THE GENERAL DIAGNOSTICS OF LIVER DISEASE

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Liver diseases 1

Inherited hyperbilirubinemia
- Gilbert’s syndrome
- Crigler-Najjar syndrome I, II
- Rotor syndrome

Viral hepatitis
- A, B, C, D, E, other (EBV, CMV), cryptogenic

Immune and autoimmune liver diseases
- Primary biliary cirrhosis (PBC)
- Autoimmune hepatitis (CAH)
- Sclerosing cholangitis (PSC)
- Graft-versus-host disease (GVHD)
- Allograft rejection

Liver involvement in systemic diseases
- Sarcoidosis
- Amyloidosis
- Glycogen storage diseases
- Celiac disease
- Tuberculosis

Cholestatic syndromes
- Benign postoperative cholestasis
- Jaundice of sepsis
- Total parenteral nutrition-induced jaundice
- Cholestasis of pregnancy
- Cholecystitis and cholangitis
- Extrahepatic biliary obstruction (stone, stricture, cancer)
- Biliary atresia
- Caroli’s disease
- Cryptosporidiosis

### Liver diseases 2

#### Genetic liver diseases
- α1-antitrypsin deficiency
- Hemochromatosis
- Wilson’s disease
- Benign recurrent intrahepatic cholestasis (BRIC)
- Progressive familial intrahepatic cholestasis (PFIC) types I-III
- Others (galactosemia tyrosinemia, cystic fibrosis, Newman-Pick disease, Gaucher’s disease)

#### Alcoholic liver diseases
- Acute fatty liver
- Acute alcoholic hepatitis
- Laënnec’s cirrhosis
- Nonalcoholic fatty liver
- Steatosis
- Steatohepatitis (NASH)

#### Acute fatty liver of pregnancy

#### Drug-induced liver disease
- Hepatocellular (INH, acetaminophen)
- Cholestatic (methyltestosterone)
- Mixed (sulfonamides, phenytoin)
- Micro- and macrovesicular steatosis (MTX, fialuridine)

#### Vascular injury
- Venoocclusive disease
- Budd-Chiary syndrome
- Ischemic hepatitis
- Passive congestion
- Portal vein thrombosis
- Nodular regenerative hyperplasia

#### Mass lesions
- Hepatocellular carcinoma (HCC), cholangiocarcinoma, adenoma, focal nodular hyperplasia (FNH), metastatic tumors, abscess, cysts, hemangioma

# History and symptoms

**Aspecific constitutional**
- Fatigue
- Weakness, malaise
- Nausea, less commonly vomiting (vomitus matutinus, too)
- Poor appetite

**More liver-specific**
- Jaundice
- Dark urine, light stools, Pruritus (in cholestasis)
- Fever
- Diminished libido
- Anorexia, weight loss
- Abdominal pain, bloating, and discomfort in the RUQ region
- Bloating
- Abdominal swelling (ascites)
- Change in sleep pattern and behavior

Major risk factors for liver disease

• Details of alcohol use
• Medications (incl. herbal compounds, birth control pills, OTC medications)
• Personal habits
• Sexual activity
• Travel
• Exposure to jaundiced or other high-risk persons
• IV drug abuse
• Recent surgery
• Remote or recent transfusion with blood or blood products
• Occupation
• Accidental exposure to blood or needlestick
• Familial history of liver disease

Physical examination

**Inspection:** icterus (sclera, skin) spider telangiectasias, palmar erythema, excoriations (pruritus!), xanthomas, xanthelasmas (hypercholesterinemia), changes in hair pattern (female type in males), gynecomastia, soft, small testes, prominence of cutaneous veins, haemorrhoid veins (portosystemic shunts)

**Palpation:** size-form-consistency: smooth, nodular, hard, rockhard, firm-sharp edge, rounded edge, irregular edge, abdominal mass, tenderness ascites (ballottment)

- cholecyst: Courvosier’s sign
- spleen (splenomegaly in portal hypertension)

**Percussion:** ascites (as dullness), size and shape of the liver

neurologic examination - flapping tremor
Constellation of symptoms reported by patients with acute hepatitis B virus (HBV)

- Fever (60%–80%)
- Jaundice (20%–30%)
- Fatigue, weakness (75%–90%)
  - Pruritus (25%–45%)
  - Anthropathy (20%–30%)
- "Flu"-like features (> 70%)
  - Nasal congestion
  - Sore throat
  - Cough
  - Headache
  - Chills
  - Myalgia
- Abdominal discomfort or pain (60%–70%)
- Nausea, emesis (50%–90%)
- Anorexia and weight loss (80%–90%)
- Dark or brown urine (75%–95%)
- Diarrhea/constipation (25%)
- Light- or clay-colored stools (20%–60%)
- Other signs
  - Macular erythema
  - Irritability
  - Decreased gustatory acuity

Source: Images MD
Icterus
Spider nevi

Source: slideshare.net

Source: Medical-On-Line Alamy
Ascites

Source: en.wikipedia.org

Source: murrasaca.com
Severe protein malnutrition in a patient with end-stage liver disease

Source: Images MD
Large esophageal varices

Source: Images MD
Pruritus and palmar erythema

Source: imgarcade.com

Source: Medical-On-Line Alamy
Caput medusae

Source: empills.com
Metabolism in liver diseases

CARBOHYDRATE METABOLISM:
• maintenance of blood glucose level in fasting state is impaired (glycogenolysis, gluconeogenesis)
• glucose intolerance (insulin is diverted to peripheral circulation via portosystemic shunts)

LIPID METABOLISM:
• in cholestasis, se. choleserin ↑, phospholipids ↑, xanthomas, xanthelasmas

AMINO ACID AND PROTEIN METABOLISM:
• albumin (hypalbuminaemia, edema, ascites)
• clotting factors (prothrombin!)
• transferrin
• α1-antitrypsin

BIOTRANSFORMATION AND DETOXIFICATION:
• ammonium → urea (Krebs-Henseleit) = hyperammoniemia
## Important diagnostic tests in common liver diseases

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Hepatitis A</td>
<td>Anti-HAV IgM</td>
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<tr>
<td>Hepatitis B</td>
<td>HBsAg and anti-HBc IgM</td>
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<tr>
<td>Acute</td>
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<tr>
<td>Chronic</td>
<td>HBsAg and HBeAg and/or HBV DNA</td>
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<tr>
<td>Hepatitis C</td>
<td>Anti-HCV and HCV DNA</td>
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<tr>
<td>Hepatitis D (delta)</td>
<td>HBsAg and anti-HDV</td>
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<tr>
<td>Hepatitis E</td>
<td>Anti-HEV</td>
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<tr>
<td>Autoimmune hepatitis</td>
<td>ANA, SMA, se. IgG↑, compatible histology</td>
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<tr>
<td>Primary biliary cirrhosis</td>
<td>AMA, se. IgM↑, compatible histology</td>
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<tr>
<td>Primary sclerosing cholangitis</td>
<td>p-ANCA, cholangiography</td>
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<tr>
<td>Drug-induced liver disease</td>
<td>History of drug ingestion</td>
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<tr>
<td>Alcoholic liver disease</td>
<td>History and compatible histology</td>
<td></td>
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<tr>
<td>Nonalcoholic steatohepatitis</td>
<td>USG or CT evidence of fatty liver, compatible histology</td>
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<tr>
<td>α1 Antitrypsin disease</td>
<td>α1-AT levels↓, phenotypes PiZZ or PiSZ</td>
<td></td>
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<tr>
<td>Wilson’s disease</td>
<td>Se. ceruloplasmin↓, urinary copper↑, hepatic copper level↑</td>
<td></td>
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<tr>
<td>Hemochromatosis</td>
<td>Iron saturation↑, se. ferritin↑, testing for HFE gene mutations</td>
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<tr>
<td>Hepatocellular cancer</td>
<td>Elevated AFP &gt; 500; USG or CT image of mass</td>
<td></td>
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A simplified diagnostic approach in patients presenting with acute hepatitis

<table>
<thead>
<tr>
<th>Serologic tests of patient's serum</th>
<th>Diagnostic interpretation</th>
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<tbody>
<tr>
<td>HBsAg</td>
<td>IgM anti-HAV</td>
</tr>
<tr>
<td>+</td>
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<td>+</td>
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Markers of inflammation in liver disease

- **SGOT** = serum glutaminic acid-oxalacetic acid transaminase = **ASAT** = aspartate aminotransferase. Present in mitochondria and cytoplasm.
- **SGPT** = serum glutaminic acid-pyruvic acid transaminase = **ALAT** = aspartate aminotransferase. Present in cytoplasm.
  - → hepatocyte damage
- **γ-glutamyl transpeptidase (γGT)**
Markers of cholestasis

- Alkaline phosphatase (ALP, SAP)
- Leucine aminopeptidase (LAP)
- 5’-nucleotidase
Tests of protein synthetizing capacity of the liver

**SERUM ALBUMIN AND GLOBULIN:**
- albumin decreases (so is colloid osmotic pressure)
- globulins increase, A/G ↓

**PROTHROMBIN TIME:**
- vitamin K-dependent clotting factor, produced exclusively by the liver
Zone electrophoresis pattern in liver cirrhosis

SOTE III. Belklinik

Patient
Test spe Gel 1-10 2002-07-12
beküldő ha 151

Patient
Test spe Gel 1-10 2000-10-05
beküldő HA 113

<table>
<thead>
<tr>
<th>Fraction</th>
<th>Rel%</th>
<th>g/L</th>
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<tbody>
<tr>
<td>Albumin</td>
<td>60.9</td>
<td>43.83</td>
</tr>
<tr>
<td>Alpha 1</td>
<td>2.1</td>
<td>1.51</td>
</tr>
<tr>
<td>Alpha2</td>
<td>8.2</td>
<td>5.9</td>
</tr>
<tr>
<td>Beta</td>
<td>11.3</td>
<td>8.14</td>
</tr>
<tr>
<td>Gamma</td>
<td>17.5</td>
<td>12.6</td>
</tr>
<tr>
<td>Total g/L</td>
<td>72.00</td>
<td>A/G: 1.56</td>
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<tr>
<th>Reference ranges</th>
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<tr>
<td>Albumin</td>
<td>58.8 - 69.6</td>
</tr>
<tr>
<td>Alpha 1</td>
<td>1.8 - 3.8</td>
</tr>
<tr>
<td>Alpha2</td>
<td>3.7 - 13.1</td>
</tr>
<tr>
<td>Beta</td>
<td>8.9 - 13.6</td>
</tr>
<tr>
<td>Gamma</td>
<td>8.4 - 18.3</td>
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<tr>
<td>Albumin</td>
<td>31.1</td>
<td>20.53</td>
</tr>
<tr>
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<td>2.7</td>
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<tr>
<td>Alpha2</td>
<td>3.9</td>
<td>2.57</td>
</tr>
<tr>
<td>Beta</td>
<td>19.0</td>
<td>12.54</td>
</tr>
<tr>
<td>Gamma</td>
<td>43.3</td>
<td>28.58</td>
</tr>
<tr>
<td>Total g/L</td>
<td>66.00</td>
<td>A/G: 0.45</td>
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Other serum markers of liver disease

- Liver-specific glycoproteins: α2-macroglobulin
- Acute phase reactants:
  - positive: C-reactive protein, (CRP), α1-acid glycoprotein (orosomucoid), serum amyloid A (SAA)
  - negative: albumin, transferrin, fetuin-A
- Serum lipids and lipoproteins
- Elements: iron, copper
Evaluation of abnormal liver tests

Suspected Liver Disease

Abnormal liver tests

Acute < 6 months

- Hepatic: ↑↑ALT
  - Mixed: ↑ALT, ↑AlkP

  Diagnostic evaluation
  1. IgM Anti-HAV
  2. HBsAg
  3. IgM Anti-HBc
  4. Anti-HCV
  5. ANA, SMA
  6. Monospot, heterophile
  7. Ceruloplasmin
  8. Alcohol history
  9. Drug history

  Liver biopsy in acute liver disease:
  Reserved for patients in whom the diagnosis remains unclear despite medical evaluation

- Cholestatic: ↑↑AlkP, ↑↑gGT, ↑ALT

  Diagnostic evaluation
  1. AMA
  2. Drug history
  3. Ultrasound/MRI
  4. MRCP/ERCP

Chronic > 6 months

- Hepatic: ↑↑ALT
  - Mixed: ↑ALT, ↑AlkP

  Diagnostic evaluation
  1. HBsAg
  2. Anti-HCV
  3. Fe saturation, ferritin
  4. Ceruloplasmin
  5. α, AT
  6. ANA, SMA
  7. Ultrasound
  8. Alcohol history

  Liver biopsy in chronic liver disease:
  Often valuable for diagnosis as well as staging and grading liver disease

- Cholestatic: ↑↑AlkP, ↑↑gGT, ↑ALT

  Diagnostic evaluation
  1. Drug history
  2. AMA
  3. P-ANCA
  4. Ultrasound
  5. MRCP/ERCP

Evaluation of chronically abnormal liver tests

Variant syndromes in autoimmune hepatitis

Overlap features:
- PBC: 5%
- AIH: 19%
- AIC: 7%

Principal clinical diagnoses:
- AIH
- PBC: 54%
- PSC

Source: Images MD
Mitochondrial and smooth muscle antibodies
Imaging techniques in liver disease

- Ultrasonography
- CT
- MRI
- Angiography
- Fibroscan
Liver abscess on abdominal USG

Source: Images MD
Ultrasound and liver scan: hepatic angioma

Source: Images MD
Ultrasound: periportal fibrosis

Source: Images MD
CT: small hepatocellular adenoma (upper) and cyst (lower) in the liver
Multiple liver abscess

Source: Images MD
Abscess on liver $^{99}$Tc scan
MRI: Hepatocellular carcinoma

Source: Images MD
MRI for hepatic metastases of colon cancer

Source: Images MD
Hepatic arteriogram in focal nodular hyperplasia
Positron emission tomography for hepatic metastases of colon cancer

Source: Images MD
Fibroscan - alternative to liver biopsy?

Source: samitivehospital.com
Liver biopsy

A, Prominent portal inflammation and occasional peripheral piecemeal necrosis.

B, Section displaying one of many portal-containing lymphoid aggregates with germinal center formation. Portal lymphoid infiltrates with germinal center formation, although not pathognomonic, occur with relatively increased frequency in chronic hepatitis C.

Source: Images MD
Fatty liver (left) and cirrhosis (right)

Source: Images MD
Primary biliary cirrhosis
Genetic testing

- HCV infection
- Hemochromatosis (HFE)
- Wilson’s disease (ATP7)

PCR

For the determination of viral copy number („viral load”) in hepatitis B and hepatitis C