



## DIFFERENTIAL DIAGNOSTIC CRITERIA FOR CHRONIC HEPATITIS AND LIVER CIRRHOSIS

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**Annotation:** Liver fibrosis is defined by progressive accumulation of extracellular matrix components in the liver, leading to scar tissue formation as a consequence of chronic hepatic injury. The condition most commonly develops in the setting of chronic hepatitis, where ongoing inflammation and hepatocyte damage drive fibrotic remodeling. Other contributing factors include hereditary metabolic disorders, portal hypertension, systemic diseases, and prolonged use of certain drugs.

**Keywords:** liver fibrosis; chronic hepatitis; hepatic fibrosis; connective tissue proliferation; fibrogenesis; liver disease

### **Introduction: Differential diagnosis is performed with:**

Chronic hepatitis

Chronic hepatitis

Chronic viral hepatitis C

In viral hepatitis C, three phases are distinguished: the **acute phase**, the **latent phase**, and the **reactivation phase**.

#### **Acute phase**

The acute phase is diagnosed only in a proportion of patients and, in many cases, remains unrecognized. It is characterized by moderately expressed clinical syndromes.

The most common manifestations include **asthenic syndrome and hepatomegaly**. Symptoms of asthenic syndrome comprise anorexia, weakness, and general malaise. A **dyspeptic syndrome** may also be present.

A highly informative laboratory finding is a marked elevation of **alanine aminotransferase (ALT)** levels, exceeding the upper limit of normal by fivefold or more and persisting for 1.5–2 months. In many cases, ALT elevation occurs as recurrent peaks. In patients with low inflammatory activity, ALT levels do not exceed 1.5–3 times the normal range but demonstrate a wave-like pattern.

**Cholestatic syndrome** may be observed, manifested by increased levels of gamma-glutamyltransferase (GGT) and alkaline phosphatase. At the same time, serum bilirubin, albumin levels, and the prothrombin index usually remain within normal limits.

Another characteristic feature of hepatitis C virus infection is that **specific antibodies to hepatitis C virus (anti-HCV)** appear 1–2 months after the initial elevation of ALT levels.

An additional feature of the acute phase is the presence of **extrahepatic manifestations**, such as polyarteritis nodosa, rheumatoid arthritis, Sjögren's syndrome, chronic glomerulonephritis, vasculitis, and others, which may often mask hepatic manifestations.

The duration of the acute phase is typically **1–2 months**.

#### **Latent Phase**

During the latent phase, the manifestations of **asthenic and dyspeptic syndromes** decrease or disappear, and jaundice resolves; however, **hepatomegaly persists**. An elevation of **alanine**



**aminotransferase (ALT)** levels is still observed, typically exceeding the upper limit of normal by **2–3 times**. In cases where other organs and systems are involved, the duration of the latent phase is shortened.

Extrahepatic manifestations of **chronic hepatitis C virus (HCV) infection** may include:

- **Endocrine disorders:** hyperthyroidism or hypothyroidism, autoimmune thyroiditis, diabetes mellitus
- **Cutaneous manifestations:** dermatomyositis, urticaria, lichen planus, erythema multiforme, necrotizing vasculitis
- **Ocular involvement:** uveitis, ulcerative keratitis
- **Renal disorders:** glomerulonephritis
- **Hematological disorders:** mixed cryoglobulinemia, thrombocytopenia, aplastic anemia, non-Hodgkin B-cell lymphoma, Waldenström macroglobulinemia
- **Musculoskeletal and vascular manifestations:** arthritis, arthralgia, polyarteritis nodosa

### **Reactivation Phase**

The reactivation phase is characterized by **intensification of the infectious process**. Clinically, manifestations of the **asthenic syndrome** become more pronounced, including rapid fatigability, weakness, progressive decline in work capacity, sleep disturbances, reduced appetite, a sensation of heaviness in the right upper quadrant, and weight loss.

A characteristic feature of the reactivation phase is the **hepatolienal syndrome**, manifested by marked enlargement and increased density of the liver and moderate enlargement of the spleen. A **wave-like hyperenzymemia syndrome** is frequently observed, with a more pronounced elevation of ALT levels at the onset of the reactivation phase.

At the same time, **extrahepatic manifestations** tend to worsen, including membranoproliferative glomerulonephritis, vasculitis, aplastic anemia, and other systemic complications.

In some cases, the reactivation phase may present solely as a **cytolytic syndrome** (“biochemical exacerbation”), although ALT levels during reactivation are usually lower than those observed in the acute phase.

Among intravenous drug users, as well as in a small proportion of other patients, the disease may lack clear phase differentiation, and features of chronic hepatitis develop within the first six months. In severely ill patients, the latent phase may be absent.

### **Chronic Viral Hepatitis B**

Chronic viral hepatitis B progresses through **two phases: the replication phase and the integration phase**.

#### **Replication Phase**

During the replication phase, the clinical presentation includes the following syndromes and symptoms:

- **Asthenovegetative syndrome:** general weakness, fatigue, irritability, depressed mood, and weight loss ranging from 2–3 kg to 5–10 kg
- **Pain syndrome:** persistent, dull pain localized in the right upper quadrant, intensifying after physical exertion; in some cases, pain may be severe, while in others only a sensation of heaviness is reported
- **Dyspeptic syndrome:** varying in severity and manifested by persistent or transient nausea, abdominal bloating, and unstable bowel movements



**Hepatomegaly** in the replication phase is characterized by liver enlargement of **3–7 cm**. The liver is moderately firm, with a sharp edge, and is tender on palpation. Splenomegaly is usually absent.

#### **Syndrome of Mild Hepatic Failure**

The syndrome of mild hepatic insufficiency is manifested by **drowsiness, pronounced bleeding of the mucous membranes, spider angiomas, hypoalbuminemia, and a decrease in prothrombin levels and prothrombin index.**

#### **Cholestatic Syndrome**

In a proportion of patients with **chronic viral hepatitis B**, a cholestatic syndrome is observed. It is manifested by **transient pruritus, increased levels of bilirubin, cholesterol, alkaline phosphatase, and gamma-glutamyltransferase (GGT)** in the blood.

#### **Extrahepatic Manifestation Syndrome**

The extrahepatic manifestation syndrome is characterized by **joint and muscle pain in the absence of swelling or deformities, sexual dysfunction** (amenorrhea, decreased libido, gynecomastia), and **glomerulonephritis.**

#### **Mesenchymal-Inflammatory Syndrome**

During the replication phase of chronic viral hepatitis B, a **mesenchymal-inflammatory syndrome** is frequently observed. It is characterized by **hypergammaglobulinemia, hypoalbuminemia, elevated thymol turbidity test values, and polyclonal hyperimmunoglobulinemia.**

#### **Integration Phase**

During the integration phase, clinical manifestations of hepatitis may be absent. However, in some patients, **moderate asthenic, dyspeptic, and pain syndromes** persist, along with **mild hepatomegaly** and laboratory signs of **cytolysis** (ALT levels exceeding the upper limit of normal by 1.5–2 times) and mesenchymal-inflammatory activity.

#### **Chronic Viral Hepatitis D**

Since hepatitis D virus (HDV) infection represents a **superinfection** and is characterized by a pronounced **cytopathic effect**, the pathological process proceeds in a **single active phase.**

In most patients, chronic viral hepatitis D presents with a **severe asthenic syndrome** (marked weakness, daytime somnolence, nocturnal insomnia, weight loss), **hepatic insufficiency syndrome** (hypoalbuminemia, bleeding tendency, reduced prothrombin levels), and **cholestatic syndrome** (pruritus, jaundice).

Hepatomegaly is initially pronounced; however, with high disease activity, liver size may subsequently decrease. Extrahepatic manifestations are also characteristic of chronic hepatitis D. Persistent elevation of transaminase activity and pronounced biochemical features of cholestasis are observed.

Moderate **hypergammaglobulinemia, dysimmunoglobulinemia, elevated thymol test values, and increased erythrocyte sedimentation rate (ESR)** indicate the presence of a mesenchymal-inflammatory syndrome.

Superinfection with HDV leads to a **progressive disease course with rapid development of liver cirrhosis.**

#### **Autoimmune Hepatitis (AIH)**



Autoimmune hepatitis occurs more frequently in **women** and in **children and adolescents aged 2–14 years** (type II). Clinical manifestations vary widely, ranging from **asymptomatic forms to severe, sometimes fulminant disease**, with or without extrahepatic manifestations.

The disease often develops latently, presenting with asthenic symptoms and a moderately expressed pain syndrome. In some cases, autoimmune hepatitis begins with extrahepatic manifestations such as **fever, vasculitis, arthralgia and arthritis, autoimmune thyroiditis, glomerulonephritis, ulcerative colitis, hemolytic anemia, lymphadenopathy, fibrosing alveolitis, idiopathic thrombocytopenia, and diabetes mellitus**.

On physical examination, **spider angiomas** are frequently observed on the neck, face, and hands; **striae** on the thighs and abdominal wall; as well as **hirsutism** and a **Cushingoid facial appearance**.

A highly characteristic feature of autoimmune hepatitis is **marked hepatomegaly with disproportionate enlargement of the left hepatic lobe**, combined with **splenomegaly in the absence of portal hypertension**. The liver is typically of **dense consistency**. **Jaundice syndrome** is also common, usually with **moderate hyperbilirubinemia**.

The **endocrine disorder syndrome**, in addition to hirsutism, striae, and acne, includes **menstrual disturbances and reduced sexual function**.

Another important marker of autoimmune hepatitis is the **hemorrhagic syndrome**, characterized by **normocytic normochromic hemolytic anemia**, occasionally posthemorrhagic anemia, **leukopenia**, and **thrombocytopenia**. In some cases, a **hypereosinophilic syndrome** is observed. Among clinical and biochemical syndromes of liver injury in autoimmune hepatitis, the most characteristic are:

- **Cytolytic syndrome** (serum transaminase activity increased 5–10 times above normal),
- **Mesenchymal-inflammatory syndrome** (hypergammaglobulinemia >18 g/L, polyclonal hyperimmunoglobulinemia),
- **Moderately expressed cholestatic syndrome** (total bilirubin and alkaline phosphatase elevated 1.5–3 times compared with normal values).

Based on antibody profiles and clinical features, **three types of autoimmune hepatitis** are distinguished:

#### **Autoimmune Hepatitis Type I**

Accounts for approximately **85% of cases**, occurs **eight times more frequently in women**, predominantly affects older individuals, and is associated with a **more favorable prognosis**. Autoantibodies to **DNA, smooth muscle (particularly actin), and soluble liver antigen** are detected.

#### **Autoimmune Hepatitis Type II**

More common in **children and adolescents (2–14 years)**, especially girls, and is often associated with **vitiligo, diabetes mellitus, and thyroiditis**. This type is characterized by a **fulminant course** but responds well to **corticosteroid therapy**. Antibodies to **liver–kidney microsomal antigen and cytochrome P450** are present.

#### **Autoimmune Hepatitis Type III**

Occurs in younger individuals and is characterized by antibodies to **smooth muscle**, as well as possible detection of **antinuclear antibodies and antibodies to soluble liver antigen**. This type is not recognized by all clinicians.

#### **Chronic Alcoholic Hepatitis**

Chronic alcoholic hepatitis is characterized by:

- high serum **gamma-glutamyltransferase (GGT)** activity;
- increased **immunoglobulin A (IgA)** levels;



- elevated **aspartate aminotransferase (AST)**;
- **leukocytosis** ( $10-20 \times 10^9/L$ ) with neutrophil predominance;
- increased **ESR**;
- **ballooning degeneration of hepatocytes**, with cellular swelling and cytoplasmic clearing;
- presence of **alcoholic hyaline (Mallory–Denk bodies)** in hepatocytes;
- inflammatory infiltration of hepatic lobules by **neutrophils and lymphocytes**.

Established liver cirrhosis with pronounced clinical manifestations usually does not pose diagnostic difficulties. However, distinguishing **chronic hepatitis from clinically latent cirrhosis**, particularly in the inactive phase, remains challenging.

The most common early manifestations of both conditions include **right upper quadrant pain, weakness, hepatomegaly**, and occasionally **jaundice**. The presence of this symptom complex, especially in individuals with a history of **acute viral hepatitis (Botkin’s disease)**, should prompt comprehensive **clinical and biochemical evaluation**, including liver function tests.

In some cases, definitive diagnosis is possible only through **in vivo morphological examination of the liver**. Assessment of disease activity relies on clinical symptoms and abnormalities in liver function tests, including elevations of **transaminases, alkaline phosphatase, LDH isoenzyme 5**, and liver-specific enzymes, as well as decreased **cholinesterase activity** and alterations in protein fractions.

However, these indicators do not always reflect active liver pathology. The most reliable conclusions are drawn from **histological and histochemical examination of liver biopsy specimens**. Accurate staging of disease requires a **comprehensive approach**, combining clinical and biochemical assessment with **laparoscopy and histological evaluation**.

Differentiation between chronic hepatitis and liver cirrhosis represents a particular diagnostic challenge. Advanced stages of cirrhosis can usually be distinguished clinically, whereas **borderline stages** of the pathological continuum can be differentiated only by **morphological examination**.

A laparoscopic sign of progression from chronic hepatitis to cirrhosis is the “**mottled nodular liver**” described by Kalk (1954), microscopically characterized by disruption of lobular architecture with bands of connective tissue. Nevertheless, even morphological studies cannot precisely determine the onset of cirrhosis, as this process develops gradually and heterogeneously throughout the liver. Therefore, attempts to rigidly separate the precirrhotic stage of chronic hepatitis from early cirrhosis are considered **methodologically unjustified**.

### Conclusion

Chronic liver diseases represent a continuous pathological spectrum in which chronic hepatitis, liver fibrosis, and cirrhosis are closely interconnected and often difficult to distinguish, particularly in the early and clinically latent stages. The differential diagnosis of chronic hepatitis and cirrhosis remains a significant clinical challenge, as clinical manifestations may be nonspecific and laboratory abnormalities may overlap across disease stages.

The clinical course and diagnostic features of chronic viral hepatitis B, C, and D, autoimmune hepatitis, and chronic alcoholic hepatitis demonstrate considerable heterogeneity. Each etiology is characterized by distinct combinations of cytolytic, cholestatic, mesenchymal-inflammatory, hepatic insufficiency, and extrahepatic syndromes. However, none of these features alone is sufficiently specific to reliably determine the stage of disease or the presence of cirrhosis.

Biochemical markers, including transaminases, alkaline phosphatase, gamma-glutamyltransferase, immunoglobulin levels, and coagulation parameters, provide valuable



information regarding disease activity but do not consistently reflect the extent of structural liver damage. Similarly, clinical signs such as hepatomegaly, splenomegaly, asthenic syndrome, and extrahepatic manifestations may persist throughout different phases of chronic liver disease and therefore lack sufficient discriminatory value.

Morphological assessment of the liver remains the most reliable method for differentiating chronic hepatitis from cirrhosis, particularly in borderline cases. Histological and histochemical examination of liver biopsy specimens allows evaluation of architectural remodeling, fibrosis progression, and inflammatory activity, which cannot be accurately determined by clinical and biochemical methods alone. Nonetheless, even morphological changes develop gradually and heterogeneously, limiting the possibility of defining a precise transition point from chronic hepatitis to cirrhosis.

Therefore, accurate diagnosis and staging of chronic liver diseases require a comprehensive, integrative approach that combines clinical evaluation, biochemical testing, imaging techniques, and morphological examination. Such an approach is essential for timely diagnosis, appropriate therapeutic decision-making, and prognostic assessment, ultimately improving patient outcomes and preventing progression to advanced liver disease.

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