtypes.
- 170 million infected worldwide; 4-7 million in USA (1.8%); 38,000 new infections/year.
- Risk of Transmission:
  - a) Needle stick: 1.8%
  - b) Sexual intercourse: 1/95 patient-year (2.2%),
  - c) Perinatal:
    - HIV(-) mother: 5%;
    - HIV(+): 14%

Prevalence of HCV

GROUP	%
Hemophilia <’87	82
IVDA	80
Hemodialysis	10
Transfusion < ’90	7
Person w STD	6

GROUP	%
Infant of RNA(+) mother	5
Homosexual men	4
Monogamous partner	2
General population	1.8
Volunteer blood donor	.16

Risk of HCV in IVDU (% infected)



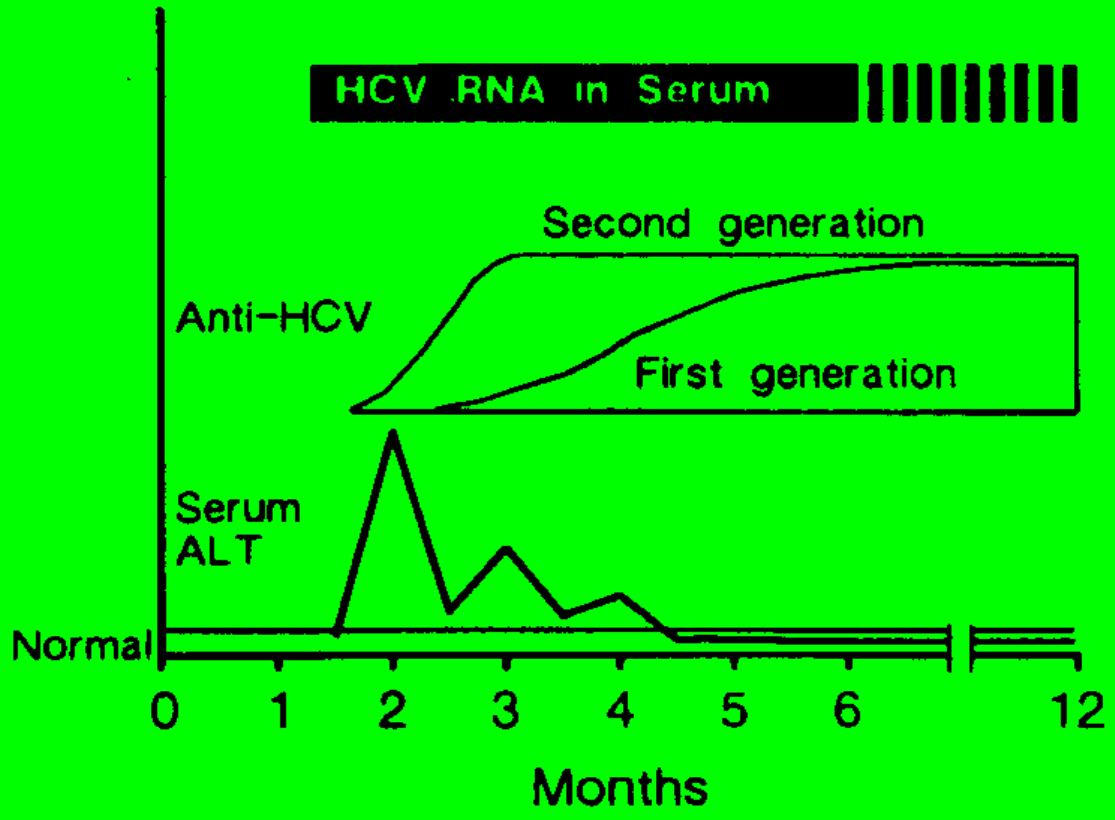
HCV Prevalence Hemodialysis Patients

	general=	HD=
Egypt	18.1%	80%
Moldavia	4.9%	75%
Bulgaria	1.1%	66%
Saudi Arabia	1.8%	57%
Turkey	1.5%	31%
Italy	0.5%	22%
France	1.1%	16%
Belgium	0.9%	9%
USA	***1.8%***	***9%***
Netherlands	0.1%	3%

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


HCV RNA in Serum
Second generation
Anti-HCV
First generation
Serum
ALT
Normal
0
1
2
3
4
5
6
12
Months

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).

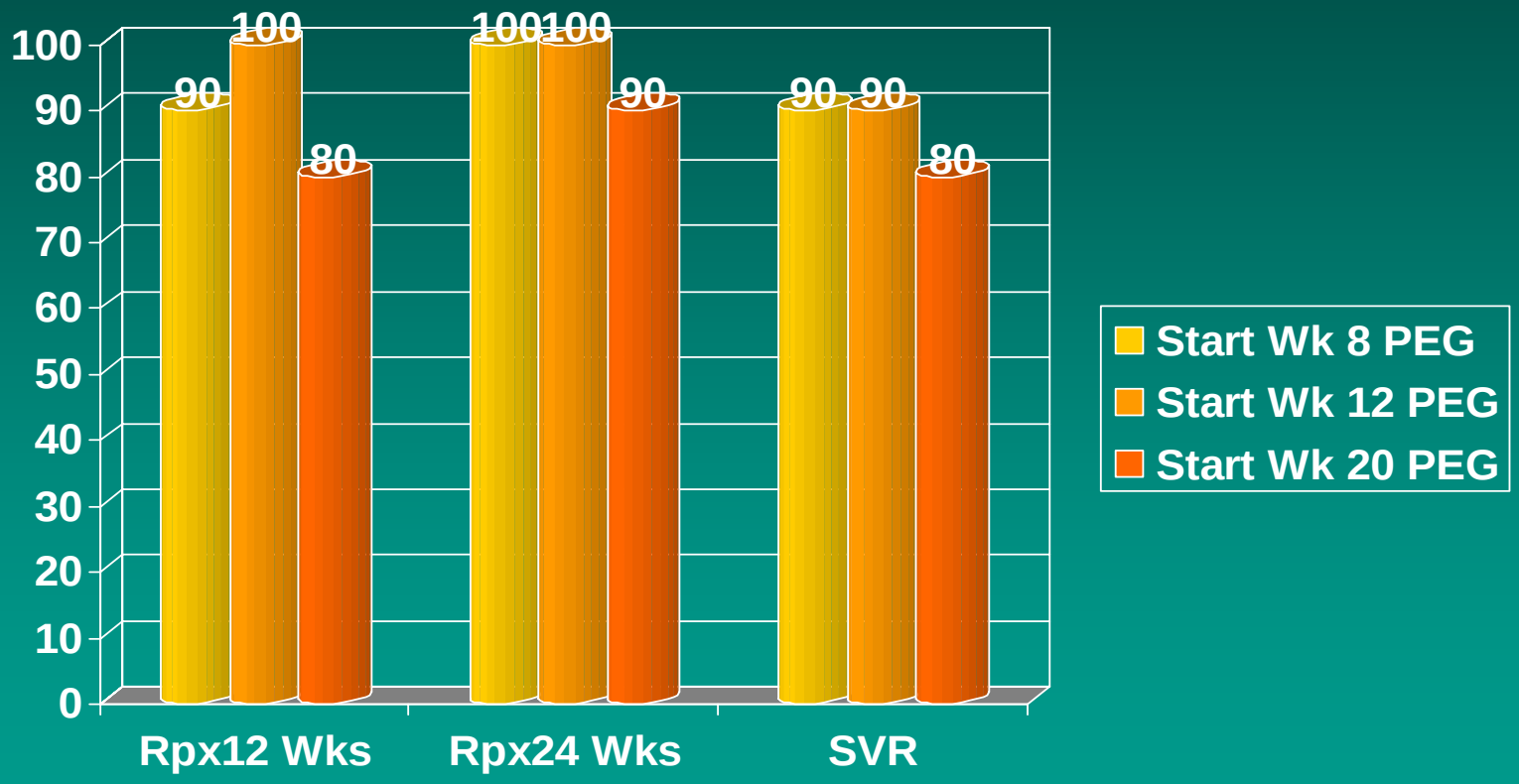
Treatment of Acute HCV @ 8,12, & 20 wks, Pegasys vs Rebetron x 12 wks

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



RESULTS

Abstr # 37

- 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-LKM$_1$, 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 bilirrubin, 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, α_1-antitrypsin, overlap syndrome

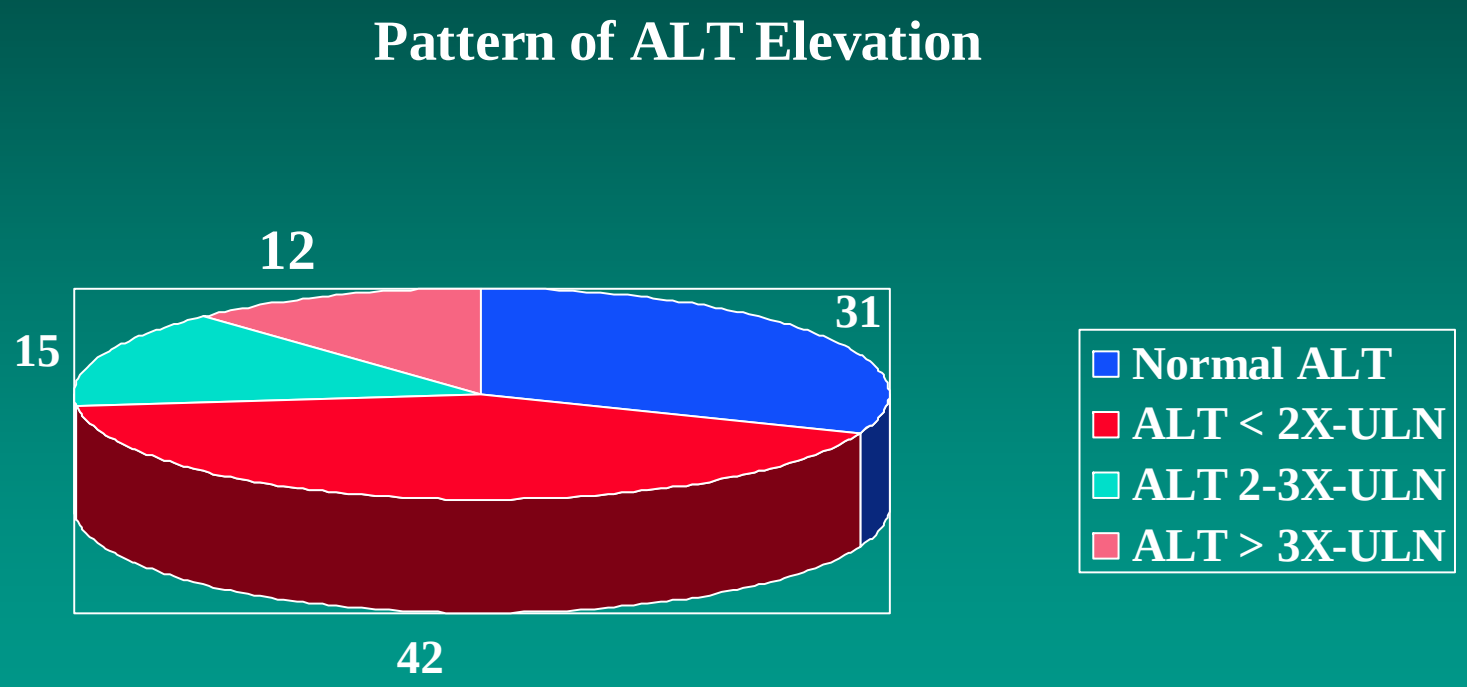
Chronic HCV

- 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,

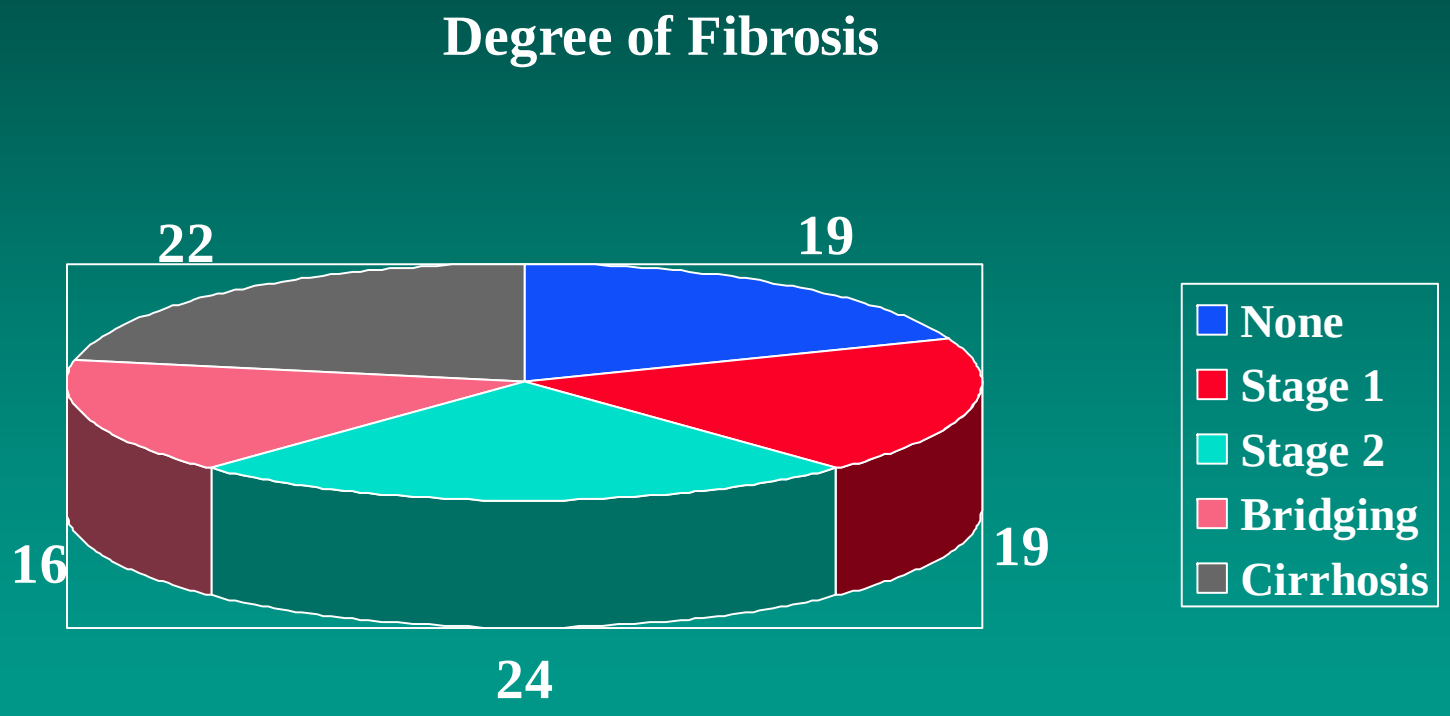
Chronic HCV

- **Diagnosis**:
  - Persistent HCV-RNA (+);
  - Most patients are anti-HCV(+).
  - Liver Bx useful to asses severity of disease.
- **False (-)** anti-HCV: 0.45% in HIV & hemodyalisis.
- **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

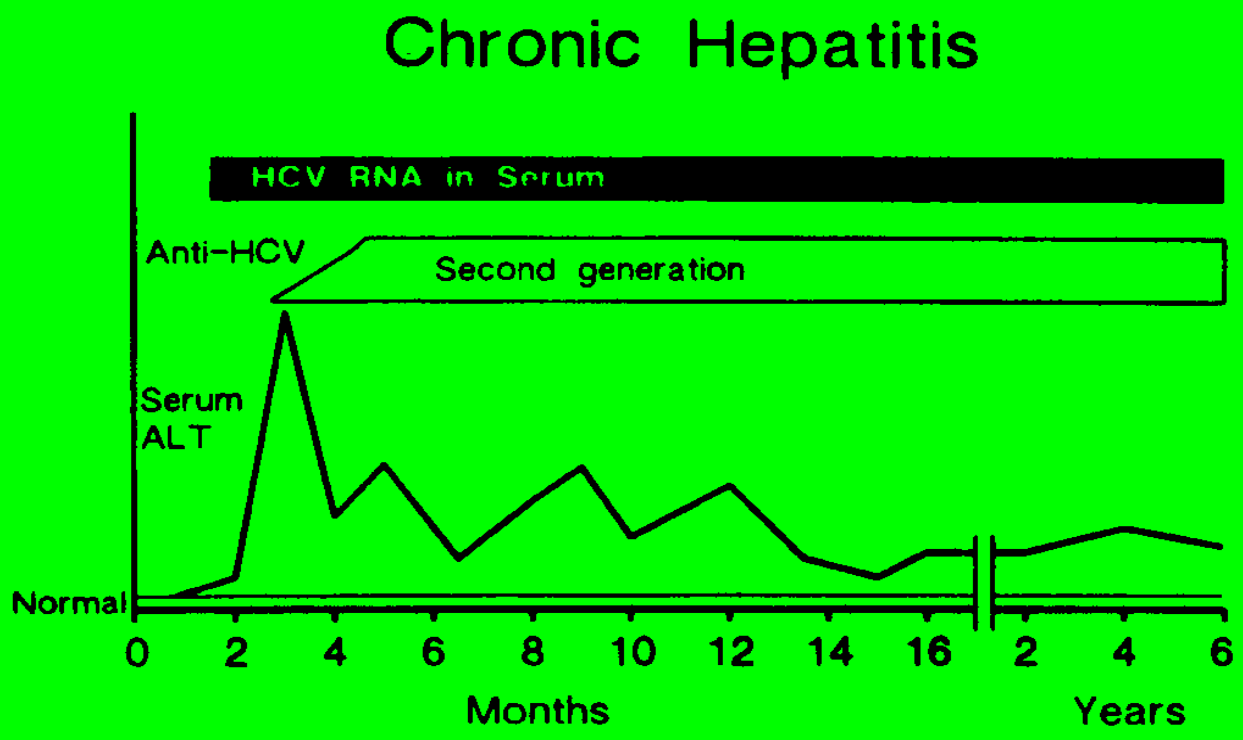


Degree of Fibrosis in Chronic HCV

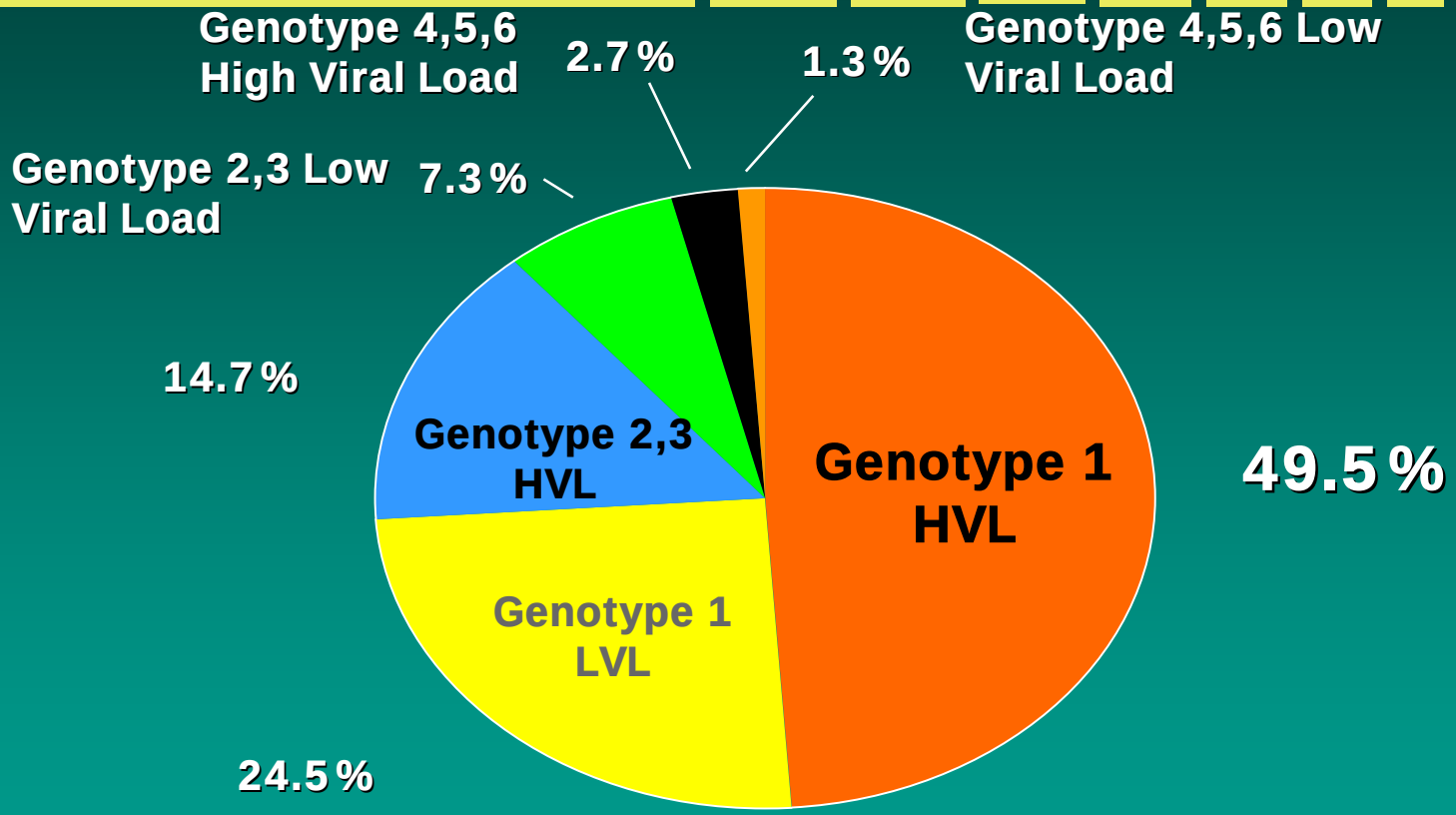


Chronic HCV

HEPATITIS C VIRUS

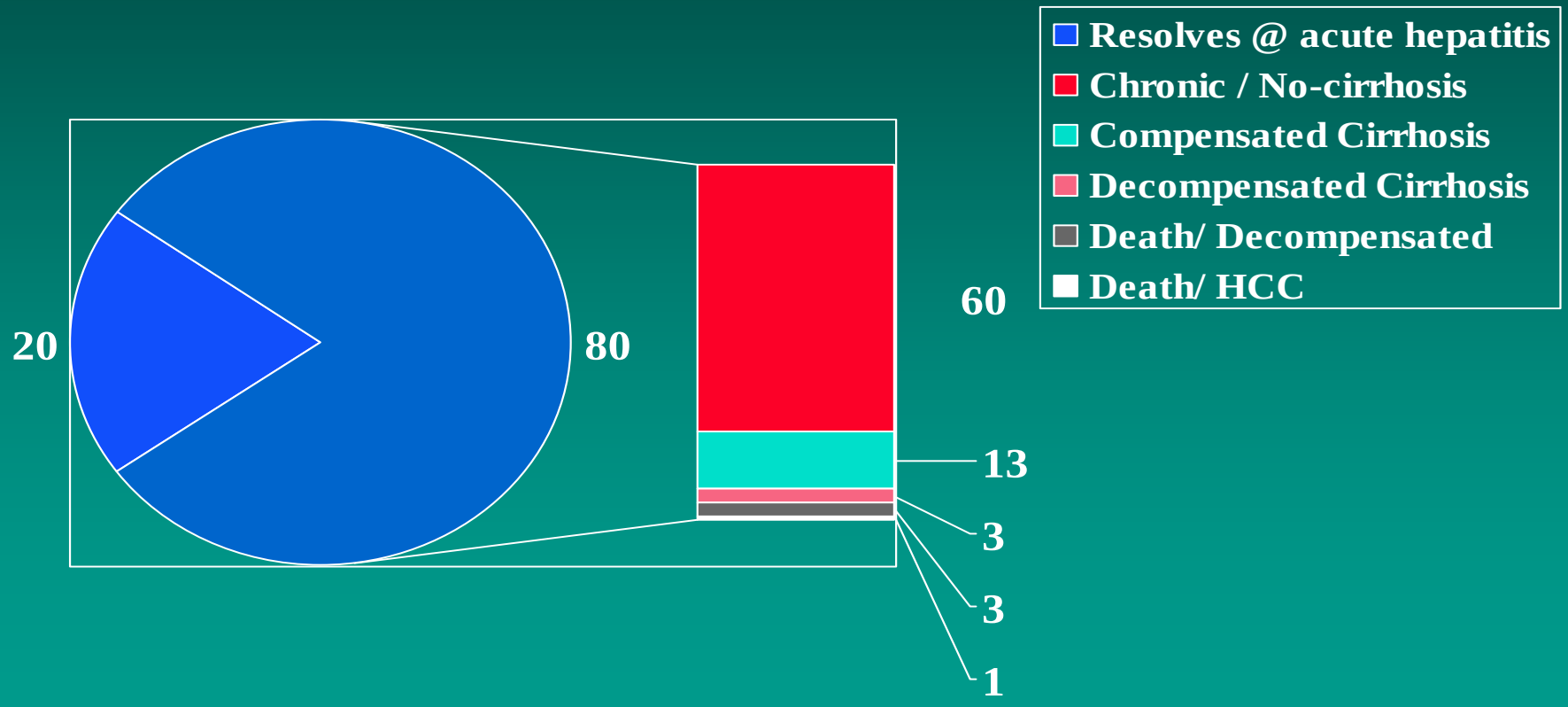


Genotype and Viral Load in US Patients



Alter et al. *N Engl J Med.* 1999;341;556-562.
Blatt et al. *J Viral Hepatitis.* 2000;7:196-202.

Outcome of HCV 25-30 year Follow-up



Factors Associated With Disease Progression

Associated with disease progression[1]	Not Associated with disease progression[1]
Alcohol consumption 30 g/day for males 20 g/day for females } ~2 drinks/day	Alanine aminotransferase level
	Viral load
	Transmission mode
Disease acquisition at >40 years	Genotype
Male gender	
Coinfection: HIV or HBV[2]	
Immunosuppression[2]	

[1]Poynard et al. *Lancet.* 1997;349:825-832.
[2]NIH. *NIH Consens State Sci Statements.* 2002;19(3):1-46.

Histological Scoring of Fibrosis

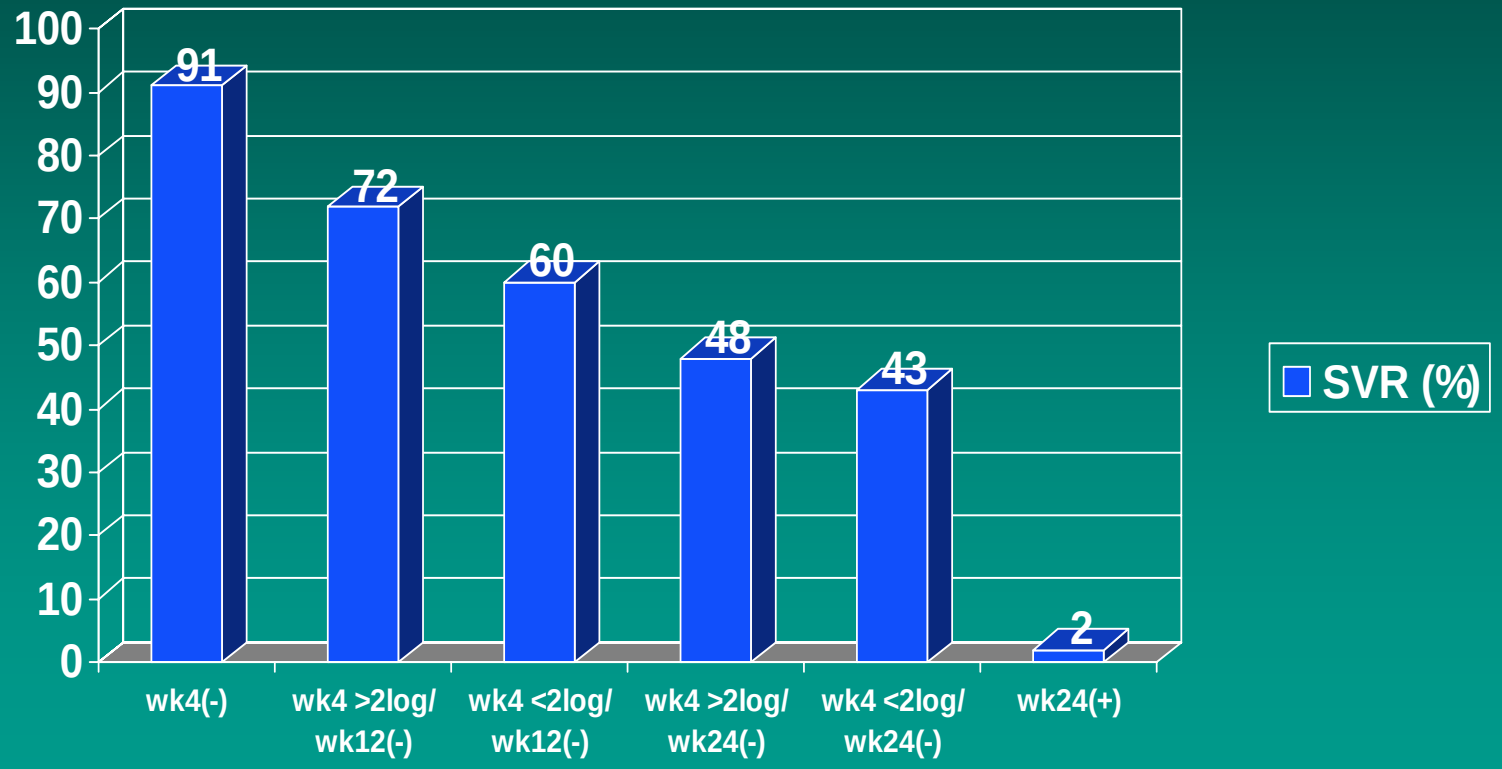
Description	Modified HAI (Ishak)	HAI (Knodell)	Batts-Ludwig, Scheuer, or IASL	METAVIR
None	0	0	0	0
Mild: Portal fibrosis (some p. areas)	1	1	1	1
Moderate: Periportal Fibrosis (most p. areas, or occasional portal-portal septa)	2	3	2	2
Severe: ***Bridging fibrosis (few / occasional bridges, any portal-central)***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

Treat METAVIR =/> 2, or Ishak/Batts-Ludwig/Scheuer/Knodell =/> 3

Treatment of Chronic HCV

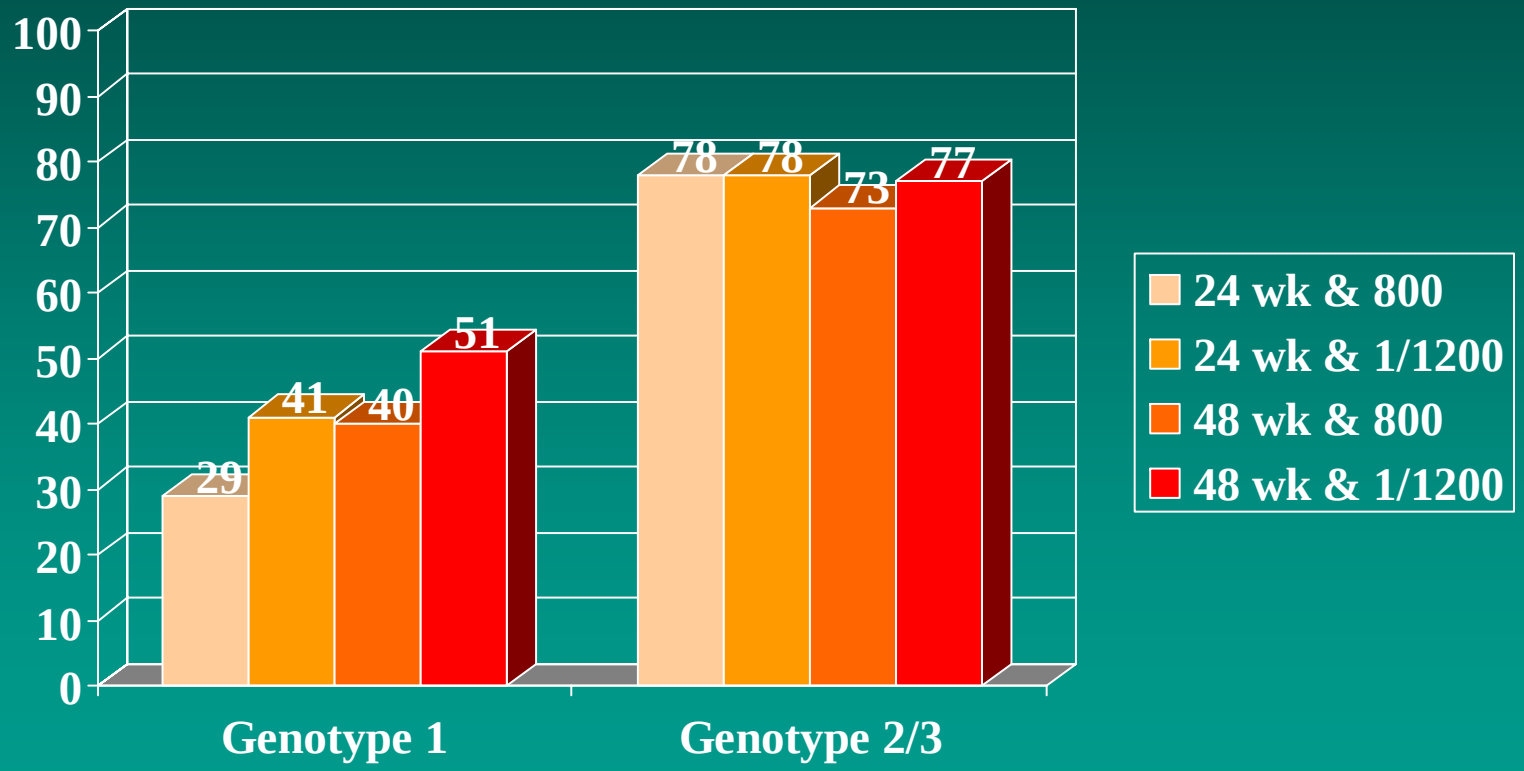
- **Genotype 1:** Peg-Interferon weekly + Ribavirin 1000-1200 mg/d + Boceprevir or Telaprevir x 24 to 48 weeks (response guided)
  - SVR: 66-75%
- **Genotypes 2 and 3:** Peg-Interferon weekly + RBV 800 mg/d x 24 weeks
  - SVR: 78-80%
- **Genotypes 4, 5, or 6:** Peg-Interferon weekly + Ribavirin 1000-1200 mg/d x 48 weeks
  - SVR: 55-60%

Predicting SVR by HCV-RNA fall
Peg-IFN alpha 2a + RBV



Ferenci P, et al. J Hepatol 2005; 43:425-433

PEGASYS + Ribavirin
Sustained Virologic Response

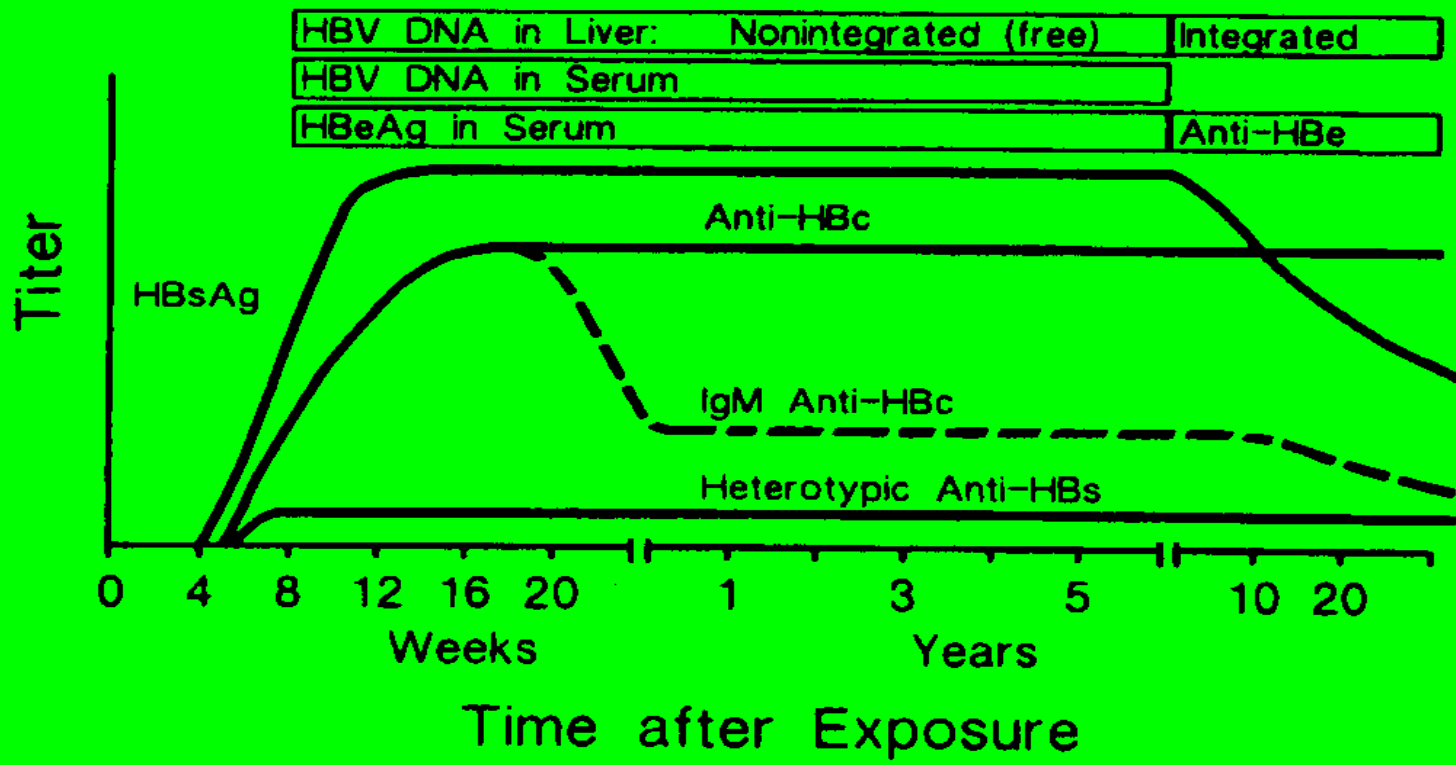


Chronic Hepatitis B

- 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



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

Fung S and Lok A. *Clin Gastro and Hepatology*. 2004;2:839-848.

Chronic Hepatitis B

- **<u>Diagnosis</u>:**
  - ***HBsAg (+)*** **& HBV-DNA (+) for > 6 months , with anti-HBc IgM (-) but anti-HBc total (+) [excludes incubation]**

States of Chronic Hepatitis B

- Inactive Carrier
- Immunotolerant
- Immunoactive
- 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

Factors	P-value
Older age	.0001
HBV-DNA persistance	.0001
Virus genotype C	.001
Recurrent acute flares	.001
Histologic Staging	.0002
Alcohol consumption	.001
HCV, HDV co-infection	.001
HIV co-infection	.02

McMahon et al. *Ann Intern Med.* 2001; 135: 759-768.

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)

Zoulim F et al. J of Hepatology 2008;48: S2-S19

	Lamivudine	Telbivudine	Entecavir	Adefovir	Tenofovir
Wild	S	S	S	S	S
M204I	R	R	R	S	S
L180M + M204V	R	R	I	S	S
A181T/V	I	S	S	R	S
N236T	S	S	S	R	I
I169T + V173L + M250V	R	R	R	S	S
T184G + S202I/G	R	R	R	S	S
I233V				Resistance ?	
A194T					Resistance ?

Treatment Options for Antiviral Resistance

Resistance to	Rescue Therapy
Lamivudine or Telbivudine	**Add:** Adefovir, or Tenofovir, or **Switch to:** Tenofovir + Emtricitabine (Truvada)
Adefovir	**Add:** Lamivudine, or Entecavir, or **Switch to:** Tenofovir + Emtricitabine (Truvada)
Entecavir	**Add:** Adefovir, or Tenofovir
Multidrug	**?**

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 immunosupression.
  - 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.
  - 1st 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

Surveillance Test

- **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
- [HBsAg(+) & increased liver enzymes > 6 months] + [anti-HDV(+) high titers **or** HDAg(+) in liver biopsy]
- More aggressive than chronic HBV
- INFα 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 = 13.3g)**
- 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%

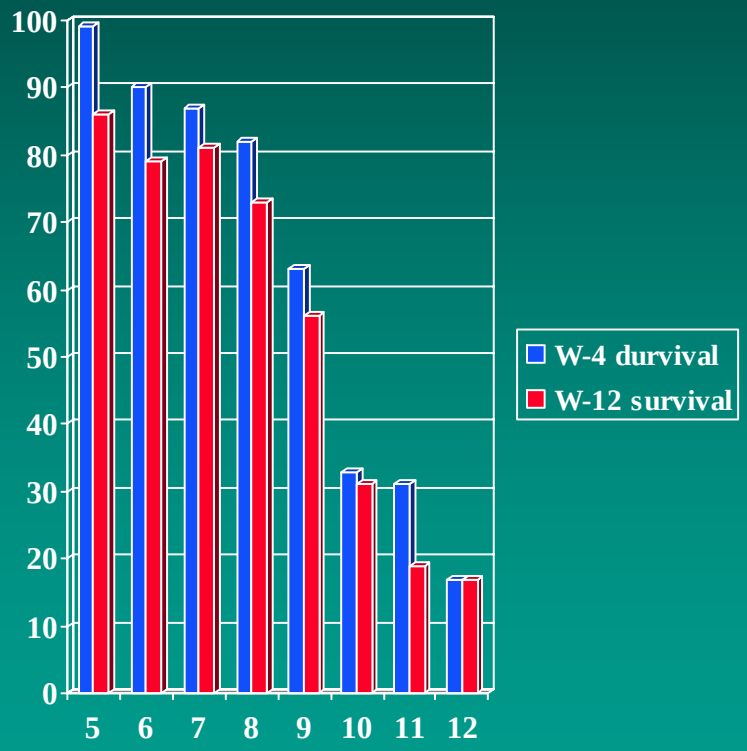
Glasgow Alcoholic Hepatitis Score

GUT 2005;54:1174-1179

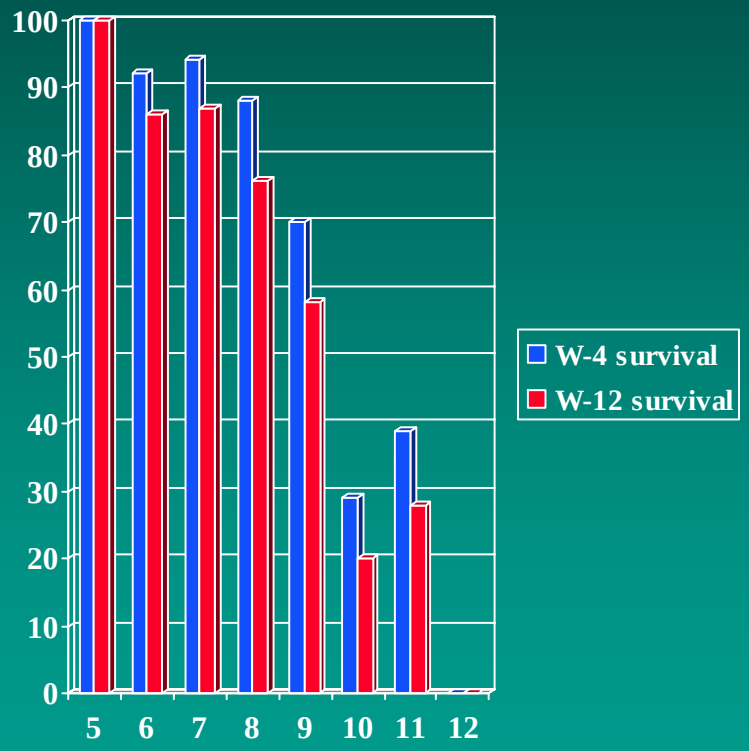
POINTS	1	2	3
Age	< 50	> 50	
WBC count	< 15	> 15	
BUN	< 14	> 14	
INR	< 1.5	1.5 - 2	> 2
T. Bili	< 7.35	7.35 – 14.7	> 14.7

Minimum = 5; Maximum = 12 points

Survival by GAHS

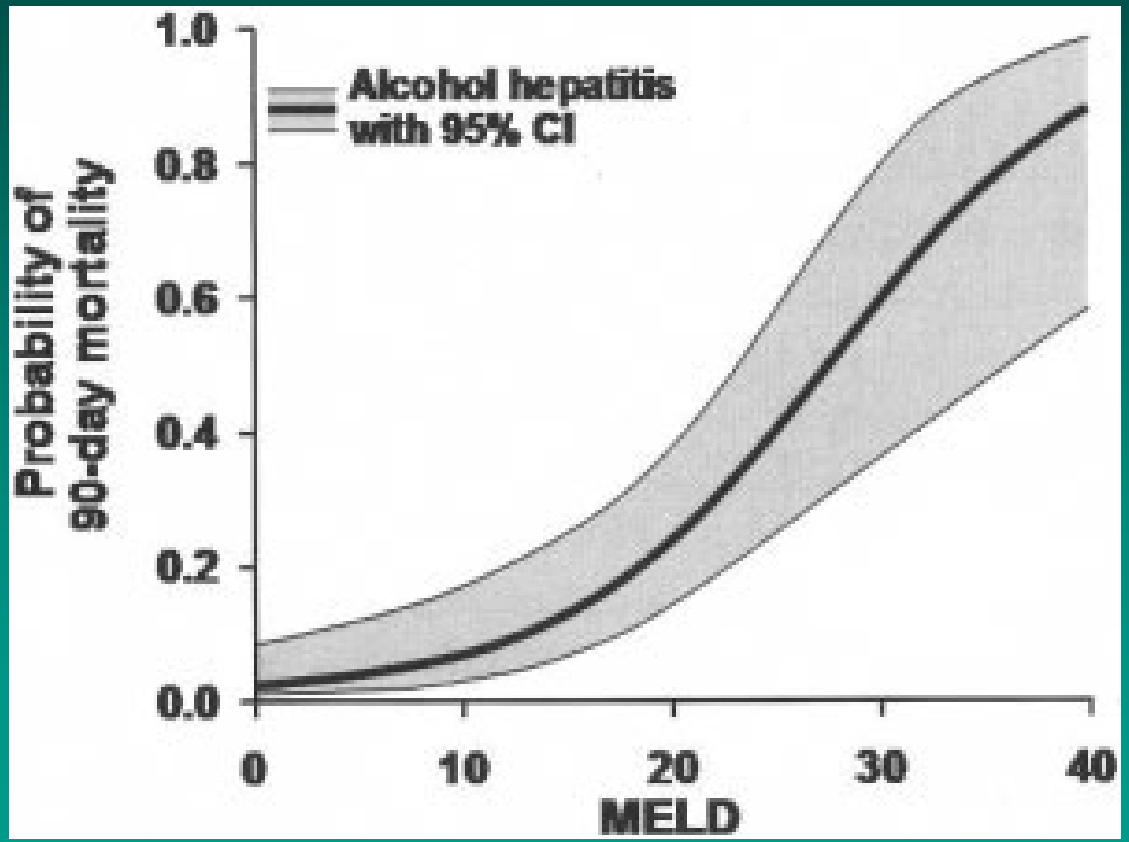


Day 1 score



Day 7 score

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**).



HEPATOLOGY 2005;41:353-358

http://www.mayoclinic.org/meld/mayomodel7.html

MELD was calculated using the following formula:
MELD9.57loge (Cr mg/dL)3.78loge (bili mg/dL)11.20loge (INR)6.43.16

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, - diabetes 66%,
  - obesity 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 > 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-LC_1, 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)

Gender	Female	**+3**
Alk Ph/AST ratio	>3	**-2**
	< 1.5	**+2**
IgG or gamma-glob above Normal	> 2	**+3**
	1.5-2	**+3**
	1-1.5	**+1**
ANA, ASMA, or anti-LKM1 titer	> 1:80	**+3**
	1:80	**+2**
	1:40	**+1**
	< 1:40	**0**
AMA	Positive	**-4**
Viral markers	Positive	**-3**
	Negative	**+3**
Drugs	Yes	**-4**
	No	**+1**
Alcohol	< 25 g/day	**+2**
	> 60 g/day	**-2**

Revised AIH Score (2 of 2)

HLA	DR3 or DR4	**+1**
Immune disease	Thyroiditis, colitis, other	**+2**
Other auto-Ab	Anti-SLA, anti-actin, anti-LC1, pANCA	**+2**
Histology	Interface hepatitis	**+3**
	Plasmacytic infiltrate	**+1**
	Rosettes	**+1**
	None of above	**-5**
	Biliary changes	**-3**
	Other feature	**-3**
Treatment response	Complete	**+2**
	Relapse	**+3**
Pre-Treatment Aggregate Score	> 15	**Definite Diagnosis**
	10-15	**Probable Diagnosis**
Post-Treatment Aggregate Score	> 17	**Definite Diagnosis**
	12-17	**Probable diagnosis**

Auto-Immune Hepatitis Simplified Scoring

Variable	Result	Points
ANA or ASMA	>/= 1:40	+1*
	>/= 1:80	+2*
Anti-LKM1	>/= 1:40	+2*
Anti-SLA	+	+2*
Immunoglobulins level	> ULN	+1
	> 1.1 ULN	+2
Histology	Compatible	+1
	Typical	+2
Viral hepatitis markers	Absent	+2
DEFINITIVE AIH		**>/= 7**
PROBABLE AIH		**6**

*** 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-LKM_1
  - 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 & Other Primary Fe-Overload

- **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^{nd}-3^{rd} decade.**
    - » **Onset 1-2 decade before HHC (2^{nd} to 4^{th}).**
    - » **Mild to severe Liver Fe overload (periportal hepatocytes). Hypochromic anemia.**
    - » **May cause cirrhosis.**

Non-HFE Hemochromatosis & Other Primary Fe-Overload

- **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 1st & 2nd decade**
- **H-FERRITIN ASSOCIATED HEREDITARY Fe-Overload**
  - **Autosomal dominant.**
  - **Increased Fe influx.**
  - **Liver Fe overload in 4th-5th decade**

α_1-antitrypsin Storage Disease

- Phenotype Pi ZZ (Mmalton, Mduarte, MZ, SZ, and MS may worsen other types of liver disease).
- Low serum α_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 recesive.
- 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.

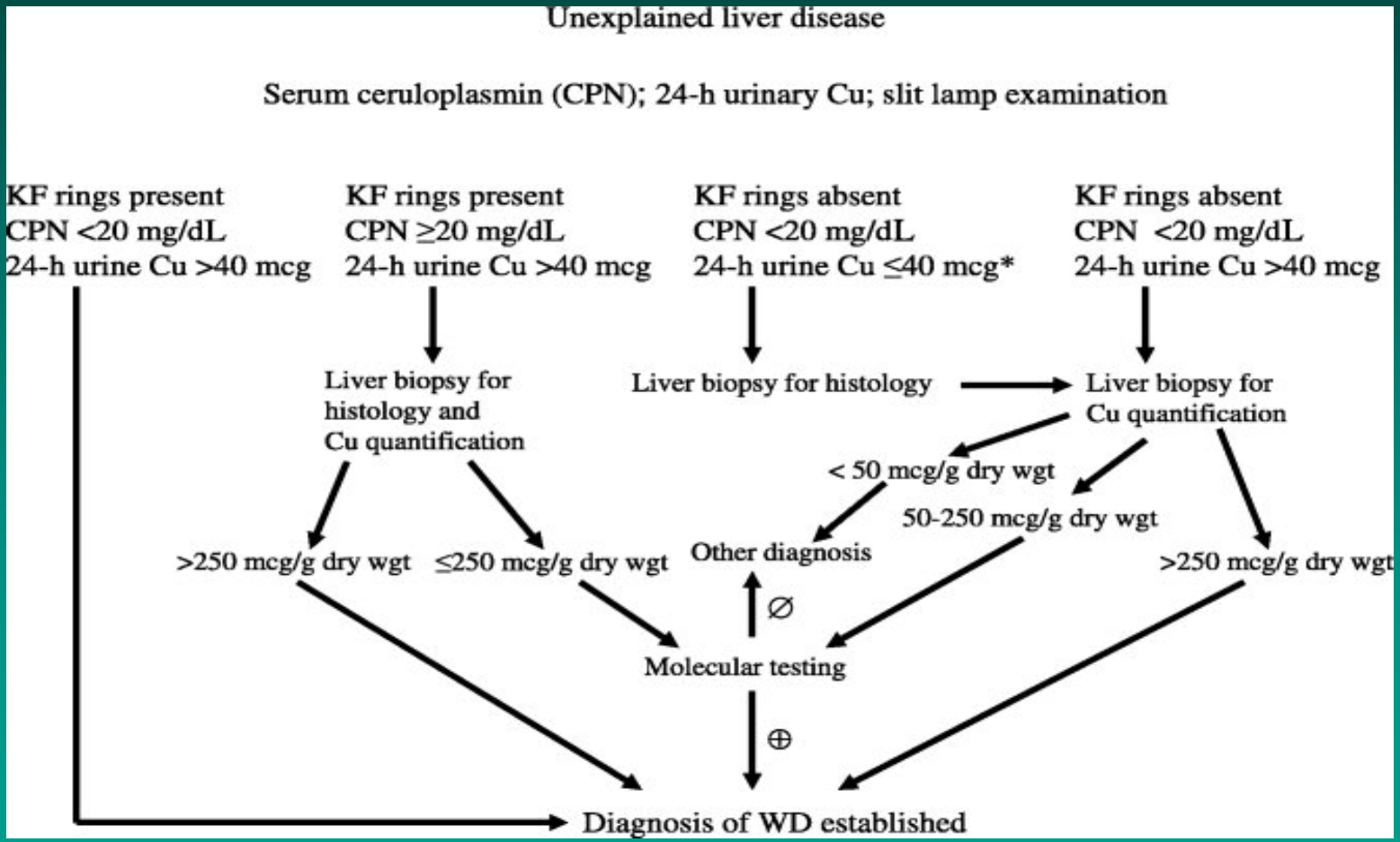
Wilson's Disease

- 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

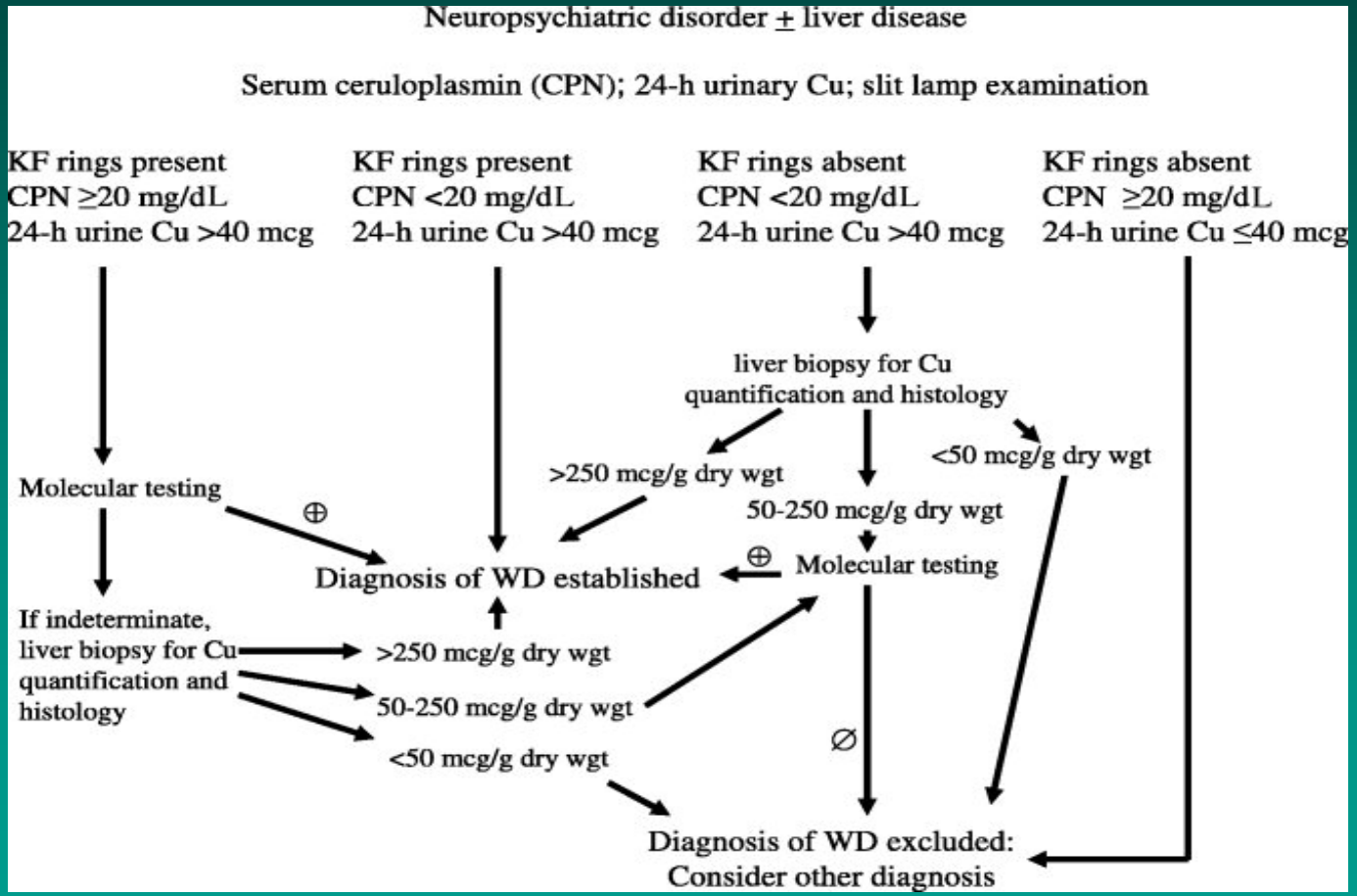
- **Diagnosis:** consider diagnosis in ages 3 to 55.
  - 1) Low ceruloplasmin + K-F Rings;
  - 2) Hepatic copper > 250 μg/g dry weight (1-2 cm core) in absence of chronic cholestasis + consistent histology
  - 3) 24 hour urine Cu > 40 mcg/day
  - 4) Direct mutation analysis (whole-gene sequencing), or studies based in "proband" mutant, for ATP7B mutation.

Algorithm for Diagnosis of Wilson disease: Unexplained Liver Disease



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



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#fig2

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 compliace; < 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, solfonamides, 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-E_2, 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/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

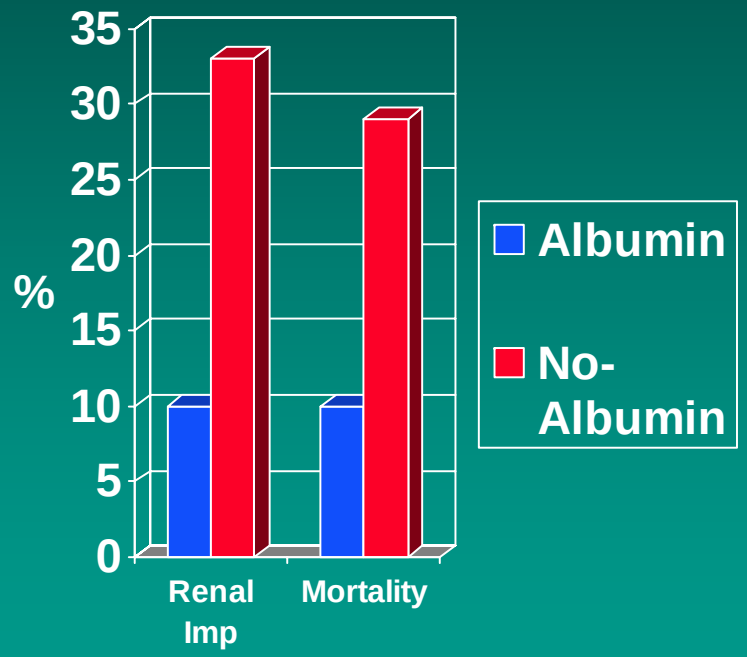
- ***ALBUMIN in SBP***

- 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

SBP & HRS

(Sort et al. NEJM 1999;341:404-409)

- 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

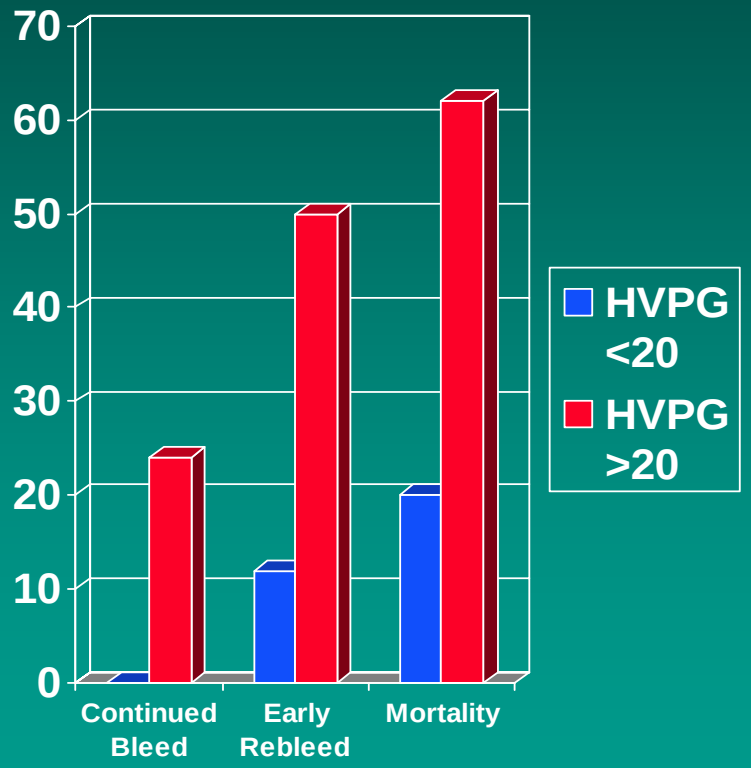


Variceal Bleeding

- 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



Gastrenterology 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

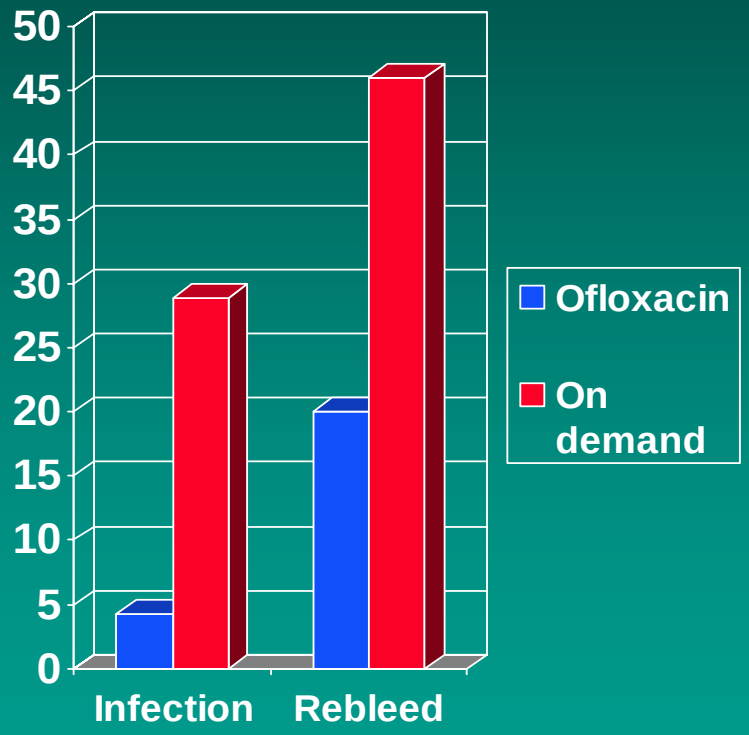
Risk Factors
Rebleeding in > 6 weeks

- 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