Approach to abnormal LFT in Rheumatology patients and update on autoimmune hepatitis

Rheumatology Training Day
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Approach to abnormal LFT in Rheumatology patients

• Liver disease could be the consequence of various factors such as
  – Fatty infiltration
  – Drug toxicity
  – Superadded infection by hepatotrophic viruses
  – Vascular thrombosis
  – Diabetes
  – Overlap with autoimmune hepatitis

• Advanced liver disease with cirrhosis and liver failure is rare but clinical and biochemical evidence of associated liver abnormalities is commonly seen eg abnormal LFT found in 43% of rheumatology pts

Ann Rheum Dis. 2004
Semin Arthritis Rheum 1982
Liver enzyme abnormalities

• Are typically mild and transient and the histologic abnormalities are usually non progressive.
• Such biochemical and histologic findings are typically ascribed to the primary rheumatologic condition and require no specific management.
• In a subset of patients further evaluation identifies a coexisting, primary liver disease or medication-related liver toxicity.
• Liver test abnormalities in patients with a coexisting primary liver disease are more likely to be persistent.
<table>
<thead>
<tr>
<th>Rheumatic Disease</th>
<th>Signs-LFt's</th>
<th>Liver Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systemic Lupus Erythematosus</strong></td>
<td>Hepatomegaly, Splenomegaly, Jaundice, ALT-</td>
<td>Steatosis, Autoimmune hepatitis, granulomas, haemochromatosis, cholestasis, primary biliary cirrhosis, non-specific reactive changes,</td>
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<tr>
<td><strong>Antiphospholipid Syndrome</strong></td>
<td>Hepatomegaly, Jaundice, ALT-</td>
<td>Autoimmune hepatitis, Nodular Regenerative Hyperplasia, Budd Chiari syndrome</td>
</tr>
<tr>
<td><strong>Rheumatoid Arthritis</strong></td>
<td>ALP-, γ-GT-</td>
<td>Necrotizing hepatic arteritis, Non specific histological findings, Steatosis, Primary biliary cirrhosis, Nodular Regenerative Hyperplasia</td>
</tr>
<tr>
<td><strong>Felty's Syndrome</strong></td>
<td>Hepatomegaly, Portal hypertension, ALP-</td>
<td>Non specific histological findings, Steatosis, Nodular Regenerative Hyperplasia</td>
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<tr>
<td><strong>Myositis</strong></td>
<td>Jaundice, ALT-</td>
<td>Autoimmune hepatitis, Primary biliary cirrhosis,</td>
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<tr>
<td><strong>Scleroderma</strong></td>
<td>Hepatomegaly, Jaundice, liver enzymes-</td>
<td>Primary biliary cirrhosis, autoimmune hepatitis, Cryptogenic cirrhosis, &quot;idiopathic&quot; portal hypertension, primary sclerosing cholangitis, nodular regenerative hyperplasia</td>
</tr>
<tr>
<td><strong>Sjogren's Syndrome</strong></td>
<td>liver enzymes-, Jaundice</td>
<td>Primary biliary cirrhosis, Autoimmune hepatitis, Cryptogenic cirrhosis,</td>
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<td><strong>Polyarteritis nodosa</strong></td>
<td>Hepatomegaly, Jaundice, liver enzymes-</td>
<td>Hematomas, aneurysm,</td>
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<td><strong>Hypersensitivity vasculitis</strong></td>
<td>Hepatomegaly, Jaundice, liver enzymes-</td>
<td>Hepatitis,</td>
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<tr>
<td><strong>Granulomatous vasculitis</strong></td>
<td>ALP-, γ-GT-</td>
<td>Granulomas,</td>
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Table 1: Hepatic manifestations of autoimmune rheumatic diseases. LFt’s = liver function tests
<table>
<thead>
<tr>
<th></th>
<th>AIH</th>
<th>PBC</th>
<th>PSC</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIH</td>
<td>—</td>
<td>4.2 to 9%</td>
<td>1.4 to 49.1%</td>
<td>[30]</td>
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<tr>
<td>SLE</td>
<td>2.7 to 20%</td>
<td>2.7 to 15%</td>
<td>1 case</td>
<td>[18,27,31]</td>
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<tr>
<td>pSS</td>
<td>6 to 47%</td>
<td>35 to 57%</td>
<td>11 cases</td>
<td>[31,34,35]</td>
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<tr>
<td>SSc</td>
<td>11 cases</td>
<td>51.2%</td>
<td>1 case</td>
<td>[31-33]</td>
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</tbody>
</table>

AIH, autoimmune hepatitis; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; pSS, primary Sjögren’s syndrome; SLE, systemic lupus erythematosus; SSc, systemic sclerosis.
Nodular regenerative hyperplasia-NRH

• Diffuse development of thickened and irregularly oriented liver cell plates with areas of compressed, atrophic cell plates, in the absence of significant portal or sinusoidal fibrosis.

• An uneven microcirculatory perfusion-> atrophy of the poorly perfused areas, and compensatory (regenerative) hypertrophy of the areas of maintained perfusion.

• Due to obstructed sinusoids or portal or hepatic venules.

• PC: cholestasis, little or no liver dysfunction and marked portal hypertension.

J of Hepatology 2012
Presentation of DILI

- There is no specific signs/symptoms or tests.
- Manifestation is highly variable:
  - asymptomatic elevation of liver enzymes
  - acute liver failure (presence of jaundice, INR > 1.5 and HE).
  - fever, rash, mucositis, lymphadenopathy and vasculitis.
- Clinically, biochemically and histologically, DILI can simulate almost all forms of acute and chronic liver injuries.
- Clinically significant DILI is defined as ALT > 3 ULN.
- Can even lead onto cirrhosis but rare.

How to diagnosis DILI?

• Having a high level of suspicion for DILI is essential for diagnosis.
• It is a diagnosis by exclusion
• Need comprehensive clinical assessment (good history taking and thorough examination).
• Causality assessment-scoring system with Roussel Uclaf Causality Assessment Method (RUCAM).

T = temporal relationship
E = exclusion
S = sensitivity
T = track record
S = signature
How to describe the pattern of DILI?

- **DRUG INDUCED LIVER INJURY**
  - **HEPATOCELLULAR**
    - ALT > 2ULN
    - or
    - ALT/ALP > 5
  - **CHOLESTATIC**
    - ALP > 2ULN
    - or
    - ALT/ALP < 2
  - **MIXED**
    - ALT > 2ULN
    - ALP > 2ULN
    - or
    - 2 < ALT/ALP < 5
  - **ACUTE LIVER FAILURE**
    - **HYPERACUTE LIVER FAILURE**
    - **ACUTE LIVER FAILURE**
    - **SUBACUTE LIVER FAILURE**
<table>
<thead>
<tr>
<th>Pattern of liver injury</th>
<th>Associated drugs</th>
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<tbody>
<tr>
<td>Acute Hepatocellular (ALT &gt;3× ULN)</td>
<td>Amoxicillin/clavulanate</td>
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<td></td>
<td>Anabolic steroids</td>
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<tr>
<td></td>
<td>Azathioprine</td>
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<td></td>
<td>Chlorpromazine</td>
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<td></td>
<td>Clopidogrel</td>
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<td>Cytarabine</td>
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<td>Erythromycin</td>
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<td>Estrogen</td>
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<td>Fosinopril</td>
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<td>Irbesartan</td>
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<td></td>
<td>Phenothiazines</td>
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<td></td>
<td>Sulindac</td>
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<td></td>
<td>Terbinafine</td>
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<td></td>
<td>Tricyclics</td>
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<tr>
<td>Cholestatic (AP &gt;2× ULN, ALT/AP &lt;2)</td>
<td>Amitriptyline</td>
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<td></td>
<td>Azathioprine</td>
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<td>Captopril</td>
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<td>Carbamazepine</td>
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<td>Clindamycin</td>
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<td></td>
<td>Cyproheptadine</td>
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<td>Enalapril</td>
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<td>Flutamide</td>
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<td></td>
<td>Ibuprofen</td>
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<td>Nitrofurantoin</td>
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<td></td>
<td>Phenobarbital</td>
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<td></td>
<td>Phenytoin</td>
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<tr>
<td>Mixed (elevated AP and ALT)</td>
<td>Acarbose</td>
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<tr>
<td></td>
<td>Acetaminophen</td>
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<td></td>
<td>Allopurinol</td>
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<td>Bupropion</td>
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<td>Bromfenac</td>
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<td>Diclofenac</td>
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<td>Fluoxetine</td>
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<td>Isoniazid</td>
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<td>Ketoconazole</td>
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<td>Lisinopril</td>
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<td>Losartan</td>
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<td>Nefazodone</td>
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<td>Nevirapine</td>
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<td>Pyrazinamide</td>
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<td>Ritonavir</td>
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<td>Sertraline</td>
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<td>Statins</td>
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<td>Tetracycline</td>
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<td>Trazodone</td>
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<td>Troglitazone</td>
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<td>Trovafloxacin</td>
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<td>Valproic acid</td>
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<td>Pattern of liver injury</td>
<td>Associated drugs</td>
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<td>----------------------------------------------</td>
<td>-------------------------------------------------------</td>
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<tr>
<td>Chronic</td>
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<td>Steatohepatitis</td>
<td>Sulfonamides</td>
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<td></td>
<td>Trazodone</td>
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<td></td>
<td>Trimethoprim/sulfamethoxazole</td>
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<td>Verapamil</td>
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<td>Microvesicular steatosis</td>
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<td>Granulomatous hepatitis</td>
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<td>Sinusoidal obstruction syndrome</td>
<td>Amiodarone, tamoxifen</td>
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<td></td>
<td>NRTIs, valproic acid, tetracycline</td>
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<td></td>
<td>Diltiazem, sulfa drugs, quinidine</td>
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<td>Busulfan, cyclophosphamide</td>
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<td>Methotrexate</td>
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<td>Fibrosis</td>
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<td>Hepatic adenoma</td>
<td>Oral contraceptives</td>
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<tr>
<td>Autoimmune hepatitis</td>
<td>Nitrofurantoin, minocycline</td>
</tr>
</tbody>
</table>
Diagnostic approach to abnormal LFTs in general

1. Begins with a careful history (*DILI) and physical examination, and screening laboratory studies.

2. Clues to the aetiology are usually present in the history.

3. A differential diagnosis is formulated and appropriate further testing is performed to narrow the diagnostic possibilities.

NB-HBV reactivations from biologics and immunomodulatory therapies eg (TNF alpha blockers and monoclonal antibodies) in SLE, rheumatoid arthritis, vasculitis.
## Initial lab test: LFT (ALT and AST) + INR

<table>
<thead>
<tr>
<th>LFT</th>
<th>Possible Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predominant elevation of serum transaminase</td>
<td>Indicators of more severe hepatocellular disease with impaired synthetic function (hypoalbuminemia and a prolonged PT not correctable with vitamin K).</td>
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<tr>
<td></td>
<td>- <strong>Alcoholic hepatitis</strong>: AST /ALT ratio &gt; 2 with both values being less than 500 IU/L.</td>
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<tr>
<td></td>
<td>- <strong>Viral hepatitis, DILI, Ischemic hepatitis</strong>: ALT &gt; 1000</td>
</tr>
<tr>
<td></td>
<td>- Elevated globulin, gender and age: <strong>AIH</strong></td>
</tr>
<tr>
<td></td>
<td>- Family history, consanguinity: <strong>FWD/WD</strong></td>
</tr>
<tr>
<td></td>
<td>- CVS signs: <strong>cardiac congestions, ischemic hepatitis, DILI</strong> from CVS meds.</td>
</tr>
<tr>
<td></td>
<td>- Eosinophilia, rash, fever: <strong>DILI, DRESS</strong></td>
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<tr>
<td></td>
<td>However, exceptions do occur. As an example, viral hepatitis can present as a predominantly cholestatic syndrome with marked pruritus.</td>
</tr>
</tbody>
</table>
ALT > 500 iu/ml

- 96 patients with ALT > 500 iu/ml
- The mean age=34.9 years and duration of admission were 9.8 days.

The symptoms and signs were
- loss of appetite 76%
- lethargy 67.7%
- jaundice 66.7%
- abdominal pain 50%
- vomiting 47.9%
- fever 47.9%
- encephalopathy 4.2%.

The aetiology were
1. Hepatitis B related 36.5%
2. Presumed drug induced 24%
3. Acute hepatitis A 17.7%
4. Autoimmune 6.2%
5. Dengue hepatitis 4.2%
6. Ischemic hepatitis 3.1%
7. Acute cholelithiasis 2.1%
8. Leukemia 1%
9. Acute hepatitis C 1%
10. Cause is uncertain 4.2%

More specific lab tests: to evaluate the potential causes of hepatocellular dysfunction

- Serologic tests for viral hepatitis - IgM anti HAV, HBsAg and IgM antiHBcore, antiHCV.
- Antinuclear antibody, anti-smooth muscle, and anti-liver-kidney microsomal (LKM) antibodies, IgG (for AIH), antimitochondrial antibodies, IgM (for PBC). Liver specific auto-antibody (SLA/LP, LC1)
- Serum ceruloplasmin, copper and 24 H urine copper (for Wilson disease)
- Rarely: Alpha-1 antitrypsin activity (for alpha-1 antitrypsin deficiency), Ferritin
Use of Liver Biopsy

• For many diseases, clinical and/or blood based tests suffice to establish a diagnosis (eg HBV/HCV)
• Liver biopsy is particularly useful in patients with atypical clinical features.

The indications for Liver Biopsy

1. Diagnosis
   - Multiple parenchymal liver diseases
   - Abnormal liver tests of unknown etiology
   - Fever of unknown origin
   - Focal or diffuse abnormalities on imaging studies

2. Prognosis—Staging of known parenchymal liver disease
3. Management—Developing treatment plans based on histologic analysis

A liver biopsy examine 1/50,000 of the liver: potential for errors

AASLD Position Paper on Liver Biopsy HEPATOLOGY, March 2009
Initial lab test: LFT (ALT and AST) + INR

<table>
<thead>
<tr>
<th>LFT</th>
<th>Possible Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>A predominant elevation in ALP in relation to AST and ALT. (The cut-off levels of ALP and GGT requiring diagnostic work-up : ALP ≥ 1.5 ULN and GGT &gt;3 ULN)</td>
<td>Biliary obstruction or intrahepatic cholestasis.</td>
</tr>
<tr>
<td></td>
<td>RUQ pain -&gt; extrahepatic biliary obstruction.</td>
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<tr>
<td></td>
<td>PT prolongation that corrects with Vit K administration , pale stool -&gt; obstructive jaundice.</td>
</tr>
<tr>
<td></td>
<td>Increased ALP is also found in granulomatous liver diseases (eg TB or sarcoidosis.)</td>
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</tbody>
</table>
Fig. 1. Diagnostic approach to cholestasis in adult patients.
Imaging in patients with jaundice

- **US**-sensitivity for detection of dilated bile ducts= 55 to 91% (increase with level and duration of jaundice). Also can detect GB stone. 
  
  Advantages: non-invasive, portable and relatively inexpensive. 
  Disadvantages: operator-dependent. The lower common bile duct (gas in duodenum) and pancreas are usually not well depicted.

- **EUS**-as good as ERCP to detect small CBD stone, small pancreatic lesion. Is equivalent to MRCP in the detection of bile duct stones and lesions causing extrahepatic obstruction. 
  Disadvantages: invasive, risk of perforation.

- **ERCP**-for therapeutic intervention (stone extraction or papillotomy). 
  Disadvantages: risk of pancreatitis in 3–5% of cases; when combined with sphincterotomy, bleeding 2%, cholangitis 1%, procedure-related mortality 0.4%

Imaging in patients with jaundice

- **CT scan** - only detects calcified stones but give a more comprehensive imaging of the abdomen and pelvis. Disadvantages: risk of radiation, contrast induced nephropathy/allergic reaction.

- **MRCP cholangiogram** - is diagnostic in 90 to 100% of patients with dilated ducts; it also reveals the level of obstruction in 80 to 100% of cases and has a sensitivity and specificity of 90 to 100% for the detection of choledocholithiasis and bile duct stenosis. MRCP is as accurate as ERCP for detecting choledocholithiasis. MRCP is expensive and may replace diagnostic ERCP. However, it is unlikely to replace US or helical CT as the initial imaging test in the diagnostic evaluation of jaundice, and ERCP is preferred in the patient with cholangitis because it permits therapeutic drainage of the obstruction.
Liver Biopsy

A liver biopsy should be performed when the diagnosis is still unclear. Particular attention to the condition of bile ducts is critical.

Biopsy findings should be classified under

(i) **Disorders involving bile ducts** (for typical biliary lesions). Main causes = AMA-negative PBC, isolated small duct PSC, ABCB4 deficiency, sarcoidosis, idiopathic ductopenia or prolonged drug-induced cholestasis;

(ii) **Disorders not involving bile ducts**. Main causes=a variety of storage or infiltrative liver diseases, hepatic granulomas (without cholangitis), nodular regenerative hyperplasia, peliosis, sinusoidal dilatation and cirrhosis;

(iii) **Hepatocellular cholestasis** with only minimal histologic abnormalities as observed in benign recurrent intrahepatic cholestasis (BRIC), estrogen or anabolic steroid therapy, sepsis, total parenteral nutrition or as a paraneoplastic phenomenon.
Intrahepatic cholestasis is the cause of most chronic cholestatic jaundice of > 6 mo

- May result from hepatocellular functional defects or from obstructive lesions of the intrahepatic biliary tract distal from bile canaliculi.
- Isolated serum GGT elevation—little specificity for cholestasis (enzyme induction in response to alcohol or drug intake).
- Isolated serum AP elevation is seen in cholestatic liver diseases including certain rare disorders (e.g., progressive familial intrahepatic cholestasis (PFIC) 1 & 2, bile acid synthesis defects), but may also result from bone (e.g., in children, Paget’s disease), or pregnancy.
Causes of intrahepatic cholestasis - adult.

A) Hepatocellular cholestasis
1. Sepsis, endotoxemia-induced cholestasis
2. Cholestatic variety of viral hepatitis
3. Alcoholic or non-alcoholic steatohepatitis
4. Drug- or parenteral nutrition-induced cholestasis
5. Genetic disorders: e.g., BRIC, PFIC, ABCB4 deficiency, intrahepatic cholestasis of pregnancy (ICP), erythropoietic protoporphyria
6. Malignant infiltrating disorders: e.g., hematologic diseases, metastatic cancer
7. Benign infiltrating disorders: e.g., amyloidosis, sarcoidosis hepatis and other granulomatoses, storage diseases
8. Paraneoplastic syndromes: e.g., Hodgkin disease, renal carcinoma
9. Ductal plate malformations: e.g., congenital hepatic fibrosis
10. Nodular regenerative hyperplasia
11. Vascular disorders: e.g., Budd–Chiari syndrome, veno-occlusive disease, congestive hepatopathy
12. Cirrhosis (any cause)

B) Cholangiocellular cholestasis
1. Primary biliary cirrhosis (AMA+/AMA)
2. Primary sclerosing cholangitis
3. Overlap syndromes of PBC and PSC with AIH
4. IgG4-associated cholangitis
5. Idiopathic adulthood ductopenia
6. Ductal plate malformations: biliary hamartoma, Caroli syndrome
7. Cystic fibrosis
8. Drug-induced cholangiopathy
9. Graft vs. host disease
10. Secondary sclerosing cholangitis: e.g., due to various forms of cholangiolithiasis, ischemic choangiopathies (hereditary hemorrhagic telangiectasia, polyarteritis nodosa and other forms of vasculitis), infectious cholangitis related to AIDS and other forms of immunodepression, etc.
Liver stiffness correlates with methotrexate cumulative dose in patients with RA

- 100 RA pts with a cumulative MTx dose (1530 - 13,000 mg) over a mean period of 7.07±3.89 yrs
- Multivariate analysis: a significant association between liver stiffness and MTx cumulative dose.
- 5 of 11 patients with liver stiffness >7.0 kPa were subjected to liver biopsy
- Mild or moderate perisinusoidal fibrosis was detected in 2 patients with a cumulative dose >4000 mg and liver stiffness >9 kPa.
Figure 1 Primary targets of immune-mediated injury in autoimmune liver diseases. The illustration depicts the liver cellular subpopulations (cholangiocytes and hepatocytes) known to be the target of autoimmune aggression in patients with primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), and autoimmune hepatitis (AIH), respectively.
Autoimmune hepatitis (AIH)

• The current concept of pathogenesis is: initiation by environmental trigger in an individual with genetic predisposition which leads to the loss of immunological tolerance to liver autoantigens. The loss of tolerance heralds the generation of unregulated T-cell–mediated immune attack against those autoantigens and also production of non–specific autoantibodies.

• AIH is characterized by three salient features:
  1) Elevation in amino transaminases,
  2) Hypergammaglobulinemia
  3) Interface hepatitis

  (histological description of inflammation of hepatocytes at the portal tract and hepatic parenchymal junction which can occur in numerous other liver diseases)

• Is an acute relapsing disease, untreated AIH exhibits a waxing and waning course. Spontaneous recovery or progression to cirrhosis or acute exacerbation with jaundice/ALF
“In 1950, the condition we now know as autoimmune hepatitis was described in six patients with impaired liver functions and markedly elevated globulins. It was noted that there was a female preponderance and they responded to corticosteroids. Subsequently a previously described cell called lupus erythematosus (LE) cells were found in the ascites fluid of cirrhotic patients and the blood of patients with hepatitis. Because of the finding of LE cells, autoimmune hepatitis was initially called lupoid hepatitis. About one decade later, it became apparent that lupoid hepatitis and systemic lupus erythematosus (SLE) were separate entities. The presence of LE cells was due to a circulating autoantibody which was finally named as anti-nuclear antibody (ANA). Lupoid hepatitis was renamed as autoimmune hepatitis and anti-nuclear antibody became the first autoantibody associated with autoimmune hepatitis.”
Bridging necrosis on HT has 45% mortality rate and 82% of those who survived will become cirrhotic. However the life expectancy of correctly treated patients can approach that of age and gender matched controls.

Gastroenterology 1996;110:848-857
# Types of AIH

<table>
<thead>
<tr>
<th>Features</th>
<th>Type 1 AIH (80% of AIH)</th>
<th>Type 2 AIH (3-4% of AIH)</th>
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<tbody>
<tr>
<td>Age at presentation</td>
<td>All age groups</td>
<td>Childhood and young adulthood</td>
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<tr>
<td>Gender (F:M)</td>
<td>3:1</td>
<td>10:1</td>
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<td>Characteristic autoantibodies</td>
<td>ANA, SMA, Anti-SLA (present in 25% of patients with negative ANA)</td>
<td>Anti-LKM1, Anti-LC1</td>
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<tr>
<td>Clinical presentation</td>
<td>Variable</td>
<td>More likely to be severe</td>
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<tr>
<td>Treatment Response</td>
<td>Good</td>
<td>More likely to be non responders to treatment and relapse with stopping. Usually need long term maintenance.</td>
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<tr>
<td>Autoantibody</td>
<td>Autoantigen</td>
<td>Liver Disease*</td>
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<tr>
<td>ANA</td>
<td>Centromere, ribonucleoproteins</td>
<td>AIH, PBC, PSC, HCV, HBV, HDV, NASH, drug-induced hepatitis</td>
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<tr>
<td>SMA (anti-G-actin,</td>
<td>Monomeric/glomerular form of actin, tubulin, vimentin, desmin, cytokeratins</td>
<td>AIH, PBC, PSC, HCV, HBV, HDV, NASH, drug-induced hepatitis</td>
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<td>anti-Intermediate</td>
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<td>filaments)</td>
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<td>SMA (anti-F-actin)</td>
<td>Native/filamentous form of actin</td>
<td>AIH-1</td>
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<tr>
<td>LKM-1</td>
<td>Cyp P450 2D6</td>
<td>AIH-2, HCV</td>
</tr>
<tr>
<td>LKM-3</td>
<td>UGT1A</td>
<td>AIH-2, HDV, HCV, APECED</td>
</tr>
<tr>
<td>LC-1</td>
<td>Formiminotransferase cyclodeaminase</td>
<td>AIH-2, HCV</td>
</tr>
<tr>
<td>SLA</td>
<td>UGA repressor tRNA-associated protein</td>
<td>AIH, HCV</td>
</tr>
<tr>
<td>ASGPR</td>
<td>Asialoglycoprotein receptor</td>
<td>AIH, PBC, HCV, HBV, HDV, drug-induced hepatitis</td>
</tr>
<tr>
<td>Chromatin</td>
<td>Chromatin</td>
<td>AIH, HCV, HBV</td>
</tr>
<tr>
<td>CLA</td>
<td>Cardiolipin</td>
<td>AIH, HCV, HBV</td>
</tr>
<tr>
<td>p-ANCA/p-ANNA</td>
<td>Unknown</td>
<td>AIH, PSC</td>
</tr>
</tbody>
</table>

*HCV can be associated with almost every autoantibody but usually at lower levels.
AIH, autoimmune hepatitis; ANA, antinuclear antibody; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D virus; LC-1, liver-cytosol type 1; LKM, liver-kidney microsome; NASH, nonalcoholic steatohepatitis; p-ANCA, peripheral antineutrophil cytoplasmic antigen; p-ANNA, peripheral antineutrophil nuclear antibody; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; SLA, soluble liver antigen; SMA, smooth muscle antibody.
Scoring systems in AIH

### Revised scoring system for diagnosis of autoimmune hepatitis

<table>
<thead>
<tr>
<th>Parameters/Features</th>
<th>Score</th>
<th>Notes*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex</td>
<td>+2</td>
<td></td>
</tr>
<tr>
<td>ALP: AST (or ALT) ratio:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1.5</td>
<td>+2</td>
<td>1</td>
</tr>
<tr>
<td>1.5–3.0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>&gt;3.0</td>
<td>−2</td>
<td></td>
</tr>
<tr>
<td>Serum globulins or IgG above normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;2.0</td>
<td>+3</td>
<td></td>
</tr>
<tr>
<td>1.5–2.0</td>
<td>+2</td>
<td></td>
</tr>
<tr>
<td>1.0–1.5</td>
<td>+1</td>
<td></td>
</tr>
<tr>
<td>&lt;1.0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>ANA, SMA or LKM-1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥1:80</td>
<td>+3</td>
<td>2</td>
</tr>
<tr>
<td>1:80</td>
<td>+2</td>
<td></td>
</tr>
<tr>
<td>1:40</td>
<td>+1</td>
<td></td>
</tr>
<tr>
<td>&lt;1:40</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>AMA positive</td>
<td>−4</td>
<td></td>
</tr>
<tr>
<td>Hepatitis viral markers:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>−3</td>
<td>3</td>
</tr>
<tr>
<td>Negative</td>
<td>+3</td>
<td></td>
</tr>
<tr>
<td>Drug history:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>−4</td>
<td>4</td>
</tr>
<tr>
<td>Negative</td>
<td>+1</td>
<td></td>
</tr>
<tr>
<td>Average alcohol intake</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25 g/day</td>
<td>+2</td>
<td></td>
</tr>
<tr>
<td>&gt;60 g/day</td>
<td>−2</td>
<td></td>
</tr>
<tr>
<td>Liver histology:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interface hepatitis</td>
<td>+3</td>
<td></td>
</tr>
<tr>
<td>Predominantly lymphoplasmacytic infiltrate</td>
<td>+1</td>
<td></td>
</tr>
<tr>
<td>Rosetting of liver cells</td>
<td>+1</td>
<td></td>
</tr>
<tr>
<td>None of the above</td>
<td>−5</td>
<td></td>
</tr>
<tr>
<td>Biliary changes</td>
<td>−3</td>
<td>5</td>
</tr>
<tr>
<td>Other changes</td>
<td>−3</td>
<td>6</td>
</tr>
<tr>
<td>Other autoimmune disease(s)</td>
<td>+2</td>
<td>7</td>
</tr>
<tr>
<td>Optional additional parameters:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seropositivity for other defined autoantibodies</td>
<td>+2</td>
<td>9</td>
</tr>
<tr>
<td>HLA DR3 or DR4</td>
<td>+1</td>
<td>10</td>
</tr>
<tr>
<td>Response to therapy:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete</td>
<td>+2</td>
<td>11</td>
</tr>
<tr>
<td>Relapse</td>
<td>+3</td>
<td></td>
</tr>
</tbody>
</table>

**Interpretation of aggregate scores:**

- **Pre-treatment:**
  - Definite AIH: >15
  - Probable AIH: 10–15
- **Post-treatment:**
  - Definite AIH: >17
  - Probable AIH: 12–17

**Typical AIH**

Presence of all of the following:

1) Interface hepatitis (lymphocytic/lymphoplasmacytic infiltrates in portal tracts and extending into the lobule), 2) Emperipolesis (active penetration by one cell into and through a larger cell) and 3) Hepatic rosette.

**Compatible with AIH**

Chronic hepatitis with lymphocytic infiltration without all the features above.

**Atypical**

Has histological features of other diagnosis.
### Table 5. Indications for Immunosuppressive Treatment

<table>
<thead>
<tr>
<th>Absolute</th>
<th>Relative</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum AST ≥ 10 fold ULN</td>
<td>Symptoms (fatigue, arthralgia, jaundice)</td>
<td>Asymptomatic with normal or near normal serum AST and γ globulin levels</td>
</tr>
<tr>
<td>Serum AST ≥ 5 fold ULN and γ globulin level ≥ 2 fold ULN</td>
<td>Serum AST and/or γ globulin less than absolute criteria</td>
<td>Inactive cirrhosis or mild portal inflammation (portal hepatitis)</td>
</tr>
<tr>
<td>Bridging necrosis or multiainar necrosis on histological examination</td>
<td>Interface hepatitis</td>
<td>Severe cytopenia (white blood cell counts &lt;2.5 × 10^9/L or platelet counts &lt;50 × 10^9/L) or known complete deficiency of TPMT activity precludes treatment with azathioprine</td>
</tr>
<tr>
<td>Incapacitating symptoms</td>
<td>Osteopenia, emotional instability, hypertension, diabetes, or cytopenia (white blood cell counts ≤2.5 × 10^9/L or platelet counts ≤50 × 10^9/L)</td>
<td>Vertebral compression, psychosis, brittle diabetes, uncontrolled hypertension, known intolerances to prednisone or azathioprine</td>
</tr>
</tbody>
</table>

### Table 6. Immunosuppressive Treatment Regimens for Adults in Autoimmune Hepatitis

<table>
<thead>
<tr>
<th>Monotherapy</th>
<th>Combination Therapy</th>
<th>Azathioprine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisone only* (mg/day)</td>
<td>Prednisone* (mg/day)</td>
<td>USA (mg/day)</td>
</tr>
<tr>
<td>Week 1</td>
<td>60</td>
<td>30</td>
</tr>
<tr>
<td>Week 2</td>
<td>40</td>
<td>20</td>
</tr>
<tr>
<td>Week 3</td>
<td>30</td>
<td>15</td>
</tr>
<tr>
<td>Week 4</td>
<td>30</td>
<td>15</td>
</tr>
<tr>
<td>Maintenance until endpoint; 20 and below</td>
<td>10</td>
<td>50</td>
</tr>
</tbody>
</table>

**Reasons for Preference**

- Cytopenia
- Thiopurine methyltransferase deficiency
- Pregnancy
- Malignancy
- Short course (≤6 months)

*Prednisolone can be used in place of prednisone in equivalent doses.*
<table>
<thead>
<tr>
<th>Compound</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Budesonide</td>
<td>High first pass-effect</td>
<td>Cirrhosis (portosystemic shunts) and side effects</td>
</tr>
<tr>
<td></td>
<td>Immunosuppressive action</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Inactive metabolites</td>
<td></td>
</tr>
<tr>
<td>Cyclosporine A</td>
<td>Satisfactory experience</td>
<td>Renal toxicity</td>
</tr>
<tr>
<td></td>
<td>Potent immunosuppressant</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Transplant immunosuppressant</td>
<td></td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Potent immunosuppressant</td>
<td>Renal toxicity</td>
</tr>
<tr>
<td></td>
<td>Transplant immunosuppressant</td>
<td></td>
</tr>
<tr>
<td>Mycophenolic acid</td>
<td>Favorable toxicity profile</td>
<td>Disappointing effectivity</td>
</tr>
<tr>
<td></td>
<td>Transplant immunosuppressant</td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Effective</td>
<td>Continuous therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hematological side effects</td>
</tr>
</tbody>
</table>
Of the 20% who did not respond, only 9% are true nonresponders. Others are due to noncompliance.

80% response in 3-6 wks

Remission = disappearance of symptoms, normalization of aminotransferases, bilirubin, IgG, and liver histology/inactive cirrhosis
Concurrent autoimmune diseases in patients with AIH.

- 278 patients with AIH
- 111 patients (40%) were diagnosed with additional autoimmune diseases
- Types of concurrent autoimmune diseases:
  - PBC, PSC, Autoimmune thyroiditis (28 pts, 10%).
  - Vitiligo, Rheumatoid arthritis (5 patients each)
  - Sjogren syndrome, Ulcerative colitis, Conjunctivitis (4 patients each)
  - Celiac disease (3 patients)
  - SLE, T1DM, MS, Polymyalgia rheumatica, Urticaria (2 patients each)
  - Crohn's disease, autoimmune gastritis, collagenous colitis, hypophysitis, and sarcoidosis. (1 patient each)
- Concurrent autoimmune diseases are common in patients with AIH and mirror the full range of known autoimmune diseases.

Clin Gastroenterol. 2010
Thank you