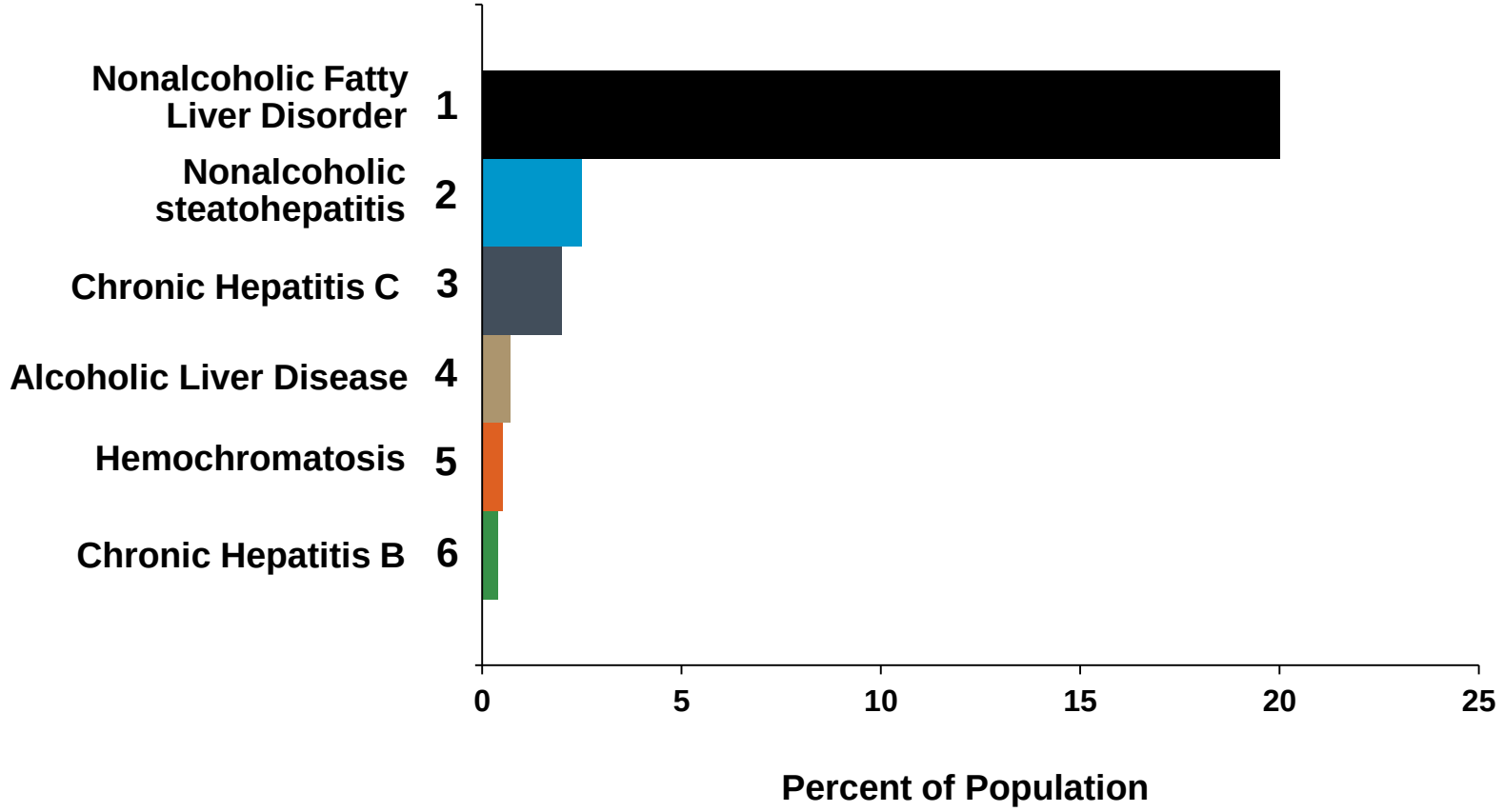
Not All Patients With Liver Disease Have HCV

Diagnosis and Management of Some Common Non HCV Liver Diseases

Prevalence of Chronic Liver Disorders in the United States



1. Hilden M et al. *Scand J Gastroenterol*. 1977;12:593-597.
2. Ground KEU. *Aviat Spac Environ Med.* 1982;53;14-18.
3. Alter MF et al. *N Engl J Med.* 1999;341:556-562.
4. Venkataramani A et al. In: Maddrey WC, Feldman M, eds. *Atlas of the Liver.* Philadelphia: Current Medicine;1999:9.0.
5. Adapted from http://www.nhlbi.nih.gov/new/press/01/09 -25.htm. Accessed 11/01/02.
6. McQuillan GM et al. *Am J Public Health* 1999;89:14-18.

Chronic Liver Disease Prevalence In New York University Clinical Practice

- Chronic Hepatitis C
- Non Alcoholic Fatty Liver Disease
- Cryptogenic Cirrhosis
- Alcohol Related Liver Disease
- Chronic Hepatitis B
- Primary Biliary Cirrhosis
- Autoimmune Liver Disease
- Hemochromatosis
- (Hepato Celllular Carcinoma)

Non Alcoholic Fatty Liver Disease

- Major risk factors
  - Central obesity
  - Diabetes
  - Hyperlipidemia
  - Metabolic syndrome (insulin resistance, hypertension)
- Usual age 40s – 50s

- Possible associated conditions
  - Polycystic ovarian syndrome
  - Hypothyroidism
  - Hypogonadism

Alternate Causes of Hepatic Steatosis

- Alcoholic Liver disease
- Hepatitis C (esp. Genotype 3)
- Starvation
- Parenteral Nutrition
- Abetalipoproteinemia
- Reye's syndrome
- AFLPregnancy
- HELLP Syndrome
- Wilson's Disease
- DILI
- Medications:
  - Methotrexate
  - Amiodarone
  - Tamoxifen
  - Steroids
  - Valproate
  - HIV drugs
- Various inborn errors of metabolism, lypodystrophy

NAFLD and Cirrhosis

- NAFLD is major cause of “cryptogenic cirrhosis”
- Cirrhosis occurs when steatosis progresses to steatohepatitis (inflammation) and fibrosis
- Major risk factor for progression to cirrhosis is presence of inflammation on liver biopsy
- Other risk factors: older age, DM, ALT >2X ULN, ballooning degen on liver bx, BMI>28, obesity, alcoholic intake >60g/day
- Increased risk of HCC with or without cirrhosis

Diagnosis of NAFLD/NASH

- Demonstration of steatosis by imaging or biopsy
- Exclusion of alcohol etiology & other specific causes
- Hepatomegaly (only 10-18%)
- Abnormal enzymes: AST & ALT 2X-5X ULN, AST: ALT ratio <1,(vs ETOH >2) AP 2-3X ULN
- Normal enzymes do not preclude significant histopathology
- Increased iron and ferritin may be present

Imaging Studies in Diagnosis of NAFLD

- Ultrasound
  - 85% sensitivity
  - 94% specificity
  - Sensitivity markedly reduced in morbid obesity (49%)
- Non Contrast CT
  - Sensitivity 33%
- Contrast CT
  - Sensitivity 50%
- MRI
  - Sensitivity 88%

- Transient elastography (Fibroscan®) of limited value to evaluate fibrosis in patients with marked steatosis
- Liver biopsy to definitively establish level of inflammation

NAFLD/NASH Treatment

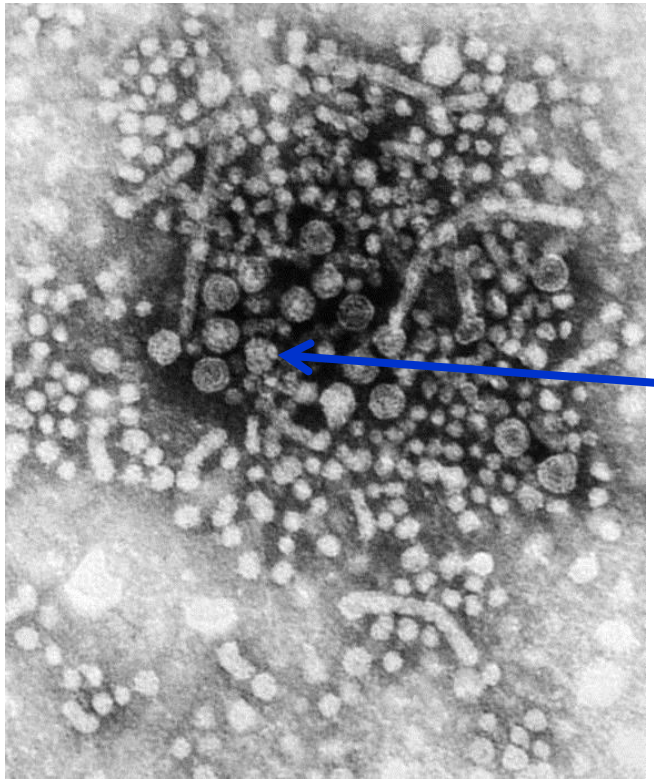
- Low carbohydrate weight loss diet
  - Aim for 1-2 lbs/week
- Exercise
- Avoid alcohol
- Screen all NASH cirrhosis for cancer

NAFLD/NASH Treatment

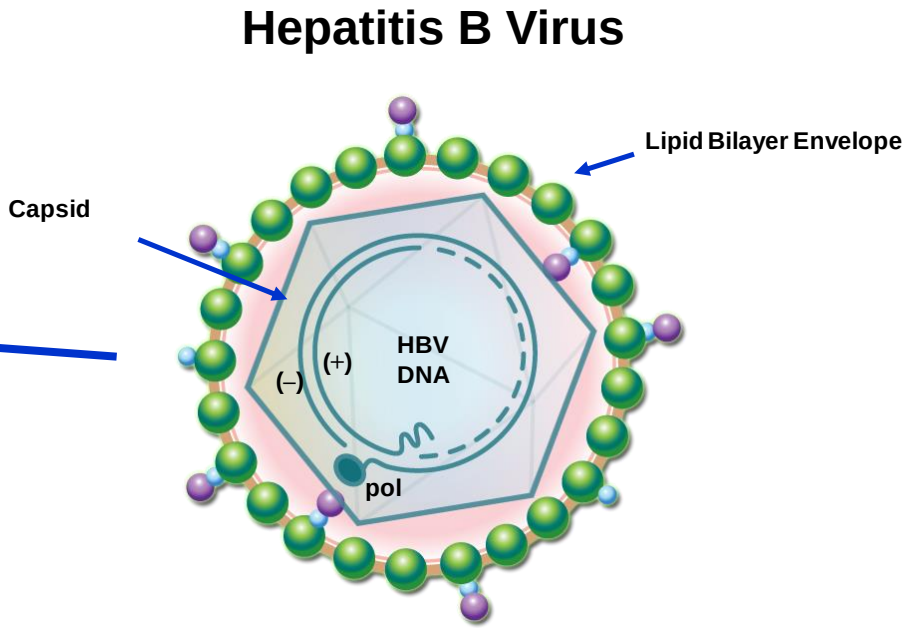
- Vitamin E 800 ug/day
- Pioglitazone
- Rosiglitazone
- Atorvastatin,
- Pentoxifylline
- Omega 3 fatty acids
- Branched Chain Amino Acids
- SAMe
- Losarten
- Metformin & Urso: not proven helpful

Chronic Hepatitis B

Hepatitis B Virus (HBV)



Transmission electron micrograph of HBV from blood of patient with hepatitis B



Hepatitis B Epidemiology

- About 2 billion persons world wide are infected with HBV
- About 800 million people have chronic hepatitis B
- Over 2 million persons in US have chronic hepatitis B
- Highest incidence in US is in Asian population with estimates of 8 to 12%
- Patients infected with HBV at birth have 95% chance developing chronic disease
- Those infected in adulthood– 5% CHB

Presentations of Hepatitis B

- Asymptomatic carrier of hepatitis B virus with normal liver enzymes
- Asymptomatic carrier of hepatitis B virus with ongoing hepatitis
- HBV infected patient with cirrhosis, stable or decompensated
- HBV infected patient with HCC
- HBV patient with acute liver failure
- ***Acute HBV flare resulting from non prophylaxis prior to chemotherapy or immunosuppression***

Evaluation for HBV Liver Disease

- Asian population is high risk group and must be screened, whether or not they have evidence of ongoing hepatitis
- Majority of virus carriers are unaware they have disease
- Panel of HBV serologic tests should be performed
- Patients with any serologic positivity should have HBV DNA determination
- Imaging studies need to be done to r/o occult cirrhosis and HCC

ALT as Measure of HBV

- Elevation of ALT indicates liver injury
- New surveys indicate normal as 19 for woman and 30 for men
- Initial normal levels of ALT may fluctuate and should be assessed every three months
- Poor correlation between normal ALT and the extent of liver injury
- Up to 40% of CHB individuals with normal ALT may have significant fibrosis on liver biopsy

Serological Markers of HBV

- HBsAg: marker of HBV infection
- HBsAB: marker of HBV immunity / recovery
- HBeAg clinical marker of infectivity and replication
- Anti Hbe: antibody to HBeAg, may indicate recovery from infection
- Anti HBc: IGM (current acute infection or flare)or IGG (current, non acute or past infection)

Hepatitis B and Hepatocellular Carcinoma

- Hepatitis B patients develop carcinoma without developing cirrhosis
- 70% of HBV deaths are due to HCC
- Asian Americans are almost 3X as likely to develop HCC as other Americans
- Persons with highest viral counts are most likely to develop HCC

The Reveal Study

- Almost 4000 chronic hepatitis B patients in Taiwan
- Risk of cirrhosis increased directly with viral HBV DNA load
  - Starting with viral loads as low as 300 c/ml (1.4X) up to viral loads of 1 million (9.8X)
- Risk of hepatocellular carcinoma also increases directly with viral load
  - Highest risk when HBVDNA >1 million

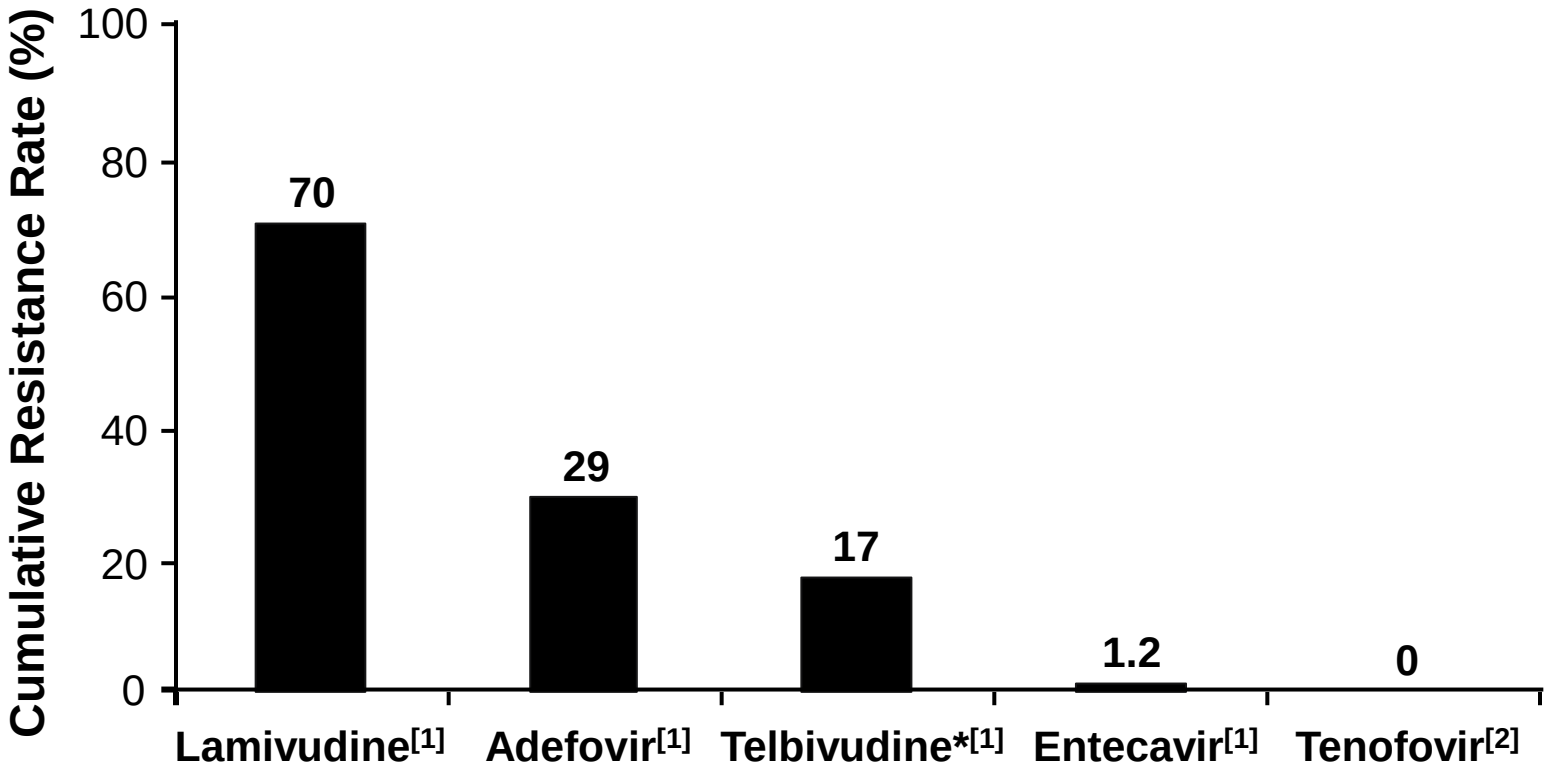
Progression of HBV Disease

- Up to half of chronically infected patients will develop progressive liver disease with ongoing liver injury and increasing fibrosis
- Ultimate progression to cirrhosis and HCC
- ***Viral suppression prevents progression***

HBV: Who Should Be Treated?

- Multiple guidelines from various professional societies differ in recommendations
- Essentially all HBV patients with elevated ALT are candidates for treatment
- All HBV patients with viral counts above 10K are potential candidates for treatment
- All HBV cirrhotics are candidates for treatment

5-Yr Rates of Resistance With Oral Agents in Nucleos(t)ide-Naive Patients



*Telbivudine rate determined at Yr 2.

1. EASL. *J Hepatol*. 2009;50:227-242. 2. Marcellin P, et al. AASLD 2011. Abstract 1375

Primary Biliary Cirrhosis

Primary Biliary Cirrhosis

- A chronic autoimmune liver disease caused by T-Lymphocyte mediated destruction of small intralobular bile ducts
- 90-95% women
- Onset typically between 30-65 years of age
- > 60% of patients are asymptomatic at diagnosis
- Fatigue is most common complaint
- Pruritus may present in pregnancy and be mistaken for cholestasis of pregnancy (but doesn't resolve post partum)

PBC: Autoimmune Markers

- High IgM
- Anti-mitochondrial antibody (AMA)
  - 95% positive
- **M-2**, M-4, M-8, M-9 antibodies
  - Directed at pyruvate dehydrogenase E-2

PBC: Diagnosis

- Middle aged women with cholestasis
- Alkaline phosphatase 3-4X normal or more
- Mild transaminase elevations
  - Up to 5X normal
- Positive AMA (95% of cases)
- Positive ANA (70%)
- Elevated IgM
- Elevated serum bile acids
- Liver biopsy confirms and stages

PBC Associated Conditions

- *Sjogrens* syndrome: keratoconjunctivitis (dry eyes) and xerostomia (dry mouth) in 40-70%
- “Classic *rheumatoid arthritis* 5-10%
- *Scleroderma* and *CREST* syndrome (calcinosis cutis, raynauds, esophageal dysmotility, sclerodactyly, telangiectasia) up to 15% patients
- Right upper quadrant discomfort
- Osteoporosis & osteomalacia
- Hyperpigmentation (not jaundice) and xanthoma

Treatment of PBC

- **Ursodeoxycholic Acid**
  - 13-15mg/kg is first line treatment suppressing in inflammatory bile ductule destruction
  - Stage 1 & 2 patients treated with UDCA generally have normal life expectancy
  - 20-25% of PBC patients do not respond adequately to UDCA
  - Combination therapy with **UDCA** and **budesonide** may be promising
  - Triple therapy with **UDCA, budesonide**, and **micophenolate mofetil** under study
  - Fibrates (**fenofibrate**) added to UDCA has been shown to improve biochemical response
- **Obeticholic Acid (**farnesoid X receptor agonist) positive trials in UDCA non responders
- Use of methotrexate and colchicine is questionable and discouraged
- Liver Transplantation is relatively uncommon in era of UDCA treatment

Primary Sclerosing Cholangitis

- Chronic cholestasis associated with chronic inflammation of the biliary epithelium
- Multifocal bile duct strictures that can affect the entire biliary tree.
- Progression can lead to fibrosis and eventually cirrhosis as well as cholangiocarcinoma
- Median age onset 40 years
  - > 90% male
- Survival:
  - Asymptomatic patients: median 12-18yrs
  - Symptomatic patients median 9 yrs

PSC: Presentation

- Asymptomatic
- Fatigue
- Pruritus
- Cholangitis
- Jaundice

Diagnosis of PSC

- Increased serum alkaline phosphatase is hallmark of disease
- Aminotransferase frequently normal but may be up to 2X-3X ULN
- Higher values indicated acute obstruction or overlap (AIH) syndrome
- MRCP can identify changes in biliary system (partiuclarly in IBD subjects)
- No specific serologic tests available
- IGG4 disease should be ruled out-especially in those with pancreatitis

Immunoglobulin Associated G4 Cholangitis

- 23% of liver explants from PSC patients have infiltration with IgG4 positive cells
- These patients have a more aggressive disease course
- 40% of subjects with increased IgG4 levels did not have IgG4 positive tissue
- IgG4 disease is usually accompanied by pancreatitis
- IgG4 disease responds to steroids
  - PSC does not

IBD and PSC

- All patients with PSC should undergo colonoscopy and biopsy for IBD even when asymptomatic
- Recent studies suggest more patients are being diagnosed with PSC before IBD
- PSC increases the colon cancer risk of IBD
  - Surveillance colonoscopy indicated in all PSC patients
- PSC can be diagnosed after colectomy
- IBD can develop after liver transplant

PSC: Therapy and Role of Liver Transplant

- Ursodiol is treatment of choice
  - Proof that it affects natural history of disease in most patients is lacking
- 5th most common cause of liver transplantation (in U.S.)
- Survival 1/5 years = 90%/80%
- Exception points for recurrent cholangitis
- 25% of OLTX recipients suffer recurrent PSC within ten years.

PSC and Cholangiocarcinoma

- PSC life time risk of cholangiocarcinoma is up to 10%
- Not found in conjunction with cirrhosis
- Monitoring with levels of CA 19-9
- Cut off of Ca 19-9 of 130 U/ml, in absence of bacterial cholangitis detects CCA with 79% sensitivity and 98% specificity
- Brush cytology with “FISH” may be useful
- Transplant survival after dx of CCA is very poor unless cancer has been totally eradicated preop (Mayo Clinic protocol)
- Increased risk of GB neoplasia

Autoimmune Hepatitis

- Chronic inflammation of the liver of unknown cause
- T cell mediated immune attack upon liver antigens leads to progressive necroinflammatory /fibrotic process with progression to cirrhosis
- May present asymptomatically or with severe liver failure
  - 40% present asymptomatically
- 70% of asymptomatic patients become symptomatic in their life time

AIH Diagnostic Criteria

- Elevated ALT/AST
- Elevated gamma globulin (IgG)
- Positive smooth muscle antibody / and ANA, or LKM1 (in children)/sometimes AMA
- Negative viral markers
- Negative DILI history
- Coexistent immune diseases
- Histology: plasma cell infiltrate, interface hepatitis
- Other autoimmune serologies: soluble liver antigen (SLA), anti liver cytosol (anti LC1), p-ANCA

Type 1 AIH

- 70% women
- Bimodal incidence
- Presentation
  - Insidious
  - Acute hepatitis
- Antibodies
  - 33% ANA
  - 100% ASMA
  - 2% AMA
- 43% cirrhosis in 3 yrs

Adapted from Czaja DDS 1995

Type 2

- Children 2-14 yo
- Europe > USA
- + LKM
- >80% cirrhosis in 3 yrs
- 30% anti-parietal cell Ab

- Extrahepatic associations
  - Vitiligo
  - IDDM
  - AIHA
  - Thyroiditis
  - ITP

Homberg Hepatology 1987

Treatment of AIH

- Untreated asymptomatic patients have marked impairment of survival
- Patients with AST/ALT >5X ULN, elevated gamma globulin, and histologic disease activity must be treated
- Initial treatment regimen 40-60mg prednisone or 30 mg prednisone plus 50mg azathioprine
- After response prednisone is tapered
- Azathioprine can be increased up to 2 mg/kg
- Budesonide (9mg) has been used for induction and maintenance in milder cases
- Goal of therapy is normalization of enzymes
- Liver biopsy assessment prior to termination of treatment is the only way to ensure full resolution.
- Histologic resolution lags up to 8 months behind enzyme resolution
- Patients should be treated 1-2 years post enzyme resolution
- Post treatment patients should be carefully monitored regularly for recurrence

AIH Treatment Failure

- Treatment failures should be managed with high dose prednisone (60mg/day) or prednisone of varying dose combined with 150mg azothioprine
- Alternate therapies of cyclosporine, mycophenolate mofetil or tacrolimus may be considered
- Liver Transplantation for those presenting with acute liver failure or developing decompensated cirrhosis
- Recurrent autoimmune disease (30%) following transplantation remains a significant problem
- Immunosuppressive therapy does not help in “burned out” cirrhosis patient
- HCC Cancer risk in AIH is 3% within 10 years and related to development of cirrhosis