Title: Statin Liver Safety Task Force: Update

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Introduction / Outline

- Causes of elevated liver enzymes
- Elevated liver enzyme algorithm
- Summary & take home messages
Causes of Elevated Liver Enzymes
### Table 3  Illustrative causes of elevated liver enzymes in adolescents and adults*

<table>
<thead>
<tr>
<th>Category</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celiac disease</td>
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<td>Congestive cardiomyopathy</td>
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<tr>
<td>Endocrine diseases</td>
<td>Adiposity resulting in adiposopathy, Diabetes mellitus and insulin resistance syndromes, Hyperthyroidism and hypothyroidism, Metabolic syndrome</td>
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<tr>
<td>Excessive ethanol intake (with or without alcoholic hepatitis)</td>
<td>In patients without underlying liver disease, ethanol intake that is more likely to cause increases in liver enzymes include &gt;2 units a day for men and 1 unit per day for women (unit = generally defined as 12 oz of beer, 5 oz of wine, 1.5 oz for 80 proof mixed drinks)</td>
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<tr>
<td>Fatty liver</td>
<td>Nonalcoholic fatty liver disease, Nonalcoholic steatohepatitis</td>
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<td>Gallbladder disease (e.g., cholelithiasis with obstruction)</td>
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<tr>
<td>Genetic diseases</td>
<td>Alpha 1 antitrypsin deficiency, Cystic fibrosis, Hemochromatosis (excessive iron storage), Hepatic porphyrias, Wilson’s disease (excessive copper storage)</td>
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<tr>
<td>Infections</td>
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</table>
- Viral infection
  - Adenovirus
  - Cytomegalovirus
  - Coxsackievirus
  - Echovirus
  - Epstein-Barr (eg, mononucleosis)
  - Hepatitis A, B, C, and E
  - Herpes simplex virus
  - Human immunodeficiency virus
  - Rubella
- Bacterial infection, especially with sepsis
  - Chlamydia
  - Rickettsia
  - Spirochetes
  - Tuberculosis and other mycobacteria
- Fungal infection
  - Candidiasis
  - Histoplasmosis
- Parasitic infections (protozoa and helminthes)
  - Schistosomiasis
  - Leptospirosis
  - Toxoplasmosis
  - Visceral larva migrans

Malignancies
- Primary liver cancer
- Metastatic cancer
- Leukemia and lymphoma

Other liver diseases
- Autoimmune hepatitis (eg, idiopathic, inflammatory bowel disease, ulcerative colitis, rheumatoid arthritis, systemic lupus erythematosus)
- HELLP syndrome in pregnancy (Hemolysis, Elevated liver enzymes, Low Platelet count)
- Primary biliary cirrhosis
- Primary sclerosing cholangitis
- Thrombotic occlusion of the hepatic veins (Budd-Chiari syndrome)

Selected medications
- Antibiotics
  - Amoxicillin
  - Amphotericin
  - Azole antifungal agents (eg, fluconazole, ketoconazole)
  - Ciprofloxacin
  - Erythromycin
  - Isoniazid
  - Nitrofurantoin
  - Protease inhibitors
  - Rifampin
  - Sulfonamide antibiotics (eg, sulfamethoxazole)
  - Tetracycline
  - Trimethoprim
- Cardiovascular disease medications
  - Amiodarone
  - Ezetimibe when combined statins
  - Fibrates (gemfibrozil, fenofibrate)
  - Hydralazine
  - Labetalol
  - Methyldopa
  - Niacin (especially over-the-counter slow-release preparations at doses greater than 1500 mg/d)
  - Quinidine
  - Statins

- Statins

- Herbal supplements
  - Chaparral
  - Ephedra
  - Gentian
  - Germander
  - Jin Bu Huan
  - Kavakava
  - Ma-huang
  - Scutellaria
  - Senecio/crotalaria (bush teas)
  - Senna
  - Shark cartilage

- Hormones
  - Anabolic steroids (eg, testosterone)
  - Estrogens
  - Excessive thyroid hormone
  - Systemic corticosteroids
  - Tamoxifen

- Illicit drugs
  - Anabolic steroids
  - Cocaine
  - Methyleneoxymethamphetamine (MDMA or ecstasy)
  - Phencyclidine (PCP)

- Neurologic and psychiatric medications
  - Carbamazepine
  - Chlorpromazine
  - Phenobarbital
- Phenytoin
- Trazodone
- Valproic acid
- Pain medications
  - Acetaminophen
  - Aspirin
  - Nonsteroidal anti-inflammatory drugs
- Other medications
  - Dantrolene
  - Disulfiram
  - Etretinate
  - Halothane
  - Heparin
  - Orlistat
  - Propylthiouracil
  - Sulfonylureas
  - Vitamin A and derivatives
  - Zafirlukast
Toxins

- 2-Nitropropane
- Carbon tetrachloride
- Chloroform
- Dimethylformamide
- Hydrazine
- Hydrocarbons
- Hydrochlorofluorocarbons
- Hypervitaminosis A
- Insecticides
- Mushrooms
- Organophosphates
- Toluene
- Trichloroethylene

“Weight loss” or “workout” or “body building” supplements†
- Liver injury from the supplement itself
- Liver injury from other toxic ingredients
- Liver injury from a bad batch of the supplement

Elevated Liver Enzyme Algorithm
If on a statin, then stop the statin until greater diagnostic clarity is obtained
- If not on a statin, then hold statin until etiology of elevated liver blood tests is determined, then re-evaluate start of statin therapy
- Stop other concurrent drugs that have the potential to cause liver toxicity
- If the patient is overweight or obese, implement lifestyle as per scenario #1
- Perform blood testing to better access liver function:
  - Albumin
  - Prothrombin time
  - Complete blood count with platelets
- Perform blood testing to evaluate potential causes of liver toxicity as listed in Table 3, with a preliminary & partial list of potential testing being:
  - Alkaline phosphatase
  - Hepatitis A, B, C, and possibly E blood testing
  - Fasting glucose, hemoglobin A1c
  - (Free) T4, thyroid stimulating hormone
  - Antinuclear and anti-smooth muscle antibodies for autoimmune disease
  - Antimitochondrial antibody
  - Anti-liver-kidney microsomal antibodies
  - Tissue-transglutaminase antibody
  - Ferritin and transferrin saturation for hemochromatosis
  - Ceruloplasmin for Wilson’s disease
  - Alpha-1 antitrypsin
  - Abdominal ultrasound (e.g. fatty liver, obstructive biliary disease, cirrhosis, etc.)

If the above testing does not reveal the diagnosis, and if the liver blood testing does not improve with discontinuing drugs and implementing lifestyle changes, then consider liver biopsy and/or imaging studies such as magnetic resonance spectroscopy.

ALT = alanine aminotransferase
AST = aspartate aminotransferase
Patient with elevated liver enzymes (ALT or AST > 3 x upper limits of normal)

- Perform history and physical exam to determine potential causes (Table 3)
- Review prior liver blood tests for comparison

Immediately repeat liver blood testing

- Clinical scenario #3
  - Transaminases remain greater than 3 times upper limits of normal
  - Creatine kinase is normal, suggesting the increase in transaminases is not muscle in etiology

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  - Alpha-1 antitrypsin
  - Abdominal ultrasound (e.g. fatty liver, obstructive biliary disease, cirrhosis, etc.)

If the above testing does not reveal the diagnosis, and if the liver blood testing does not improve with discontinuing drugs and implementing lifestyle changes, then consider liver specialist consultation and additional testing (Table 3) including liver biopsy and/or imaging studies such as magnetic resonance spectroscopy.

ALT = alanine aminotransferase
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Figure 2 Comprehensive approach to patients with elevated liver blood testing (transaminases >3 times the upper limits of normal).
### Summary and take home messages

#### Table 2  Questions addressed by liver experts in the 2006 and 2014 National Lipid Association Statin Safety Task Force Report

<table>
<thead>
<tr>
<th>2006 National Lipid Association Statin Safety Task Force Questions</th>
<th>Answer</th>
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<tbody>
<tr>
<td>Are elevations in serum aminotransferase levels associated with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor, or statin, therapy?</td>
<td>Yes</td>
</tr>
<tr>
<td>Are statin-associated elevations in aminotransferase levels indicative of liver damage or dysfunction?</td>
<td>No</td>
</tr>
<tr>
<td>Are statin-associated elevations in aminotransferases a class effect?</td>
<td>Yes</td>
</tr>
<tr>
<td>Does statin therapy increase the incidence of liver failure, liver transplants, or death associated with liver failure in the general population?</td>
<td>Yes</td>
</tr>
<tr>
<td>Should liver enzymes and liver function tests be monitored in patients receiving long-term statin therapy?</td>
<td>No</td>
</tr>
<tr>
<td>Are any of the following conditions a contraindication for statin therapy?</td>
<td>No</td>
</tr>
<tr>
<td>• Chronic liver disease</td>
<td>No</td>
</tr>
<tr>
<td>• Compensated cirrhosis</td>
<td>No</td>
</tr>
<tr>
<td>• Decompensated cirrhosis or acute liver failure</td>
<td>Yes</td>
</tr>
<tr>
<td>Can statins be used in patients with nonalcoholic fatty liver disease or nonalcoholic steatohepatitis?</td>
<td>Yes</td>
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<table>
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<tr>
<th>2014 National Lipid Association Statin Safety Task Force Questions</th>
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<tr>
<td>Have any unexpected safety concerns arisen since the regulatory recommendation that liver enzymes need not be measured after initiating statin therapy?</td>
<td>No</td>
</tr>
<tr>
<td>Should baseline liver enzymes be obtained before initiating statin therapy?</td>
<td>Yes</td>
</tr>
<tr>
<td>Are statins safe to use in patients with nonalcoholic fatty liver disease?</td>
<td>Yes</td>
</tr>
<tr>
<td>Do statins have drug interactions with medications used to treat infections (eg, hepatitis B, C) that require change in statin, change in statin dosing, or change in antiviral regimen dosing?</td>
<td>Yes</td>
</tr>
<tr>
<td>Can statins safely be used in liver transplant recipients?</td>
<td>Yes</td>
</tr>
<tr>
<td>Can statins safely be used in patients with autoimmune hepatitis?</td>
<td>Yes</td>
</tr>
</tbody>
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