



ACOFP 46th Annual Convention & Exhibition

March 4-8, 2009

Gaylord National Resort & Convention Center
Washington, D.C.

Current Thoughts and Analysis of Hepatitis and Liver Function

Scot M. Lewey, DO, FACG, FACP, FAAP, FACOP

Saturday, March 7, 2009

11:00 am–12:00 pm

CME/CEU Information

The American College of Osteopathic Family Physicians is accredited by the American Osteopathic Association Council to sponsor continuing medical education for osteopathic physicians.

The American College of Osteopathic Family Physicians has requested that the AOA Council on Continuing Medical Education approve this program for 1 hour of AOA Category 1A CME credit. Approval is currently pending.

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Name of CME Activity: ACOFP 46th Annual Convention & Exhibition

Dates and Location of CME Activity: March 4-8, 2009, Gaylord National Resort and Convention Center, National Harbor, MD

Topic: Current Thoughts and Analysis of Hepatitis and Liver Function

Name of Faculty/Planner/Author/Editor/Reviewer: Scott M. Lewey, DO, FACP, FAAP, FACOP

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Signature: Scott M. Lewey Date: 1/28/09

Please fax this form to ACOFP at 866-328-1835 as soon as possible. Deadline: January 20, 2009.

“A Practical Approach to Abnormal Liver Enzymes and Hepatitis Tests”

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Lecture Objectives

- **Present a practical approach to ↑ liver enzymes & viral hepatitis.**
- **Review diagnostic tests, general treatment guidelines and when to refer.**



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Approach to Abnormal Liver Tests

- Acute or chronic?
- Mild (<2x), moderate (2-5x) or severe (>10-15x)
- Predominantly hepatocellular, cholestatic, mixed pattern, or an isolated abnormality?
- Additional tests?
- Is a liver biopsy indicated?
- Does patient need a referral for transplant?



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Abnormal Liver & Viral Hepatitis Tests Are Common

- Prevalence of Abnormal Liver Tests
 - 9% population
 - 2.5% of healthy people fall outside bell curve
 - Multiple tests >>likelihood a test is abnormal
- Incidence and Prevalence of Viral Hepatitis
 - ~ 1 million new cases/yr acute hepatitis A
 - ~ 3/4 million new cases/yr of acute hepatitis B
 - 2.8-4 million chronically infected with hepatitis C
 - > 1 million chronically infected with hepatitis B



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What Are Liver Tests Have Been Traditionally Known as “LFTs”?

- **AST (Aspartate Aminotransferase)**
- **ALT (Alanine Aminotransferase)**
- **Alkaline Phosphatase**
- **Total Bilirubin**
- **May be abnormal in absence of liver disease**
- **May not be abnormal with liver dysfunction**



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How Do We Measure Liver Function?

- **Biosynthetic function tests**
 - **↑ Protine (PT) and INR**
 - **↓ Albumin**
- **Clinical scores of hepatic decompensation**
 - **Childs-Pugh Grade or Childs Turcotte Pugh**
 - **MELD, MELD-PELD Scores**
 - **Online calculator at www.unos.org**



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Childs-Pugh Score

Parameter	1 Point Each	2 Points Each	3 Points Each
Ascites	Absent	Slight	Moderate
Bilirubin	<2 mg/dl	2-3 mg/dl	>3 mg/dl
Albumin	>3.5 g/dl	2.8-3.5 g/dl	<2.8 g/dl
↑PT sec > control	<4	4-6	>6
INR	<1.7	1.7-2.3	>2.3
Encephalopathy	None	Grade 1-2	Grade 3-4

Childs Grade A = 5-6	Childs Grade B = 7-9	Childs Grade C = 10-15
Well-Compensated	Significant Compromise	Decompensated Disease



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Basic Lab Screen for Liver Disease

- Liver chemistries
 - AST, ALT, Alkaline phosphatase, Bilirubin
- Protine (PT)
- Albumin
- CBC with platelets
- Sedimentation rate



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Hepatocellular Predominant Pattern

- **↑↑ AST & ALT elevations predominate**
- **Alkaline Phosphatase & GGT nl to ↑**
- **Bilirubin normal in mild injury**
- **Bilirubin high in severe injury**



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Cholestatic Predominant Pattern

- **↑↑ Alkaline Phosphatase**
– **↑↑ GGT**
- **Normal to minimal ↑ AST & ALT**
- **Bilirubin usually ↑ to ↑↑ Elevated**



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Mixed Pattern

- **↑AST & ALT elevated**
- **↑Alkaline Phosphatase & ↑GGT**
- **Bilirubin usually ↑ but may be normal**



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Elevated AST & ALT <2-5x Normal

- **Hepatitis A, B, & C serology**
- **Iron Studies (Fe, Ferritin, Iron saturation)**
- **Autoimmune/ANA Panel**
- **Celiac Sprue Panel**
- **Thyroid Functions**
- **Fasting Lipid Panel**



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Initial Work-up Chronic ↑AST ALT 2-5X ULN

- Screen for alcohol use/abuse
 - Social history & problem drinking screening tools
 - AST:ALT >2:1, elevated GGT
- Viral hepatitis serology (HBsAg, HBcAb, HCV antibody)
- Screen for hemochromatosis (Fe/TIBC >45%, ↑ferritin)
- Autoimmune markers (ANA panel)
- Screen for fatty liver (AST:ALT usually <1) with imaging study, usually ultrasound*
- Thyroid functions, Celiac serology



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Very High (>10-15X) Liver Enzymes

- Acute viral hepatitis
 - Fulminant hepatitis A
 - Acute/reactivation of hepatitis B
- Drugs & Toxins
 - Acute acetaminophen/Tylenol OD
- Ischemic hepatopathy
- Autoimmune hepatitis
- Early acute bile duct obstruction



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Evaluation of ↑Alkaline Phosphatase

- **Confirm from liver not bone disease & consider physiologic causes**
- **Liver source of ↑ alkaline phosphatase**
 - ↑GGT
 - ↑Alkaline phosphatase heat stable isoenzyme
 - ↑ Heat stable fraction- liver (bone burns)
 - ↑5' nucleotidase



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↑Alkaline Phosphatase Not Due to Liver Disease

- **Pregnancy**
- **Normal childhood & teenager growth**
- **Physiologic post-prandrial increases**
 - Up to 1.5-2X
 - Repeat fasting
- **Bone disease**
 - GGT normal
 - Normal heat stable alkaline phosphatase fraction



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↑Liver Alkaline Phosphatase

- **Anti-mitochondrial antibody (AMA) for primary biliary cirrhosis (PBC)**
 - Positive AMA, refer for liver biopsy
- **Obtain a RUQ ultrasound**
 - Dilated ducts & negative AMA
 - Refer for ERCP
 - Non-dilated ducts & negative AMA
 - Refer for Liver biopsy &/or ERCP vs MRCP



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Jaundice/Elevated Bilirubin

- **Overproduction of bilirubin**
 - Hemolysis e.g. after blood transfusion
 - Resorption of a large hematoma
- **Impaired uptake, conjugation, or excretion of bilirubin**
 - Gilbert's Syndrome
 - Bile duct obstruction



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Work up of Elevated Bilirubin/Jaundice

- **Conjugated or Unconjugated (direct or indirect)?**
 - Isolated ↑conjugated
 - Unconjugated bilirubin ↑
- **Associated liver enzyme abnormalities present?**
 - Hepatocellular, cholestatic, or mixed
- **Obstructive or non-obstructive jaundice.**
 - RUQ abdominal ultrasound



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Isolated -Unconjugated Bilirubin

- **AST/ALT, alkaline phosphatase are normal**
- **Review medications**
- **Exclude hemolysis**
 - LDH, haptoglobin, CBC peripheral smear, reticulocyte count/index
- **Order a fasting total and direct bilirubin**
 - Gilbert's Syndrome



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Causes of Conjugated Hyperbilirubinemia

- Bile duct obstructon
- Hepatitis & Cirrhosis
- Medications & Toxins
- Primary Biliary Cirrhosis (PBC)
- Primary Sclerosing Cholangitis (PSC)
- Sepsis
- Total Parenteral Nutrition (TPN)



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Common Causes of Chronic Hepatitis

Liver Disease	Clinical Clues	Diagnostic Tests
Non-alcoholic fatty liver disease (NAFLD)	Obesity, DM, Hyperlipidemia AST:ALT <1	Ultrasound/CT/MRI Liver Biopsy
Alcoholic Liver Disease (ALD)	History of Alcohol AST:ALT >2, ↑GGT	Classic Liver Biopsy Improves with Abstinence
Chronic Hepatitis C	Risk Factors	Anti-HCV positive HCV Viral RNA
Chronic Hepatitis B	Risk Factors	HBsAg, HBcAg Hepatitis B Viral DNA
Autoimmune Hepatitis (AIH)	Female Gender, ALT 200-1,500, Associated Autoimmune Disease	ANA, ASMA, LKM1 Classic Liver Biopsy
Genetic Hemochromatosis	Arthritis, DM, Family History	Iron Saturation >45%, Elevated Ferritin Genetic Tests, Liver Biopsy



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Laboratory Clues to Alcoholic Liver Disease (ALD)

- **↑↑AST more than twice ↑ALT**
 - **>90% predictive when AST 2X >ALT**
- **GGT ↑↑ >2X highly predictive of alcoholic liver disease**
- **Poor prognosis**
 - **↑↑Total and direct Bilirubin**
 - **↓↓ Albumin**
 - **↑↑ PT**
 - **Child's Pugh grade C, MELD score >10**



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Non-alcoholic Fatty Liver Disease (NAFLD) & Non-alcoholic Steatohepatitis (NASH)

- **↑↑ Incidence with several known risk factors**
 - **NASH more common in women**
 - **Obesity**
 - **Hyperlipidemia**
 - **Type 2 diabetes**
 - **Syndrome X**
- **Most common cause of ↑AST & ALT <2x**
 - **AST & ALT usually <4x**
 - **AST:ALT ratio usually <1**



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Wilson's Disease

- Cause of isolated chronic \uparrow AST & ALT
- Rare cause of acute fulminant hepatic failure
- Usually <40 years of age
- Neuropsychiatric history
- Hemolysis
- Dx: low serum ceruloplasmin, high urinary copper
- Kayser Fleischer rings (requires Slit lamp eye exam)
- Treatment: Chelation of excess copper
- Acute hepatic failure: Liver transplant



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Common Causes of Acute Hepatitis

Liver Disease	Clinical Clues	Diagnosis
Alcoholic Hepatitis	AST:ALT>2 AST<5x ULN	Classic liver biopsy Improves with alcohol abstinence
Drug Hepatotoxicity	Exposure to a potentially hepatotoxic medication	Improves with stopping medication
Hepatitis A	History of exposure	Anti-HAV IgM
Hepatitis B	Risk factors for Hepatitis B	HBsAg, Anti-HBc IgM
Ischemic Hepatopathy	History of shock or hypotension	Very high transaminases that rapidly improve



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Alpha-1-Antitrypsin Deficiency

- Cause of Isolated Chronic ↑AST & ALT
- Cause of chronic end stage liver disease-cirrhosis
- Emphysema out of proportion to age or smoking history
- History of neonatal jaundice
- Family history of neonatal cirrhosis
- Screening Test: Low alpha-1-antitrypsin level
- Confirmation: Alpha-1-antitrypsin phenotype abnormal
- Liver biopsy shows classic inclusions
- Treatment: Liver transplant



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Common Causes of Cholestasis

Liver Disease	Clinical Clues	Diagnostic Tests
Primary Biliary Cirrhosis (PBC)	Middle-aged Woman, Hyperlipidemia, Elevated Alk Phos	Antimitochondrial Antibody (AMA) Classic Liver Biopsy
Primary Sclerosing Cholangitis (PSC)	Associated With Ulcerative Colitis pANCA positive	ERCP/MRCP
Cholestatic Drug Injury	Drug Exposure to Drug Causing Cholestatic Pattern Injury	Improvement After Stopping Drug Classic Liver Biopsy
Inflammatory Disease of Liver	Symptoms of Underlying Disease Known to Cause Cholestatic Pattern Liver Abnormalities	Blood Cultures, Liver Biopsy/Aspirate, Appropriate Antibody Tests Positive
Infiltrative Disease of Liver	History of Malignancy, Sarcoidosis, Amyloidosis etc.	Ultrasound or CT Imaging, Liver Biopsy
Large Bile Duct Obstruction	Jaundice With Biliary Type Abdominal Pain	Ultrasound, ERCP, MRCP



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When to Order a Liver Biopsy?

- Suspected Autoimmune hepatitis (AIH)
- Genetic Hemochromatosis
- Wilson's Disease
- Primary Biliary Cirrhosis (PBC)
- Chronic abnormal liver tests with negative or inconclusive work-up
- Alcoholic liver disease
- Suspected NASH
- Pre-treatment of Chronic hepatitis B or C



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Burden of Viral Hepatitis In US

Clinical Syndrome	Hepatitis A	Hepatitis B	Hepatitis C
Acute Infection	930,000/year	780,000/year	25,000/year
Chronically Infected	None	1-1.25 Million	3-4 Million
Acute Fulminant Liver Failure Deaths	50/year	100/year	Rarely Occurs
Chronic Liver Disease Deaths	None	5,000/year	8,000-10,000/year



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Chronic Hepatitis C Diagnosis

- HCV antibody +
- With detectable HCV RNA
- Liver enzymes often normal to < 2X ULN
- 30% have persistently normal ALT rarely progress
- Genotype important in treatment and prognosis



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Course of Chronic Hepatitis C

- Chronic indolent 10-30 year course
- Overall low risk (20-30%) progression to end-stage liver disease
- Morbidity & mortality related to cirrhosis
 - 20-30% have progressive liver disease over 10-20 years
 - 2-4%/year risk of Hepatocellular Carcinoma (HCC)
 - Risk increased by alcohol intake >50g/day



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Patients Who Should be Considered for Treatment for Chronic Hepatitis C?

- Viral Genotypes 2 & 3 statistically good response
- Genotype 1 with -risk factors
- Need to reduce potential of transmission
 - e.g. health care workers doing invasive procedures
- Those with increase risk of cirrhosis
 - History long duration
 - History of alcohol abuse
 - Presence of fibrosis on liver biopsy
- Extra-hepatic manifestations/complications
- Anticipated long life span e.g. age < 40



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Chronic Active Hepatitis B

- Persistent (> 6 months) HBsAntigen
- Liver enzymes (>2x ULN) &/or
- Elevated HBV DNA > 10⁴⁻⁵ copies/ml
- Liver biopsy confirms active disease



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When to Refer for Liver Biopsy in Chronic Hepatitis C?

- Not mandatory but helpful for following:
- Determining activity and fibrosis for prognosis and treatment decisions
- Baseline before treatment
- Establishing presence or absence of other liver diseases that may influence treatment and/or prognosis.



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Guide to Hepatitis B Tests

Hepatitis B Test	Interpretation or Clinical Significance
Hepatitis B Surface Antigen (HBsAg)	Currently Infected with Hepatitis B
Antibody to Hepatitis B Surface Antigen (anti-HBs)	Immunized Status or Resolved Infection
IgM Antibody to Hepatitis Core (anti-HBc IgM)	Recent Infection or Occasionally Represents Reactivation of Chronic B
IgG Antibody to Hepatitis Core (anti-HBc IgG)	Remote Infection Absent in Immunized Individual
Hepatitis B e Antigen (HBeAg) &/or $>10^5$ copies/ml HBV DNA	Active Viral Replication, Highly Infective State



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Who Should be Tested for Hepatitis B?

- Individuals born in high risk countries*
- Pregnant women
- Patients on dialysis
- Family, household, and sexual contacts of HBV-infected persons
- Men who have sex with men
- HIV infected patients
- Injection drug users



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Who With Chronic Hepatitis B Should be Considered for Treatment?

- Chronic (>6 months) HBsAg positive hepatitis B with HBeAg positive or HBeAg negative
- Compensated cirrhosis with -HBV DNA
- Decompensated cirrhosis with detectable HBV DNA by PCR assay regardless of ALT level



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Acute Hepatitis A

- **Dx: Anti-HAV IgM**
- **Tx: Supportive**
- **Prophylaxis: Serum Immune globulin**
 - Household & intimate contacts, including daycare, within two weeks of exposure
- **Prevention: HAV immunization**
- **Rare Cases of Acute Fulminant Hepatic Failure**



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When to Refer for Liver Biopsy in Chronic Hepatitis B?

- **HBsAg positive for >6 months**
- **HBV DNA >10(5) copies/mL**
- **Persistent or intermittent elevated AST/ALT**
- **Or normal ALT with elevated HBV DNA**



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Who Should You Refer for Liver Transplant Evaluation?

- Acute fulminant hepatic failure
- Chronic ESLD with major complications
 - Ascites,
 - Variceal bleeding
 - Encephalopathy
 - Hepatorenal syndrome
 - Hepatocellular carcinoma
- Patients with a MELD score of 10



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Summary

1. Decide if acute or chronic
2. Determine pattern
 - Hepatocellular, cholestatic, mixed, or isolated pattern
3. Assess severity and hepatic function score
4. Order Additional tests:
 - Exclude metabolic, autoimmune, and viral hepatitis
 - Confirm \uparrow alkaline phosphatase is liver in etiology
 - Imaging studies to exclude obstruction or infiltrative disease
 - Obtain additional viral markers and virus levels
5. Decide if need liver biopsy
6. Decide if transplant evaluation referral indicated
7. Monitor liver chemistry and synthetic function tests



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