**CHRONIC HEPATITIS**

Chronic hepatitis represents a series of liver disorders of varying causes and severity in which hepatic inflammation and necrosis continue for at least 6 months. Milder forms are nonprogressive or only slowly progressive, while more severe forms may be associated with scarring and architectural reorganization, which, when advanced, lead ultimately to cirrhosis. Several categories of chronic hepatitis have been recognized. These include chronic viral hepatitis, drug-induced chronic hepatitis, and autoimmune chronic hepatitis. In many cases, clinical and laboratory features are insufficient to allow assignment into one of these three categories; these “idiopathic” cases are also believed to represent autoimmune chronic hepatitis. Finally, clinical and laboratory features of chronic hepatitis are observed occasionally in patients with such hereditary/metabolic disorders as Wilson's disease (copper overload) and even occasionally in patients with alcoholic liver injury. Although all types of chronic hepatitis share certain clinical, laboratory, and histopathologic features, chronic viral and chronic autoimmune hepatitis are sufficiently distinct to merit separate discussions.

**CLASSIFICATION OF CHRONIC HEPATITIS**

Common to all forms of chronic hepatitis are histopathologic distinctions based on localization and extent of liver injury. These vary from the milder forms, previously labeled chronic persistent hepatitis and chronic lobular hepatitis, to the more severe form, formerly called chronic active hepatitis. When first defined, these designations were felt to have prognostic implications, which have been challenged by more recent observations. Compared to the time three decades ago when the histologic designations chronic persistent, chronic lobular, and chronic active hepatitis were adopted, much more information is currently available about the causes, natural history, pathogenesis, serologic features, and therapy of chronic hepatitis. Therefore, categorization of chronic hepatitis based primarily upon histopathologic features has been replaced by a more informative classification based upon a combination of clinical, serologic, and histologic variables.

Classification of chronic hepatitis is based upon

1) its cause,

2) its histologic activity, or grade,

3) its degree of progression, or stage.

Thus, neither clinical features alone nor histologic features—requiring liver biopsy—alone are sufficient to characterize and distinguish among the several categories of chronic hepatitis.

**Classification by Cause**

Clinical and serologic features allow the establishment of a diagnosis of chronic viral hepatitis, caused by hepatitis B, hepatitis B plus D, hepatitis C, or potentially other unknown viruses; autoimmune hepatitis, including several subcategories, types 1, 2, and 3, based on serologic distinctions; drug-associated chronic hepatitis; and a category of unknown cause, or cryptogenic chronic hepatitis. These are addressed in more detail below.

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| **Clinical and Laboratory Features of Chronic Hepatitis** |
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| ***Type of Hepatitis*** | ***Diagnostic Test(s)*** | ***Autoantibodies*** | ***Therapy*** |
|  |
| Chronic hepatitis B | HBsAg, IgG anti-HBc, HBeAg, HBV DNA | Uncommon | IFN-α, lamivudine |
| Chronic hepatitis C | Anti-HCV, HCV RNA | Anti-LKM1a | PEG-IFN-α plus ribavirin |
| Chronic hepatitis D | Anti-HDV, HDV RNA, HBsAg, IgG anti-HBc | Anti-LKM3 | IFN-α (?) |
| Autoimmune hepatitis | ANAb (homogeneous), anti-LKM1(±), hyperglobulinemia | ANA, anti-LKM1, anti-SLAc | Prednisone, azathioprine |
| Drug-associated | — | Uncommon | Withdraw drug |
| Cryptogenic | All negative | None | Prednisone (?), azathioprine (?) |
|  |
| *a* Antibodies to liver-kidney microsomes type 1 (autoimmune hepatitis type II and some cases of hepatitis C). |
| *b* Antinuclear antibody (autoimmune hepatitis type I). |
| *c* Antibodies to soluble liver antigen (autoimmune hepatitis type III). |
| ***Note***: HBsAg, hepatitis B surface antigen; IFN-α, interferon α; PEG-IFN-α, pegylated interferon α. |

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**Classification by Grade**

Grade, a histologic assessment of necroinflammatory activity, is based upon examination of the liver biopsy. An assessment of important histologic features includes the degree of periportal necrosis and the disruption of the limiting plate of periportal hepatocytes by inflammatory cells (so-called piecemeal necrosis or interface hepatitis); the degree of  confluent necrosis that links or forms bridges between vascular structures—between portal tract and portal tract or even more important bridges between portal tract and central vein—referred to as bridging necrosis; the degree of hepatocyte degeneration and focal necrosis within the lobule; and the degree of portal inflammation. Several scoring systems that take these histologic features into account have been devised, and the most popular is the numerical histologic activity index (HAI), based on the work of Knodell and Ishak Technically, the HAI, which is primarily a measure of grade, also includes an assessment of fibrosis, which is currently used to categorize stage of the disease, as described below. Based on the presence and degree of these features of histologic activity, chronic hepatitis can be graded as mild, moderate, or severe.

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| **TABLE Histologic Activity Index (HAI) (Knodell-Ishak Score) in Chronic Hepatitis** |
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|  |
|   | ***HAI*****a**  | ***Modified HAI*****b**  |
| ***Histologic Feature*** | ***Severity*** | ***Score*** | ***Severity*** | ***Score*** |
|  |
| 1.  Perioportal necrosis,including piecemealnecrosis (PN)and/or bridgingnecrosis (BN) | NoneMild PNModerate PNMarked PNModerate PN + BNMarked PN + BNMultilobular necrosis |   0  1  3  4  5  610 | NoneMildMild/moderateModerateSevere |   0  1  2  3  4 |
| 2.  Intralobular necrosis | NoneMildModerateMarked |   0  1  3  4 | Confluent  NoneFocalZone 3 someZone 3 mostZone 3 + BN fewZone 3 + BN multiplePanacinar/multiacinarFocal  None≤ 1 focus/10× field2–4 foci/10× field5–10 foci/10× field>10 foci/10× field |   0  1  2  3  4  5  6  0  1  2  3  4 |
| 3.  Portal inflammation | NoneMildModerateModerate/markedMarked |   0  1  3  3  4 |   |   0  1  2  3  4 |
| 4.  Fibrosis | NonePortal fibrosis—somePortal fibrosis—mostBridging fibrosis—fewBridging fibrosis—manyIncomplete cirrhosisCirrhosis |   0  1  1  3  3  3  4 |   |   0  1  2  3   4  5  6 |
| Maximum score |   |   22 |   | Grade 18/Stage 6 |
|  |
| *a* “Knodell Score,” Hepatology 1:431, 1981 |
| *b* “Ishak Score,” Hepatology 24:289, 1996 |

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**Classification by Stage**

The stage of chronic hepatitis, which reflects the level of progression of the disease, is based on the degree of fibrosis. When fibrosis is so extensive that fibrous septa surround parenchymal nodules and alter the normal architecture of the liver lobule, the histologic lesion is defined as cirrhosis. Staging is based on the degree of fibrosis as categorized by one of several numerical scales.

Reconciliation between Histologic Classification and New Classification

For historic purposes, and to provide the basis for navigating several decades worth of literature on chronic hepatitis, the histologic categories of chronic persistent hepatitis, chronic lobular hepatitis, and chronic active hepatitis are correlated with their contemporary counterparts in . When the early classification was devised, chronic persistent and lobular hepatitis were felt to have a good prognosis, while chronic active hepatitis was considered a progressive disorder with a poor prognosis. The prognostic value of these histologic distinctions, however, was found to be limited, and this classification scheme has been supplanted by distinctions in grade and stage.

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| **TABLE Correlation Between Earlier and Contemporary Nomenclature of Chronic Hepatitis** |
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|  |
|   | ***Contemporary Classification***  |
| ***Old Classification*** | ***Grade (Activity)*** | ***Stage (Fibrosis)*** |
|  |
| Chronic persistent hepatitisa | Minimal or mild | None or mild |
| Chronic lobular hepatitisb | Mild or moderate | Mild |
| Chronic active hepatitisc | Mild, moderate, or severe | Mild, moderate, or severe |
|  |
| *a* Inflammatory infiltrate localized to, and confined within, portal tracts. |
| *b* Portal inflammation confined within portal tracts plus foci of necrosis and inflammation in the liver lobule, resembling slowly resolving acute hepatitis. |
| *c* Erosion of the limiting plate of periportal hepatocytes by inflammatory cells (“piecemeal necrosis” or “interface hepatitis”), usually with periportal connective tissue septa extending into the liver lobule. More severe instances involve hepatocellular dropout and collapse spanning liver lobules (“bridging necrosis”), and, in the most severe form, multilobular collapse, bridging necrosis, and collapse of lobules are extensive and associated with rapid clinical deterioration. |

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**CHRONIC VIRAL HEPATITIS**

The term hepatitis describes inflammation of the liver. Hepatitis may be caused by alcohol, drugs, autoimmune diseases, metabolic diseases, and viruses. Viral infection accounts for more than half the cases of acute hepatitis in the United States.

The term viral hepatitis is often thought to be synonymous with diseases caused by the known hepatotropic viruses, including hepatitis viruses A, B, C, D, and E. However, the term hepatotropic is itself a misnomer. Infections with hepatitis viruses, especially hepatitis viruses B and C, have been associated with a wide variety of extrahepatic manifestations. Infrequent causes of viral hepatitis include adenovirus, cytomegalovirus, Epstein-Barr virus, and, rarely, herpes simplex virus infection. Newly discovered pathogens (eg, virus SEN-V) may account for additional cases of non-A/non-E hepatitis.

**Epidemiology of viral hepatitis**

Hepatitis A virus (HAV); hepatitis B virus (HBV); hepatitis C virus (HCV); hepatitis D virus (HDV), which requires coexisting HBV infection; and hepatitis E virus (HEV) cause 95% of cases of acute viral hepatitis observed in the United States. Whether hepatitis G virus (HGV) is pathogenic in humans remains unclear. HAV is the most common cause of acute hepatitis in the United States; HCV is the most common cause of chronic hepatitis. Typical patterns of virus transmission are as follows, with + symbols indicating the frequency of transmission (ie, more + symbols = higher frequency):

1. Fecal-oral transmission

* HAV (+++)
* HEV (+++)

2. Parenteral transmission

* HBV (+++)
* HCV (+++)
* HDV (++)
* HGV (++)
* HAV (+)

3. Sexual transmission

* HBV (+++)
* HDV (++)
* HCV (+)

4. Perinatal transmission

* HBV (+++)
* HCV (+)
* HDV (+)

5. Sporadic (unknown) transmission

* HBV (+)
* HCV (+)

**Natural history of chronic viral hepatitis**

Approximately 90-95% of cases of acute hepatitis B in neonates, 5% of cases of acute hepatitis B in adults, and as many as 85% of cases of acute hepatitis C demonstrate histologic evolution to chronic hepatitis. Some patients with chronic hepatitis remain asymptomatic for their entire lives. Other patients report fatigue (ranging in severity from mild to severe) and dyspepsia.

Approximately 20% of patients with chronic hepatitis B or hepatitis C eventually develop cirrhosis, histologically. While some patients with cirrhosis are asymptomatic, others develop life-threatening complications. The clinical illnesses of chronic hepatitis and cirrhosis may take months, years, or decades to evolve.

**HEPATITIS B**

* Hepatitis B virus

HBV is a member of the Hepadnaviridae family. It is a 3.2-kb partially doubled-stranded DNA virus. Its positive strand is incomplete. The complete negative strand has 4 overlapping genes. Gene S codes for HBsAg, also known as surface antigen, a viral surface polypeptide. Gene C codes for HBcAg, also known as core antigen, the nucleocapsid protein. It also codes for HBeAg, whose function is unknown. Gene P codes for a DNA polymerase that has reverse transcriptase activity. Gene X codes for the X protein that has transcription-regulating activity.

The viral core particle consists of a nucleocapsid, HBcAg, which surrounds HBV DNA, and DNA polymerase. The nucleocapsid is coated with HBsAg. The intact HBV virion is known as the Dane particle. Dane particles and spheres and tubules containing only HBsAg are found in the blood of infected patients. In contrast, HBcAg is not detected in the circulation. It can be identified by immunohistochemical staining of infected liver tissue.

Eight genotypic variants of the HBV (genotypes A-H) are described. Although preliminary studies suggest that particular HBV genotypes may predict the virus' response to therapy or may be associated with more aggressive disease, incorporating HBV genotype testing into clinical practice is premature.

* Mechanism of hepatocyte necrosis in HBV infection

HBV may be directly cytopathic to hepatocytes. However, immune system–mediated cytotoxicity plays a predominant role in causing liver damage. The immune assault is driven by human leukocyte antigen class I–restricted CD8 cytotoxic T lymphocytes that recognize HBcAg and HBeAg on the cell membranes of infected hepatocytes.

* Epidemiology of HBV

Infection with HBV is defined by the presence of HBsAg. Approximately 5% of the world's population (ie, 300 million people) is chronically infected with HBV. More than 10% of people living in sub-Saharan Africa and in East Asia are infected with HBV. Maintenance of a high HBsAg carriage rate in these parts of the world is partially explained by the high prevalence of perinatal transmission and by the low rate of HBV clearance by neonates.

Of cases of chronic HBV infection, 20% progress to cirrhosis or hepatocellular carcinoma (HCC), resulting in 1-2 million deaths each year. This makes hepatitis B the ninth leading cause of death in the world.

Approximately 200,000 new cases of HBV infection occur each year in the United States. Approximately 250-350 patients die from HBV-associated FHF each year.

* Transmission of HBV

HBV is readily detected in serum. It is seen at very low levels in semen, vaginal mucus, saliva, and tears. The virus is not detected in urine, stool, or sweat. HBV can survive storage at -20°C (-4°F) and heating at 60°C (140°F) for 4 hours. It is inactivated by heating at 100°C (212°F) for 10 minutes or by washing with sodium hypochlorite (bleach).

1. Perinatal transmission of HBV

The vast majority of HBV cases around the world result from perinatal transmission. Infection appears to be due to contact with a mother's infected blood at the time of delivery, as opposed to transplacental passage of the virus. Neonates infected via perinatal infection are usually asymptomatic. Although breast milk can contain HBV virions, the role of breastfeeding in transmission is unclear.

2. Sexual transmission of HBV

HBV is transmitted more easily than HIV or HCV. Infection is associated with vaginal intercourse, genital-rectal intercourse, and oral-genital intercourse. An estimated 30% of sexual partners of patients infected with HBV also contract HBV infection. However, HBV cannot be transmitted through kissing, hugging, or household contact such as sharing towels, eating utensils, or food. Sexual activity is estimated to account for as many as 50% of HBV cases in the United States.

3. Parenteral transmission of HBV

HBV was once a common cause of posttransfusion hepatitis. Screening of US blood donors for HBcAb, beginning in the early 1970s, dramatically reduced the rate of HBV infection associated with blood transfusion. Currently, approximately 1 HBV transmission occurs per 250,000 individuals transfused.

4. Sporadic cases of hepatitis B

The cause of HBV infection is unknown in approximately 27% of cases. Some these cases, in fact, may be due to sexual transmission or contact with blood.

* Natural history of HBV

The incubation period of HBV is 40-150 days, with an average of approximately 12 weeks. As with HAV, the clinical illness associated with acute HBV infection may range from mild disease to a disease as severe as FHF (<1% of patients).

After acute hepatitis resolves, 95% of adult patients and 5-10% of infected infants ultimately develop anti-HBV antibody, clear HBsAg (and HBV virions), and fully recover. Five percent of adult patients and 90-95% of infected infants develop chronic infection.

* Inactive carrier state

With the development of chronic infection (as marked by a positive HBsAg finding), 70-90% of HBsAg carriers enter the inactive carrier state (previously known as the healthy carrier state). They have no symptoms, normal liver chemistry test results, and normal or minimally abnormal liver biopsy results. Blood test evidence of HBV replication should be nonexistent or minimal, with a serum HBV DNA level in the range of 0-30,000 copies (genomes)/mL. Inactive carriers remain infectious to others through parenteral or sexual transmission.

Inactive carriers may ultimately develop HBsAb and clear the virus. However, some inactive carriers develop chronic hepatitis, as determined by liver chemistry results, liver biopsy findings, and HBV DNA levels. Inactive carriers remain at risk, albeit low, to develop HCC. At this point, no effective antiviral therapies are available for patients in an inactive carrier state.

**Chronic hepatitis B**

Of HBsAg carriers, 10-30% develop chronic hepatitis. These patients are often symptomatic. Fatigue is the most common symptom of chronic HBV infection. Patients may occasionally experience an acute flare of their disease, with symptoms and signs similar to those of acute hepatitis. Patients also may have extrahepatic manifestations of their disease, including polyarteritis nodosa, cryoglobulinemia, and glomerulonephritis.

Chronic hepatitis B patients have abnormal liver chemistry results, blood test evidence for active HBV replication, and inflammatory or fibrotic activity on liver biopsy specimens. Patients with chronic hepatitis may be considered either HBeAg-positive or HBeAg-negative.

Ultimately, approximately 20% of HBsAg carriers (approximately 1% of all adult patients infected acutely with HBV) go on to develop cirrhosis or HCC.

Patients with HBeAg-positive chronic hepatitis have signs of active viral replication with an HBV DNA level greater than 105 copies (genomes)/mL. HBV DNA levels may be as high as 1011 copies/mL.

Patients with HBeAg-negative chronic hepatitis were presumably infected with wild-type virus at some point. Over time, they acquired a mutation in either the precore or the core promoter region of the viral genome. In such patients with a precore mutant state, HBV continues to replicate but HBeAg is not produced. Patients with a core mutant state appear to have down-regulated HBeAg production. HBeAg-negative patients typically have lower HBV DNA levels than HBeAg-positive patients. More than half are noted to have an HBV DNA level less than 105 copies/mL.

**Diagnosis of chronic HBV infection**

HBsAg may remain detectable for life in many patients. Individuals who have positive findings for HBsAg are termed carriers of HBV; they may be inactive carriers or they may have chronic hepatitis. Anti-HBc is present in all patients with chronic HBV infections. HBeAg and HBV DNA may or may not be present. If present, they reflect a state of active viral replication and a high level of infectivity. Anti-HBs are usually absent in patients with chronic infection. If anti-HBs are present in a patient who has positive HBsAg findings, it reflects the presence of a low level of antibody that was unsuccessful at inducing viral clearance.

**Pathologic findings of HBV infection**

Inactive carriers of HBV have no or minimal histologic abnormalities detected on liver biopsy specimens.

Patients with chronic hepatitis B may have a number of classic histologic abnormalities. Inflammatory infiltrates composed of mononuclear cells may either remain contained within the portal areas or disrupt the limiting plates of portal tracts, expanding into the liver lobule (interface hepatitis). Periportal fibrosis or bridging necrosis (between portal tracts) may be present. The presence of bridging necrosis places the patient at increased risk for progression to cirrhosis. Ground-glass cells may be seen. This term describes the granular homogeneous eosinophilic staining of cytoplasm caused by the presence of HBsAg. Sanded nuclei reflect the presence of an overload of HBcAg. Special immunohistochemical stains may help detect HBsAg and HBcAg.

**Treatment of chronic hepatitis B**

The key goal of antiviral treatment of HBV is the inhibition of viral replication, as marked by the loss of HBeAg and HBV DNA. Secondary goals are to reduce symptoms, if any, and to prevent or delay the progression of chronic hepatitis to cirrhosis or HCC.

Antiviral therapy infrequently leads to viral eradication, as marked by the loss of HBsAg. Currently, no antiviral therapy is available for inactive carriers who do not have actively replicating virus.

Candidates for antiviral therapy must have evidence of active HBV infection. This is generally defined as the presence of HBV DNA greater than 105 copies/mL in patients who are positive for HBeAg or HBV DNA greater than 104 copies/mL in patients who are negative for HBeAg. Patients tend to have abnormal liver chemistry findings. Treatment may be offered to patients with a normal alanine aminotransferase (ALT) level, but it may be less efficacious. Although performing a liver biopsy is not mandatory prior to treatment, the author recommends it. Liver biopsy is helpful for confirming the clinical diagnosis of chronic hepatitis B and for documenting the severity of liver disease.

* Interferon alfa treatment for chronic hepatitis B

Interferons have both antiviral and immunomodulatory effects. Treatment with interferon alfa is appropriate for some patients with chronic hepatitis B.

The most commonly used dose of interferon alfa-2b is 5 million U/d subcutaneously for at least 16 weeks. Alternatively, 10 million units may be injected subcutaneously 3 times per week for at least 16 weeks. Pegylated interferon alfa may also be used once per week by subcutaneous injection.

* Lamivudine for chronic hepatitis B

Lamivudine (Epivir, GlaxoSmithKline; Research Triangle Park, NC) is the negative enantiomer of 2'3'-dideoxy-3'-thiacytidine. This synthetic nucleoside analogue inhibits DNA polymerase–associated reverse transcriptase and can suppress HBV replication. Treatment with a dose of 100 mg/d orally for 1 year result in loss of HBeAg in 32% of patients. Treatment also induces histologic improvement and a statistically significant reduction in the rate of development of hepatic fibrosis.

* HBV vaccine

Plasma-derived and recombinant HBV vaccines use HBsAg to stimulate the production of anti-HBs in noninfected individuals. The vaccines are highly effective, with a greater than 95% rate of seroconversion. Vaccine administration is recommended for all infants and for adults at high risk of infection (eg, those on dialysis, health care workers).

The recommended vaccination schedule for infants is an initial vaccination at the time of birth (ie, before hospital discharge), repeat vaccination at 1-2 months, and another repeat vaccination at 6-18 months. The recommended vaccination schedule for adults is an initial vaccination, a repeat vaccination at 1 month, and another repeat vaccination at 6 months.

**HEPATITIS C**

* Hepatitis C virus

HCV is a Flavivirus. It is a 9.4-kb RNA virus with a diameter of 55 nm. It has one serotype and multiple genotypes. HCVs have profound genetic variability throughout the world. At least 6 major genotypes and more than 80 subtypes are described, with as little as 55% genetic sequence homology. Genotype 1b is the genotype most commonly seen in the United States, Europe, Japan, and Taiwan. Genotypes 1b and 1a (also common in the United States) are thought to be less responsive to interferon therapy than other HCV genotypes. The genetic variability of HCV hampers the efforts of scientists to design an effective anti-HCV vaccine.

**Epidemiology of hepatitis C**

Hepatitis C is prevalent in 0.5-2% of populations in nations around the world. An estimated 4 million Americans are infected with HCV. In the 1980s, as many as 180,000 new cases of HCV infection were described each year in the United States. Currently, approximately 28,000 new cases are documented each year. The decreasing incidence of HCV is explained by a decline in the number of cases of transfusion-associated hepatitis (because of improved screening of blood products) and by a decline in the number of cases associated with intravenous drug use.

1. Transmission of HCV via blood transfusion

Screening of the US blood supply has dramatically reduced the incidence of transfusion-associated HCV infection. Prior to 1990, 37-58% of cases of acute HCV infection (then known as NANB) were attributed to the transfusion of contaminated blood products. Now, only approximately 4% of acute cases are attributed to transfusion. HCV is estimated to contaminate 0.01-0.001% of units of transfused blood. Acute hepatitis C remains an important issue in dialysis units, where patients' risk for HCV infection is approximately 0.15% per year.

2. Transmission of HCV via intravenous and intranasal drug use

Intravenous drug use remains an important mode of transmitting HCV. Intravenous drug use and the sharing of paraphernalia used in the intranasal snorting of cocaine and heroin account for approximately 60% of new cases of HCV infection. More than 90% of patients with a history of intravenous drug use have been exposed to HCV.

3. Transmission of HCV via occupational exposure

Occupational exposure to HCV accounts for approximately 4% of new infections. On average, the chance of acquiring HCV after a needle stick injury involving an infected patient is 1.8% (range, 0-7%). Importantly, reports of HCV transmission from health care workers to patients are extremely uncommon.

4. Transmission of HCV via sexual contact

Approximately 20% of cases of hepatitis C appear to be due to sexual contact. In contrast to hepatitis B, approximately 5% of the sexual partners of those infected with HCV contract hepatitis C. Currently, the US Public Health Service recommends that persons infected with HCV be informed of the potential for sexual transmission. Sexual partners should be tested for the presence of anti-HCV. Safe sex precautions are recommended for patients with multiple sex partners. Current guidelines do not recommend the use of barrier precautions for patients with a steady sexual partner. However, it is recommended that patients avoid sharing razors and toothbrushes with others. Additionally, contact with patients' blood should be avoided.

5. Transmission of HCV via perinatal transmission

Perinatal transmission appears to be uncommon. It is observed in fewer than 5% of children born to mothers infected with HCV. The risk of perinatal transmission of HCV is higher, estimated at 18%, in children born to mothers co-infected with HIV and HCV. Available data show no increase in HCV infection in babies who are breastfed. The US Public Health Service does not advise against pregnancy or breastfeeding for women infected with HCV.

* Natural history of chronic hepatitis C

Approximately 15% of patients acutely infected with HCV lose virologic markers for HCV. Thus, approximately 85% of newly infected patients remain viremic and may develop chronic liver disease. In chronic hepatitis, patients may or may not be symptomatic, with fatigue being the predominant reported symptom. Aminotransferase levels may fluctuate from the reference range (<40 U/L) to 300 U/L. However, no clear-cut association exists between aminotransferase levels and symptoms or risk of disease progression.

* Natural history of cirrhosis induced by hepatitis C

An estimated 20% of patients with chronic hepatitis C experience progression to cirrhosis. This process may take 10-40 years to evolve. Importantly, patients who are newly diagnosed with well-compensated cirrhosis must be counseled regarding their risk of developing symptoms of liver failure (ie, decompensated cirrhosis). Only 30% of patients with well-compensated cirrhosis are anticipated to decompensate over a 10-year follow-up period.

Patients with HCV-induced cirrhosis are also at increased risk for the development of HCC, especially in the setting of HBV co-infection. In the United States, HCC arises in 3-5% of patients with HCV-induced cirrhosis each year. Accordingly, routine screening (eg, ultrasound and AFP testing every 6 mo) is recommended in patients with HCV-induced cirrhosis to rule out the development of HCC.

End-stage liver disease caused by HCV leads to 8000-10,000 deaths each year.

* **Extrahepatic manifestations of hepatitis C**

Patients with chronic hepatitis C are at risk for extrahepatic complications. In essential mixed cryoglobulinemia, HCV may form immune complexes with anti-HCV (IgG) and with rheumatoid factor. The deposition of immune complexes may cause small-vessel damage. Complications of cryoglobulinemia include rash, vasculitis, and glomerulonephritis. Other extrahepatic complications of HCV infection include focal lymphocytic sialadenitis, autoimmune thyroiditis, porphyria cutanea tarda, lichen planus, and Mooren corneal ulcer.

* Pathologic findings of hepatitis C

Lymphocytic infiltrates, either contained within the portal tract or expanding out of the portal tract into the liver lobule (interface hepatitis), are commonly observed in patients with chronic hepatitis C. Portal and periportal fibrosis may be present. Other classic histologic features of the disease include bile duct damage, lymphoid follicles or aggregates, and macrovesicular steatosis.

Pathologists who interpret liver biopsy specimens frequently use a histologic scoring system introduced by Batts and Ludwig in 1995, which is displayed in the Table. The METAVIR scoring system (developed by the French METAVIR Cooperative Study Group) uses similar methodology.

Histologic Grading for Hepatitis C–Induced Liver Disease

|  |  |  |  |
| --- | --- | --- | --- |
| Grade | Portal Inflammation | Interface Hepatitis | Lobular Necrosis |
| 1 - Minimal | Mild | Scant | None |
| 2 - Mild | Mild | Mild | Scant |
| 3 - Moderate | Moderate | Moderate | Spotty |
| 4 - Severe | Marked | Marked | Confluent |

The histologic staging for hepatitis C–induced liver disease is as follows:

Stage 1 - Portal fibrosis

Stage 2 - Periportal fibrosis

Stage 3 - Septal fibrosis

Stage 4 - Cirrhosis

**Diagnosis of hepatitis C**

The most common tests used in the diagnosis of hepatitis C include liver chemistries, serologic tests, HCV RNA tests, and liver biopsies.

* Diagnosis of hepatitis C using liver chemistry testing

Elevations of the aspartate aminotransferase (AST) and ALT merely indicate the presence of liver injury. Patients with chronically elevated aminotransferase values should undergo a workup to exclude the possibility of chronic liver disease.

* Diagnosis of hepatitis C using serologic tests for HCV

Structural and nonstructural regions of the HCV genome have been synthesized. These can be recognized by human IgG anti-HCV. Recombinant HCV antigens are used in enzyme-linked immunoabsorbent assays (ELISAs) to detect anti-HCV in patients' sera.

* Diagnosis of hepatitis C using HCV RNA tests

PCR assays and branched DNA assays have been used since the early 1990s to detect HCV RNA in serum. In contrast to ELISA and RIBA testing, HCV RNA testing can confirm the presence of active HCV infection.

* Diagnosis of hepatitis C using liver biopsy

Liver biopsy is an important diagnostic test in possible cases of chronic hepatitis C. Biopsy can help confirm the diagnosis and can help exclude other diseases that might have an impact on antiviral therapy, such as autoimmune hepatitis or hemochromatosis. Furthermore, liver biopsy offers the most reliable assessment of the severity of disease.

Patients with minimal inflammatory or fatty changes on biopsy specimens may elect to not receive antiviral therapy. Such patients may return for repeat biopsy in 3-4 years to rule out progression of liver disease. Patients with previously unsuspected cirrhosis on biopsy specimens should be monitored to ensure they do not develop large esophageal varices or HCC. Furthermore, knowledge of the severity of histologic changes may influence the patient and the physician to be more aggressive or less aggressive in the pursuit of effective antiviral therapy. Patients with advanced histologic findings may seek experimental therapies should they not respond to standard antiviral therapy.

**Treatment of HCV infection**

Antiviral therapy has a number of major goals. These include (1) to decrease viral replication or eradicate HCV, (2) to prevent progression of disease, (3) to decrease the prevalence of cirrhosis, (4) to decrease the frequency of HCC as a complication of cirrhosis, (5) to ameliorate symptoms such as fatigue and joint pain, and (6) to treat extrahepatic complications of HCV infection such as cryoglobulinemia or glomerulonephritis.

Interferons are a class of naturally occurring compounds that have both antiviral and immunomodulatory effects. Currently, they are the backbone of antiviral strategies used against HCV infection. Future medications may target the enzymes responsible for HCV replication and may have activity against viral helicases, proteases, and polymerases.

* Treatment of chronic hepatitis C

Interferon alfa-2b, dosed at 3 million units subcutaneously 3 times per week, was approved by the FDA in 1991 for the treatment of chronic HCV infection. Patients treated with this interferon, and with subsequently introduced interferon alfa-2a and consensus interferon, had only an 11-12% chance of obtaining a sustained virologic response (ie, a persistently undetectable HCV RNA level).

The combination of ribavirin, a nucleoside analog, with interferon significantly improved patients' responses to treatment. The sustained virologic response after 48 weeks of treatment improved from 13% in patients treated with interferon alfa-2b alone to 38% in patients treated with interferon alfa-2b in combination with ribavirin at 1000-1200 mg/d orally. So-called combination therapy received approval from the FDA in 1998.

* Limitations of antiviral therapy

Not all patients with chronic hepatitis C are appropriate candidates for therapy with interferon and ribavirin. First, the medications have well-known adverse effects, which lead to drug discontinuation in approximately 15% of patients. Interferon can induce fatigue, joint pain, depression, alopecia, neutropenia, and thrombocytopenia. Interferon has been known to induce the development of thyroid disease or exacerbate an underlying immune-mediated disease (eg, psoriasis, sarcoidosis). Ribavirin commonly produces a hemolytic anemia and can induce a rash. Patients with baseline thrombocytopenia (eg, platelet count <70,000/mL) are not anticipated to tolerate interferon administration. Patients with underlying psychiatric disorders must be screened carefully before receiving a drug that has the potential to worsen underlying depression or schizophrenia or even induce suicidal ideation.

**HEPATITIS D**

* Hepatitis D virus

HDV is a single-stranded, 1.7-kb RNA virus. The viral particle is 36 nm in diameter and contains HDAg and the RNA strand. It uses HBsAg as its envelope protein. Thus, HBV co-infection is necessary for the packaging and release of HDV virions from infected hepatocytes.

* Epidemiology of HDV

HDV is believed to infect approximately 5% of the world's 300 million HBsAg carriers. The prevalence of HDV infection in South America and Africa is high. Italy and Greece are areas of intermediate endemicity and are well studied. The sharing of contaminated needles in intravenous drug use is thought to be the most common means of transmitting HDV. Persons who use intravenous drugs who are also positive for HBsAg have been found to have HDV prevalence rates ranging from 17-90%. Sexual and perinatal transmission also are described. The prevalence of HDV in prostitutes in Greece and Taiwan is high.

* Natural history of HDV co-infection

Simultaneous introduction of HBV and HDV into a patient results in the same clinical picture as acute infection with HBV alone. The resulting acute hepatitis may be mild or severe. Similarly, the risk of developing chronic HBV and HDV infection after acute exposure to both viruses is the same as the rate of developing chronic HBV infection after acute exposure to HBV (approximately 5% in adults). However, chronic HBV and HDV disease tends to progress more rapidly to cirrhosis than chronic HBV infection alone.

* Natural history of HDV superinfection

Introduction of HDV into an individual already infected with HBV may have dramatic consequences. Superinfection may give HBsAg-positive patients the appearance of a sudden worsening or flare of hepatitis B. HDV superinfection may result in FHF.

* Pathologic findings of HDV infection

Pathologic abnormalities associated with HBV/HDV infection are the same as those observed in patients infected with HBV alone.

* Diagnosis of HDV infection

A serologic diagnosis of HDV infection is made by using IgM anti-HDV and IgG anti-HDV tests. HBcAb IgM should be used to help distinguish between co-infection (HBcAb IgM–positive) and superinfection (HBcAb IgM–negative). Detecting HDV RNA in serum is also possible.

* Treatment of hepatitis D

Patients co-infected with HBV and HDV are less responsive to interferon therapy than patients infected with HBV alone. To date, lamivudine appears to be ineffective against HBV/HDV co-infection.

**HEPATITIS E**

* Hepatitis E virus

HEV is a Calicivirus. It is a 7.5-kb single-stranded RNA virus and is 32-34 nm. The virus has an incubation period of 2-9 weeks.

* Epidemiology of HEV

HEV is transmitted via the fecal-oral route. HEV appears to be endemic in some parts of the lesser-developed countries. Anti-HEV antibodies are observed in as many as 60% of Indian children younger than 5 years. Sporadic infections are observed in persons traveling from western countries to these regions.

* Natural history of HEV

HEV primarily infects adults and young adults. Acute infection is generally less severe than acute HBV infection and is characterized by fluctuating aminotransferase levels. However, pregnant women, especially when infected during the third trimester, have up to a 25% risk of mortality associated with acute HEV infection. HEV does not appear to cause chronic liver disease.

* Pathologic findings of HEV infection

The classic pathological findings include infiltration of portal tracts by lymphocytes and polymorphonuclear leukocytes, ballooned hepatocytes, acidophilic body formation, and the intralobular necrosis of hepatocytes. Submassive and massive hepatic necrosis may be observed in severe cases.

* Diagnosis of HEV infection

The serologic diagnosis is made by using IgM anti-HEV and IgG anti-HEV. HEV RNA can be detected in the serum and stool of infected patients.

* Treatment of hepatitis E

The treatment of those infected with HEV is supportive in nature.

**HEPATITIS G**

HGV is similar to viruses in the Flaviviridae family, which includes HCV. The HGV genome codes for 2900 amino acids. The virus has 95% homology (at the amino acid level) with the GB virus (ie, GBV-C), a previously described virus. HGV has 26% homology (at the amino acid level) with HCV.

HGV can be transmitted by blood transfusion. HGV co-infection is observed in 6% of chronic HBV infections and in 10% of chronic HCV infections. However, whether HGV is actually pathogenic in humans remains unclear.

**AUTOIMMUNE HEPATITIS**

During the past 30 years, remarkable advances have occurred in the understanding of the epidemiology, natural history, and pathogenesis of chronic hepatitis. The development of viral serologic tests has permitted hepatologists to differentiate chronic viral hepatitis from other types of chronic liver disease, including autoimmune hepatitis. Autoimmune hepatitis is now accepted as a chronic disease of unknown cause, characterized by continuing hepatocellular inflammation and necrosis, which tends to progress to cirrhosis. Immune serum markers frequently are present, and the disease often is associated with other autoimmune diseases. Autoimmune hepatitis cannot be explained based on chronic viral infection, alcohol consumption, or exposure to hepatotoxic medications or chemicals.

In 1950, Waldenstrom first described a form of chronic hepatitis in young women. This condition was characterized by cirrhosis, plasma cell infiltration of the liver, and marked hypergammaglobulinemia. Kunkel, in 1950, and Bearn, in 1956, described other features of the disease, including hepatosplenomegaly, jaundice, acne, hirsutism, cushingoid facies, pigmented abdominal striae, obesity, arthritis, and amenorrhea. In 1955, Joske first reported the association of the lupus erythematosus (LE) cell phenomenon in active chronic viral hepatitis. This association led to the introduction of the term lupoid hepatitis by Mackay and associates in 1956. Researchers currently know that no direct link exists between systemic lupus erythematosus (SLE) syndrome and autoimmune hepatitis; thus, lupoid hepatitis is not associated with SLE.

Autoimmune hepatitis now is recognized as a multisystem disorder that can occur in males and females of all ages. This condition can coexist with other liver diseases (eg, chronic viral hepatitis) and also may be triggered by certain viral infections (eg, hepatitis A) and chemicals (eg, minocycline).

The histopathologic description of autoimmune hepatitis has undergone several revisions over the years. In 1992, an international panel last codified the diagnostic criteria. The term autoimmune hepatitis was selected to replace terms such as autoimmune liver disease and autoimmune chronic active hepatitis. The panel waived the requirement of 6 months of disease activity to establish chronicity, expanded the histologic spectrum to include lobular hepatitis, and reaffirmed the nonviral nature of the disease. The panel also designated incompatible histologic features, such as cholestatic histology, the presence of bile duct injury, and ductopenia.

**Frequency**

In the US: The frequency of autoimmune hepatitis among patients with chronic liver disease ranges from 11-23%.

Internationally: The frequency of autoimmune hepatitis among patients with chronic liver disease in North America is 11-23%. Incidence in Western Europe is 0.69 cases per 100,000 persons per year; this statistic can be applied to other ethnically similar populations. Prevalence is greatest among northern European/Caucasian groups with a high frequency of HLA-DR3 and HLA-DR4 markers.

Women are affected more often than men (70-80% of patients are women).

Autoimmune hepatitis usually is detected in the third to fifth decades of life, but young children and older adults also are affected. Men are affected more commonly than women in older age groups.

**Causes**

Autoimmune hepatitis is a chronic disease of unknown etiology.

**Pathophysiology**

Evidence suggests that liver injury in a patient with autoimmune hepatitis is the result of a cell-mediated immunologic attack. This attack is directed against genetically predisposed hepatocytes. Aberrant display of human leukocyte antigen (HLA) class II on the surface of hepatocytes facilitates the presentation of normal liver cell membrane constituents to antigen-processing cells. These activated cells, in turn, stimulate the clonal expansion of autoantigen-sensitized cytotoxic T lymphocytes. Cytotoxic T lymphocytes infiltrate liver tissue, release cytokines, and help to destroy liver cells.

The reasons for the aberrant HLA display are unclear. It may be initiated or triggered by genetic factors, viral infections (eg, acute hepatitis A or B, Epstein-Barr virus infection), and chemical agents (eg, interferon, melatonin, alpha methyldopa, oxyphenisatin, nitrofurantoin, tienilic acid). The asialoglycoprotein receptor and the cytochrome mono-oxygenase P-450 IID6 are proposed as the triggering autoantigens.

Some patients appear to be genetically susceptible to developing autoimmune hepatitis. This condition is associated with the complement allele C4AQO and with the HLA haplotypes B8, B14, DR3, DR4, and Dw3. C4A gene deletions are associated with the development of autoimmune hepatitis in younger patients. HLA DR3-positive patients are more likely than other patients to have aggressive disease, which is less responsive to medical therapy; these patients are younger than other patients at the time of their initial presentation. HLA DR4-positive patients are more likely to develop extrahepatic manifestations of their disease.

* **Evidence for an autoimmune pathogenesis includes the following:**

1. Hepatic histopathologic lesions composed predominantly of cytotoxic T cells and plasma cells

2. Circulating autoantibodies (ie, nuclear, smooth muscle, thyroid, liver-kidney microsomal, soluble liver antigen, hepatic lectin)

3. Association with hypergammaglobulinemia and the presence of a rheumatoid factor

4. Association with other autoimmune diseases

5. Response to steroid and/or immunosuppressive therapy

The autoantibodies described in these patients include the following:

* Antinuclear antibody (ANA), primarily in a homogenous pattern
* Anti–smooth muscle antibody (ASMA) directed at actin
* Anti–liver-kidney microsomal antibody (anti–LKM-1)
* Antibodies against soluble liver antigen (anti-SLA) directed at cytokeratins types 8 and
* Antibodies to liver-specific asialoglycoprotein receptor or hepatic lectin
* Antimitochondrial antibody (AMA) - The sine qua non of primary biliary cirrhosis (PBC) but may be observed in the so-called overlap syndrome with autoimmune hepatitis
* Antiphospholipid antibodies

Based on autoantibody markers, autoimmune hepatitis is recognized as a heterogeneous disorder and has been subclassified into 3 types. The distinguishing features of these types are noted in the Table.

Clinical Characteristics of Autoimmune Hepatitis

|  |  |  |  |
| --- | --- | --- | --- |
| Clinical Features | Type 1 | Type 2 | Type 3 |
| Diagnostic autoantibodies | ASMA ANAAntiactin | Anti-LKMP-450 IID6Synthetic core motif peptides 254-271 | Soluble liver-kidney antigenCytokeratins 8 and 18 |
| Age | Bimodal (10-20 y and 45-70 y) | Pediatric (2-14 y)Rare in adults | Adults (30-50 y) |
| Women (%) | 78 | 89 | 90 |
| Concurrent immune disease (%) | 41 | 34 | 58 |
| Gamma globulin elevation | +++ | + | ++ |
| Low IgA\* | No | Occasional | No |
| HLA association | B8, DR3, DR4 | B14, Dr3, C4AQO | Uncertain |
| Steroid response | +++ | ++ | +++ |
| Progression to cirrhosis (%) | 45 | 82 | 75 |

\*Immunoglobulin A

**CLINICAL**

**History**

Clinical features of autoimmune hepatitis

Autoimmune hepatitis may present as acute hepatitis, chronic hepatitis, or well-established cirrhosis.

Approximately one third of patients present with symptoms of acute hepatitis marked by fever, hepatic tenderness, and jaundice. In some patients, the acute illness may appear to resolve spontaneously; however, patients invariably develop signs and symptoms of chronic liver disease. Other patients experience rapid progression of the disease to acute liver failure, as marked by coagulopathy and jaundice. Ascites and hepatic encephalopathy also may ensue.

Clinicians must consider the diagnosis of autoimmune hepatitis when confronted with a patient who has acute hepatitis or acute liver failure (defined by the new onset of coagulopathy). The workup of such patients should include testing for serum ANA, ASMA, serum protein electrophoresis (SPEP), and quantitative immunoglobulins. Urgent liver biopsy, transjugular if appropriate, may help to confirm the clinical suspicion of acute autoimmune hepatitis. Rapid institution of treatment with high-dose corticosteroids may rescue patients whose disease ultimately would have progressed to either fulminant hepatic failure or cirrhosis. Other patients continue to deteriorate in spite of immunosuppressant therapy. Accordingly, a low threshold should exist for transferring patients with acute liver failure to tertiary care hospitals that are capable of performing emergent liver transplantation.

The chronic hepatitis associated with autoimmune hepatitis may range in severity from a subclinical illness without symptoms and with abnormal results on liver chemistries to a disabling chronic liver disease. Symptoms and physical examination findings may stem from the various extrahepatic diseases associated with autoimmune hepatitis.

Common symptoms include the following:

* Fatigue
* Upper abdominal discomfort
* Mild pruritus
* Anorexia
* Myalgia
* Diarrhea
* Cushingoid features
* Arthralgias
* Skin rashes (including acne)
* Edema
* Hirsutism
* Amenorrhea
* Chest pain from pleuritis
* Weight loss and intense pruritus (unusual)

Without therapy, most patients die within 10 years of disease onset. Treatment with corticosteroids has been shown to improve the chances for survival significantly. Indeed, the life expectancy of patients in clinical remission is similar to that of the general population.

Many patients have histologic evidence of cirrhosis at the onset of symptoms. This is true both for patients with an initial presentation of acute hepatitis and for patients with chronic hepatitis. Thus, subclinical disease often precedes the onset of symptoms.

As many as 20% of patients present initially with signs of decompensated cirrhosis. In other patients, chronic hepatitis progresses to cirrhosis after years of unsuccessful immunosuppressant therapy marked by multiple disease relapses. Patients with cirrhosis may experience classic symptoms of portal hypertension, namely variceal bleeding, ascites, and hepatic encephalopathy. Patients with complications of cirrhosis should be referred for consideration of liver transplantation.

Disease associations: Autoimmune hepatitis, especially type 2, is associated with a wide variety of other disorders. Involvement of other systems may present at disease onset or may develop during the course of active liver disease. These conditions, most of which are immunologic in origin, include the following:

* Hematologic complications
* Hematologic manifestations of hypersplenism
* Autoimmune hemolytic anemia
* Coombs-positive hemolytic anemia
* Pernicious anemia
* Idiopathic thrombocytopenic purpura
* Eosinophilia
* Gastrointestinal complications
* The hepatitis C connection

The hepatitis C virus (HCV) has several important associations with autoimmune hepatitis. The prevalence rate of HCV infection in patients with autoimmune hepatitis is similar to that in the general population.

Although autoimmune hepatitis and chronic HCV have similar histologic features, moderate-to-severe plasma cell infiltration of the portal tracts is more common in patients with autoimmune hepatitis. Portal lymphoid aggregates, steatosis, and bile duct damage are more common in patients with chronic HCV.

**Overlap syndromes**

Patients with autoimmune hepatitis may present with features that overlap those classically associated with patients with PBC and PSC. Patients with disease that overlaps with PBC may have detectable AMA (usually in low titer), histologic findings of bile duct injury and/or destruction, and the presence of hepatic copper. These patients may improve with steroid therapy. Patients with disease that overlaps with PSC usually have concurrent inflammatory bowel disease, and the liver biopsy findings reveal bile duct injury. Findings from cholangiograms are abnormal. Such patients usually have mixed hepatocellular and cholestatic liver chemistries and typically are resistant to steroid therapy.

Autoimmune cholangitis is characterized by mixed hepatic and cholestatic liver chemistries, positive ANA and/or ASMA, negative AMA, antibodies to carbonic anhydrase, and histology that resembles PBC. Patients may have an unpredictable response to therapy with steroids or ursodeoxycholic acid.

* Cryptogenic autoimmune hepatitis is characterized by a clinical picture that is indistinguishable from autoimmune hepatitis. ANA, ASMA, and anti–LKM-1 are negative at disease onset and may appear late in the disease course, as might anti-SLA. The disease usually is responsive to steroid therapy.

**Physical**

Common findings on physical examination are as follows:

* Hepatomegaly (83%)
* Jaundice (69%)
* Splenomegaly (32%)
* Spider angiomata (58%)
* Ascites (20%)
* Encephalopathy (14%)

All of these findings may be observed in patients with disease that has progressed to the point of cirrhosis with ensuing portal hypertension; however, hepatomegaly, jaundice, splenomegaly, and spider angiomata also may be observed in patients who do not have cirrhosis.

**Lab Studies**

**1. Autoantibodies**

Autoimmune hepatitis is characterized by positive findings on autoantibody tests. Autoimmune hepatitis type 1 is characterized by positive test results for ASMA and ANA. Type 2 disease is observed infrequently in the United States, but it is well characterized in Europe. Type 2 disease is marked by a positive test result for anti–LKM-1 antibody. Type 3 disease also is observed infrequently in the United States. Type 3 is marked by a positive test result for anti-SLA antibody.

**2. Serum protein electrophoresis and quantitative immunoglobulins**

An immunoglobulin G (IgG)–predominant polyclonal hypergammaglobulinemia is a common finding in patients with untreated autoimmune hepatitis. Gamma globulin values typically range from 3-4 g/dL and frequently are as high as 5-6 g/dL. Cases of hyperviscosity syndrome secondary to high IgG levels are reported. Autoimmune hepatitis is an unlikely diagnosis in patients who have acute hepatitis without hypergammaglobulinemia.

The gamma globulin or the IgG level may be followed on a regular basis as a marker of disease responsiveness to therapy.

**3. Aminotransferases**

Serum aminotransferases (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]) are elevated in 100% of patients at initial presentation, with average values of 200-300 U/L. Aminotransferase values correlate poorly with the degree of hepatic necrosis; however, values in the thousands may indicate acute hepatitis or a severe flare of preexisting disease.

Continued elevation of the aminotransferases in the face of ongoing therapy is a reliable marker for ongoing inflammatory activity in the liver. Normalization of the aminotransferase levels during therapy is an encouraging sign, but active liver inflammation is present in more than 50% of patients with normalized liver chemistries. Indeed, biochemical remission may precede true histologic remission by 3-12 months; thus, patients should be treated for at least 1 year after documentation of normal liver chemistries. Liver biopsy then may be employed to determine whether the patient is in histologic remission. Drug withdrawal may be attempted at this time.

Worsening of aminotransferase levels in a patient undergoing treatment or in a patient who is in remission may signal a resurgence of disease activity.

**4. Other liver chemistries**

Serum bilirubin and alkaline phosphatase values are mildly to moderately increased in 80-90% of patients. A sharp increase in the alkaline phosphatase values during the course of autoimmune disease might reflect the development of PSC or the onset of hepatocellular carcinoma as a complication of cirrhosis.

Hypoalbuminemia and prolongation of prothrombin time are markers of severe hepatic synthetic dysfunction, which may be observed in active disease or decompensated cirrhosis.

**5. Other common laboratory abnormalities**

* Mild leukopenia
* Normochromic anemia
* Coombs-positive hemolytic anemia
* Thrombocytopenia
* Elevated sedimentation rate
* Eosinophilia (uncommon but counts ranging from 9-48% are described)

Autoimmune hepatitis even has been described as the sole presenting feature of idiopathic hypereosinophilic syndrome.

**Imaging Studies**

Imaging studies, in general, are not helpful in reaching a definitive diagnosis of autoimmune hepatitis; however, the presence of heterogeneous echotexture on abdominal ultrasound or abnormal contrast enhancement on abdominal CT imaging may suggest the presence of active inflammation or necrosis. The appearance of an irregular nodular liver may confirm the presence of cirrhosis. Furthermore, these imaging studies may be used to rule out the presence of hepatocellular carcinoma, a potential complication of autoimmune hepatitis–induced cirrhosis.

**Procedures**

* Liver biopsy

Liver biopsy is the most important diagnostic procedure in patients with autoimmune hepatitis. This procedure can be performed percutaneously, with or without ultrasound guidance, or by the transjugular route. The latter is preferred if the patient has coagulopathy or severe thrombocytopenia. A transjugular liver biopsy also may be preferable if ascites is present or if the liver is small, shrunken, and difficult to reach percutaneously. Liver biopsy routinely is performed in the outpatient setting to investigate abnormal liver chemistries. Liver biopsy should be performed as early as possible in patients with acute hepatitis who are thought to have autoimmune hepatitis. Confirmation of the diagnosis enables initiation of treatment at an early stage in the disease process.

The role of biopsy in patients presenting with well-established cirrhosis secondary to autoimmune hepatitis is less clear. As an example, the initiation of treatment in a patient with cirrhosis, normal aminotransferase levels, and a minimally elevated gamma globulin level is not expected to influence the disease outcome.

* Endoscopic retrograde cholangiopancreatography

 Occasionally, a patient with autoimmune hepatitis and ulcerative colitis may require endoscopic retrograde cholangiopancreatography (ERCP) to rule out coexisting PSC.

* Histologic Findings

Autoimmune hepatitis is characterized by a chronic inflammatory cell infiltrate. Plasma cells are the prominent cell type. Biopsies may show evidence for interface hepatitis (ie, piecemeal necrosis), bridging necrosis, and fibrosis. Lobular collapse, best identified by reticulin staining, is a common finding.

Interface hepatitis does not predict a progressive disease course. By contrast, a strong likelihood exists that cirrhosis will develop when bridging necrosis is present. The presence or absence of cirrhosis on liver biopsy is an important determinant of the patient's prognosis.

Liver biopsy findings can help to differentiate autoimmune hepatitis from chronic HCV infection, alcohol-induced hepatitis, drug-induced liver disease, PBC, and PSC.

**TREATMENT**

* **Diet**

Patients with acute autoimmune hepatitis and symptoms of nausea and vomiting may require intravenous fluids and even total parenteral nutrition; however, most patients can tolerate a regular diet. A high caloric intake is desirable.

Patients with cirrhosis secondary to autoimmune hepatitis may develop ascites. A low-salt diet (generally <2000 mg of sodium per d) is mandatory in these individuals. Patients should continue to consume protein (ie, >1.1 g protein per kg body weight) given the catabolic nature of the disease and patients' high risk for developing muscle wasting.

* **Activity**

 Most patients do not need hospitalization, although this may be required for clinically severe illness. Forced and prolonged bed rest is unnecessary, but patients may feel better with restricted physical activity.

* **Medical Care**

For more than 3 decades, prednisone and azathioprine have been the mainstays of drug therapy for patients with autoimmune hepatitis.

Albert Czaja (1995) recently published his treatment recommendations for autoimmune hepatitis, which are as follows:

**Absolute indications for treatment**

* Incapacitating symptoms
* Relentless clinical progression
* AST greater than 10 times the reference range
* AST greater than 5 times the reference range and IgG greater than 2 times the reference range
* Bridging necrosis on histology
* Multilobular necrosis on histology

**Relative indications for treatment**

* Mild or no symptoms
* AST 3-9 times the reference range
* AST greater than 5 times the reference range and IgG less than 2 times the reference range
* Periportal hepatitis on histology

**No indication for treatment**

No symptoms

Previous intolerance to prednisone or azathioprine

AST less than 3 times the reference range

Severe cytopenia

Inactive cirrhosis or mild portal hepatitis on histology

Decompensated cirrhosis with variceal bleeding

**Czaja's guidelines for single-drug therapy are as follows:**

* Prednisone - 60 mg/d for 1 week, 40 mg/d for 1 week, 30 mg/d for 2 weeks, and 20 mg/d until reaching the treatment end point
* Recommendations for combination drug therapy - Prednisone 30 mg/d for 1 week, 20 mg/d for 1 week, 15 mg/d for 2 weeks, and 10 mg/d until reaching the treatment endpoint with azathioprine 50 mg/d until reaching the treatment end point

**Treatment endpoints**: Patients may achieve 1 of 4 treatment endpoints.

1. Complete remission is indicated by the absence of symptoms, a serum AST level less than 2 times the reference range, and histologic improvement to normal or minimal activity.

2. Treatment failure is defined as a deterioration in patient condition during therapy.

3. An incomplete patient response is defined as an improvement that is insufficient to satisfy remission criteria.

4. Drug toxicity may occur.

Patients with severe disease have a high short-term mortality rate if they fail to show normalization of at least 1 laboratory parameter or if pretreatment hyperbilirubinemia fails to improve during a 2-week treatment trial. In contrast, patients who improve by these parameters have an excellent immediate survival rate, and their treatment should be continued.

Histologic remission tends to lag behind clinical and laboratory remission by 3-6 months. Follow-up liver biopsies can optimize management by avoiding medication withdrawal in patients who are not yet in histologic remission.

**Surgical Care**

* Liver transplantation

This procedure is an effective form of therapy for patients with decompensated cirrhosis caused by autoimmune hepatitis. This procedure also may be used to rescue patients who present with fulminant hepatic failure secondary to autoimmune hepatitis.

The long-term outlook after liver transplantation is excellent, with 5-year survival rates reported at 90% or more. Positive autoantibodies and hypergammaglobulinemia tend to disappear within 2 years of transplantation.

Recurrence of autoimmune hepatitis is uncommon after liver transplantation. It has been reported primarily in inadequately immunosuppressed patients and HLA DR3-positive recipients of HLA DR3-negative donors.