Overview of autoimmune hepatitis

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INTRODUCTION

Autoimmune hepatitis is a chronic, inflammatory disease of the liver that is characterized by circulating autoantibodies and elevated serum globulin levels. The disease may start as acute hepatitis and progress to chronic liver disease and cirrhosis. Consequently, autoimmune hepatitis has a spectrum of clinical presentations.

Although this disorder had been known by a variety of names, including lupoid hepatitis, plasma cell hepatitis, and autoimmune chronic active hepatitis, the International Autoimmune Hepatitis Group determined that autoimmune hepatitis was the most appropriate term for this disease [1].

An overview of autoimmune hepatitis will be provided here. Variant forms of autoimmune hepatitis (ie, overlap syndromes) are discussed separately. (See "Autoimmune hepatitis variants: Definitions and treatment".)

INCIDENCE AND EPIDEMIOLOGY

Autoimmune hepatitis can present at any age and in all ethnic groups, but it occurs predominantly in women [2-4]. For type 1 autoimmune hepatitis, the female to male ratio is 4:1, but for type 2 autoimmune hepatitis, the ratio is 10:1 [5,6]. (See 'Autoantibodies' below.)

The worldwide incidence of autoimmune hepatitis ranges from 0.7 (southern Israel) to 2 (Canterbury, New Zealand) per 100,000 population, while the prevalence ranges from 4 (Singapore) to 25 (Canterbury, New Zealand) per 100,000 [7-9]. In studies from Europe, the incidence is 0.9 to 2 per 100,000 population per year, with a prevalence of 11 to 25 per 100,000 population [3,7,10,11]. No prevalence data on autoimmune hepatitis exists for the United States.

PATHOGENESIS

One theory for pathogenesis is that the disease is caused by an environmental trigger in a genetically predisposed individual. The exact relationships between genes and the autoimmune process remain largely undefined, but at the molecular level, they are thought to involve the autoantigen, the major histocompatibility complex, and the T-cell receptor. (See "Autoimmune hepatitis: Pathogenesis".)

CLINICAL FEATURES

Patterns of clinical presentation — Autoimmune hepatitis has a variety of clinical phenotypes; therefore, it is included in the differential diagnosis for patients with abnormal liver biochemical tests, acute hepatitis, cirrhosis, or acute liver failure [12]. It may present as either an acute or chronic disease with a fluctuating pattern [13,14]. However, the spectrum of presentation also includes asymptomatic patients. At its extreme, patients can present with considerable and sometimes debilitating symptoms (eg, anorexia, fatigue, weight loss). Furthermore, long periods of subclinical disease may occur before or after presentation.

Patients with autoimmune hepatitis may present at any age; however, the age of presentation is bimodal, with a peak in the second decade and another peak between the fifth and sixth decade [4,11].

Physical findings range from a normal physical examination to findings suggestive of cirrhosis or liver failure (eg, jaundice, ascites, splenomegaly). (See "Cirrhosis in adults: Etiologies, clinical manifestations, and diagnosis", section on 'Clinical manifestations'.)

Asymptomatic patients may be identified when they undergo screening examinations, such as those required for insurance, for employment, or prior to blood donation. In this setting, the finding of an elevated aminotransferase level may be the only sign of liver disease. On occasion, the asymptomatic patient is discovered when abdominal surgery is performed for some other reason and the surgeon notes an abnormal, sometimes cirrhotic-appearing liver.

At the far end of the spectrum are those patients who present with acute liver failure, jaundice, and coagulopathy, but such a presentation is generally uncommon [15-17]. (See "Acute liver failure in adults: Etiology, clinical manifestations, and diagnosis".)

However, for some patients with acute liver failure of unknown etiology, autoimmune hepatitis is determined to be the cause upon further review. In a study including 303 patients with acute liver failure of unclear etiology, 34 patients (11 percent) were thought to have underlying autoimmune hepatitis as the cause after a committee review that was guided by etiology-specific algorithms [18].

In addition to asymptomatic disease and an acute presentation, some patients present with a range of mild to severe, nonspecific symptoms, such as fatigue, anorexia, nausea, abdominal pain, and itching. Arthralgia involving the small joints or a transient erythematous rash may also be present [5].

Associated extrahepatic disorders — Patients with autoimmune hepatitis may present with a coexisting extrahepatic disorder, which may also be autoimmune-mediated. For example, associated common autoimmune disorders include autoimmune thyroiditis, rheumatoid arthritis, type 1 diabetes mellitus, ulcerative colitis, celiac disease, and systemic lupus erythematosus (table 1) [19-24]. While asthma and some skin disorders (eg, acne) have been reported in association, these are not regarded as autoimmune in nature and may reflect the bias of larger referral centers.

Celiac disease is a common extrahepatic condition, and prevalence varies from approximately 3 to 6 percent [25-27]. In a cohort study involving 460 patients with autoimmune hepatitis from the Netherlands, the prevalence of celiac disease was approximately 10 times higher compared with the general population (2.8 versus 0.35 percent) [27].

Skin conditions can occur at any time during the course of the disease. At initial presentation, rashes are seen in 8 to 17 percent of patients and most commonly appear as a transient and nonspecific maculopapular rash, particularly over the face, trunk, and upper arms [3,4]. Associated skin lesions also include psoriasis [3], vitiligo [4,20], urticaria [28], acne [20], lichen planus [28], erythema nodosum [4], and pyoderma gangrenosum [29,30].

Laboratory features

Liver biochemical and function tests — In acute presentations, elevations in aminotransferases (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) may exceed 10 to 20 times the upper limit of the reference range, and the ratio of alkaline phosphatase to AST (or ALT) is often <1:5, and in some cases is <1:10 [31].

In patients with chronic symptoms or those with cirrhosis at initial presentation, AST and ALT elevations are less profound, (ie, 1.5 to 5 times the upper limit of normal), while the ratio of alkaline phosphatase to AST (or ALT) is lower and approaches 1:2.

Gamma globulins — One characteristic laboratory feature of autoimmune hepatitis, although not universally present, is an elevation in gamma globulins, particularly immunoglobulin G (IgG) (figure 1). Hypergammaglobulinemia is generally associated with circulating autoantibodies.

Levels of IgA and IgM are typically normal [32].

Autoantibodies — The major autoantibodies that may be present in patients with autoimmune hepatitis are (table 2):

- **Antinuclear antibodies** – Antinuclear antibodies (ANA) are the most common circulating autoantibodies in autoimmune hepatitis, and may be the only autoantibody present. Titers regarded as positive are dependent in part upon the methodology used and the age of the patient. In most laboratories, titers in the range of 1:80 to 1:100 or greater are regarded as positive in adults. (See "Measurement and clinical significance of antinuclear antibodies".)

- **Anti-smooth muscle antibodies** – Anti-smooth muscle antibodies (ASMA) are more specific than ANA for autoimmune hepatitis, particularly when present in titers of 1:80 or more in adults, but less prevalent.

- **Anti-actin antibodies** – Anti-actin antibodies (AAA) are more specific than ANA for type 1 autoimmune hepatitis, but have not generally been measured in laboratories in North America. ASMA titers of 1:320 or greater generally reflect the presence of AAA and can serve as a surrogate marker for these antibodies.

  AAA (IgG anti-F-actin) measured by enzyme-linked immunosorbent assay (ELISA) are available and, in some laboratories, have replaced ASMA in autoantibody profiles. They appear to be more sensitive and specific than ASMA measured by immunofluorescence [33,34].

- **Anti-soluble liver antigen/liver pancreas antibodies (anti-SLA/LP)** – Anti-SLA/LP antibodies have been found in approximately 10 to 30 percent of adult patients with type 1 autoimmune hepatitis [35,36]. Cloning and characterization of the soluble liver antigen shows an enzyme that is identical to the liver-pancreas antigen; thus, the designation SLA/LP was adopted [37,38]. (See "Autoimmune hepatitis: Pathogenesis".)

- **Anti-neutrophil cytoplasmic antibodies** – Anti-neutrophil cytoplasmic antibodies are a group of autoantibodies that recognize neutrophil proteins, and atypical peripheral anti-

neutrophil cytoplasmic antibodies (p-ANCA) have been identified in patients with type 1 disease [39,40]. Atypical p-ANCA have a perinuclear or atypical staining pattern on immunofluorescence and appear to be directed against a myeloid 50-kd nuclear envelope protein [41]. Atypical p-ANCA is also found in patients with inflammatory bowel disease and primary sclerosing cholangitis. (See "Clinical spectrum of antineutrophil cytoplasmic autoantibodies" and "Primary sclerosing cholangitis in adults: Clinical manifestations and diagnosis", section on 'Laboratory tests'.)

In one series, atypical p-ANCA was identified in 30 of 46 (65 percent) patients with type 1 autoimmune hepatitis as defined by ANA and/or ASMA at titers of 1:40 or greater [39].

- **Anti-mitochondrial antibodies** – Anti-mitochondrial antibodies (AMA) can occur in type 1 autoimmune hepatitis, and the reported frequency has generally ranged from 8 to 12 percent [42,43]. (See 'Differential diagnosis' below.)

  However, one report found no AMA in 125 patients with type 1 autoimmune hepatitis, which was due at least in part to a stricter definition of the autoimmune hepatitis/primary biliary cholangitis overlap (variant) syndrome [14]. (See "Autoimmune hepatitis variants: Definitions and treatment".)

- **Anti-DNA antibodies** – Antibodies to single-stranded DNA and double-stranded DNA, which are most commonly associated with systemic lupus erythematosus, can be found in patients with autoimmune hepatitis types 1 and 2 [44]. The clinical significance of anti-DNA antibodies is discussed separately. (See "Antibodies to double-stranded (ds)DNA, Sm, and U1 RNP".)

- **Anti-liver-kidney microsomal-1 antibodies** – Anti-liver-kidney microsomal-1 (anti-LKM-1) antibodies, which are directed at the cytochrome P450 enzyme CYP2D6, occur mostly in patients with type 2 disease [45,46].

- **Anti-liver-kidney microsomal-3 antibodies** – Anti-liver-kidney microsomal-3 antibodies (anti-LKM-3) are directed against uridine diphosphate-glucuronosyl transferases and are found rarely in patients with type 2 disease [47].

- **Anti-liver cytosol antibody-1** – Anti-liver cytosol antibody-1 (ALC-1) is a marker of type 2 autoimmune hepatitis. They generally occur in conjunction with anti-LKM-1, but may be the sole autoantibody [48]. The antigen recognized by ALC-1 is formiminotransferase cyclodeaminase, a liver-specific 58-kd metabolic enzyme [49]. Measurement of ALC-1 antibodies is not generally available in clinical laboratories.

Most of the data on autoantibodies are based upon results obtained by immunofluorescence. By contrast, commercial laboratories tend to measure autoantibodies by ELISA, and thus it is possible that results may differ from those reported in the literature. For adults with suspected autoimmune hepatitis, higher antibody titers (>1:160) provide greater support for the diagnosis compared with lower titers.

Patterns in children are described below. (See 'Children' below.)

Imaging — There are no characteristic imaging features for autoimmune hepatitis, and imaging studies are not routinely obtained in all patients [50]. (See 'Diagnostic evaluation' below.)

Histology — Autoimmune hepatitis can be characterized histologically by the following findings, although they are nonspecific:

- A portal mononuclear cell infiltrate (generally lymphoplasmacytic, often with occasional eosinophils), invades the sharply demarcated hepatocyte boundary (limiting plate) surrounding the portal triad and infiltrates into the surrounding lobule and beyond (picture 1).
- The periportal lesion, sometimes referred to as piecemeal necrosis or interface hepatitis, essentially spares the biliary tree but may involve more of the lobule (picture 2). There may also be centrizonal necrosis [51].
- Bile duct changes (eg, destructive and nondestructive cholangitis, ductal injury, and ductular reaction) are increasingly recognized in patients with autoimmune hepatitis [52]. In particular, ductal injury and ductular reaction may be seen in over 80 percent of patients at the time of diagnosis. Granulomas are uncommonly seen but, if present, should prompt an evaluation for another diagnosis such as primary biliary cholangitis or sarcoidosis.
- A plasma cell infiltrate, rosettes of hepatocytes, and multinucleated giant cells may be seen (picture 3). The presence of infiltrate in the portal areas and plasma cell infiltrates can help distinguish such patients from those with other forms of acute hepatitis [53,54].
- Some degree of fibrosis is usually present in all but the mildest forms of autoimmune hepatitis. Advanced fibrosis connects portal and central areas (bridging), which ultimately, by architectural distortion of the hepatic lobule and the appearance of regenerating nodules, results in cirrhosis.

DIAGNOSTIC EVALUATION

Autoimmune hepatitis is a diagnosis of exclusion, and for patients with suspected disease, we proceed with testing in a stepwise fashion [55].

For adults with any serum aminotransferase elevation, we initially measure the following serum globulins and serologic markers:

- Antinuclear antibody (ANA)
- Anti-smooth muscle antibody (ASMA)
- Anti-liver-kidney microsomal-1 antibodies (anti-LKM-1)
- Anti-mitochondrial antibody (AMA)
- IgG or gamma globulin level

For adult patients who are negative for the conventional autoantibodies outlined above, we obtain additional autoantibodies:

- Anti-liver cytosol antibody-1 (ALC-1)
- Anti-soluble liver antigen/liver pancreas antibody (anti-SLA/LP)
- Atypical perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA)

We obtain magnetic resonance cholangiopancreatography in the following adult patients to exclude primary sclerosing cholangitis [50]:

- Patients with an established diagnosis of inflammatory bowel disease.
- Patients with a liver biochemical pattern that suggests cholestasis (predominantly elevated alkaline phosphatase). (See "Approach to the patient with abnormal liver biochemical and function tests", section on 'Patterns of liver test abnormalities'.)

Routine liver biopsy is not always necessary because the diagnosis of autoimmune hepatitis can be strongly suspected based upon clinical features in patients with either a positive autoantibody and/or elevated IgG or gamma globulin levels [56]. We prefer to obtain a liver biopsy in patients in whom autoimmune hepatitis is suspected because histologic assessment can confirm the diagnosis and help guide treatment. (See "Management of autoimmune hepatitis".)

Histologic evaluation is particularly useful for evaluating patients who have few or atypical findings, negative autoantibodies, and/or normal IgG levels. The decision to obtain a liver

biopsy also involves a discussion of the risks and benefits of biopsy and also depends on patient preferences. The risk of adverse events related to liver biopsy is discussed separately. (See "Approach to liver biopsy", section on 'Complications'.)

We use a standardized scoring system as part of the assessment. (See 'Histology' above and 'Diagnostic scoring systems' below.)

Of note, some guidelines require liver biopsy as part of the diagnostic evaluation, including a guideline from the European Association for the Study of the Liver [57].

DIAGNOSIS

Our diagnostic criteria — The diagnosis of autoimmune hepatitis can be made in a patient with a compatible clinical presentation when the following features are present (see 'Patterns of clinical presentation' above):

- A minimum of one elevated serum aminotransferase, typically (but not always) an aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) level at least two times the upper limit of the reference range.
- A minimum of one positive laboratory test: increased total IgG or gamma-globulin levels, and/or serologic markers (antinuclear antibodies [ANA], anti-smooth muscle antibodies [ASMA] at a titer of at least 1:40, anti-liver/kidney microsomal-1 [anti-LKM-1] antibodies, anti-liver cytosol antibody-1 [ALC-1], or anti-soluble liver/liver pancreas [anti-SLA/LP] antibodies).
- Exclusion of diseases that have a similar presentation, particularly viral hepatitis, drug-induced liver injury, and alcoholic liver disease. (See 'Differential diagnosis' below.)

When a liver biopsy is obtained, the diagnosis can be confirmed by histology showing interface hepatitis and/or a predominantly lymphoplasmacytic infiltrate. (See 'Histology' above and 'Diagnostic evaluation' above.)

Disease classification — On the basis of the autoantibody profiles, patients can be categorized into two disease subtypes: type 1 or type 2, but these subtypes have not been established as distinct clinical or pathological entities (table 2) [55,58]. (See 'Autoantibodies' above.)

However, some patients lack circulating autoantibodies.

Type 1 autoimmune hepatitis — Autoantibodies characteristic of type 1 autoimmune hepatitis are:

- Antinuclear antibody (ANA).
- Anti-smooth muscle antibody (ASMA; approximately 65 percent of patients).
- Anti-actin antibodies.
- Anti-mitochondrial antibodies (AMA; rarely positive in patients without primary biliary cholangitis overlap). (See 'Other types of autoimmune liver disease' below and "Autoimmune hepatitis variants: Definitions and treatment".)
- Anti-soluble liver antigen/liver pancreas antibody antigen (SLA/LP; approximately 10 to 30 percent of adults).
- Anti-single-stranded and anti-double-stranded DNA (25 to 35 percent of patients) [44].
- Atypical perinuclear anti-neutrophil cytoplasmic antibodies [41].

Type 2 autoimmune hepatitis — Autoantibodies characteristic of type 2 autoimmune hepatitis are antibodies to LKM-1 alone or accompanied by anti-liver cytosol antibody-1 (ALC-1). Positive titers are defined as >1:20 for ANA and anti-smooth muscle antibody (ASMA), whereas titers of 1:10 may be considered positive for anti-LKM-1. However, some patients have only ALC-1 antibodies [48]. In addition, approximately 10 to 30 percent of patients with type 2 disease will have anti-SLA/LP antibodies [58]. Antibodies to liver-kidney microsomal-3 (LKM-3) are rarely seen in type 2 disease and are not useful in clinical practice [57].

Autoantibody negative autoimmune hepatitis — Approximately 20 percent of patients who present with all the features of autoimmune hepatitis lack circulating ANA, ASMA, or anti-LKM-1 antibodies [5]. These patients are usually regarded as having autoantibody negative autoimmune hepatitis or cryptogenic chronic hepatitis. A therapeutic response to antiinflammatory therapy may be the only indication that autoimmune hepatitis is the underlying disease in these patients. (See "Management of autoimmune hepatitis".)

Diagnostic scoring systems — A scoring system developed to standardize the diagnosis for population-based studies and clinical trials has had limited value in individual patients [1,59,60]. A less complicated system using simplified criteria for individual patients is based upon titers of autoantibodies, IgG levels, liver histology, and the exclusion of viral hepatitis.

- **Autoantibodies** – Assign one point if the ANA or ASMA are 1:40 OR assign two points if the ANA or ASMA are ≥1:80 (OR if the LKM ≥1:40 OR if the SLA is positive).

- **IgG** – Assign one point if the IgG is >the upper limit of normal OR assign two points if the IgG is >1.10 times the upper limit of normal.

- **Liver histology (evidence of hepatitis is a mandatory condition)** – Assign one point if the histologic features are compatible with autoimmune hepatitis OR two points if the histologic features are typical of autoimmune hepatitis. Typical histologic features were defined as the presence of interface hepatitis, lymphocytic/lymphoplasmacytic infiltrates in the portal tracts and extending into the lobule, emperipolesis (active penetration of one cell into and through a large cell), and hepatic rosette formation. Compatible features were defined as a picture of chronic hepatitis with lymphocytic infiltration without all the features considered typical.

- **Absence of viral hepatitis** – Assign two points if viral hepatitis has been excluded. In the validation study, patients were mainly tested for hepatitis B and C. However, other forms of hepatitis should be considered depending upon the clinical setting.

A probable diagnosis of autoimmune hepatitis is made if the total points are 6, while a definite diagnosis is made if the total points are ≥7.

In a validation study involving 11 international centers, the simplified scoring system had 88 percent sensitivity and 97 percent specificity compared with a clinical and histologic reference standard when using a cutoff of ≥6; the corresponding values were 81 and 99 percent, respectively, when using a cutoff of ≥7 [60]. Sensitivity was somewhat lower, but specificity remained high in a later validation study using a cutoff of ≥7 (70 and 100 percent, respectively) [61].

A potential limitation of the scoring system is the relative lack of standardization of some of the autoantibody tests across testing facilities (ie, simplified criteria are based on autoantibodies measured by immunofluorescence) [60]. Nevertheless, in the validation studies above, the local standards for autoantibody testing at each center were used, suggesting that the model is relatively robust to these differences.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of autoimmune hepatitis includes conditions associated with either acute hepatitis or chronic inflammation that may accompanied by cirrhosis (table 2).

Other types of autoimmune liver disease — The distinction between autoimmune hepatitis and other autoimmune liver diseases, including primary biliary cholangitis and overlap

syndromes, is based upon clinical, histologic, and immunologic features [62].

- **Primary biliary cholangitis** – The isolated presence of anti-mitochondrial antibodies (AMA) with the M2 subtype usually signifies primary biliary cholangitis, and further diagnostic evaluation is needed. (See "Clinical manifestations, diagnosis, and prognosis of primary biliary cholangitis", section on 'Diagnosis' and "Pathogenesis of primary biliary cholangitis (primary biliary cirrhosis)", section on 'Antimitochondrial antibodies'.)

  AMA is rarely the sole autoantibody in patients with autoimmune hepatitis [62,63]. However, some patients with autoimmune hepatitis and a positive AMA will develop primary biliary cholangitis [64]. Primary biliary cholangitis may be indistinguishable from autoimmune hepatitis on liver biopsy, but often has features involving bile duct paucity, inflammation and/or damage, or periductular fibrosis that are not seen in autoimmune hepatitis (picture 4A-C).

- **Overlap syndromes** – The diagnosis of an overlap syndrome such as primary sclerosing cholangitis/autoimmune hepatitis, can be difficult, but imaging may differentiate the disorders [62]. (See 'Diagnostic evaluation' above.)

  For example, patients with primary sclerosing cholangitis have characteristic multifocal stricturing and dilation of intrahepatic and/or extrahepatic bile ducts on cholangiogram, while patients with autoimmune hepatitis have a normal-appearing biliary tree. The diagnosis of overlap syndromes and primary sclerosing cholangitis is discussed in more detail separately. (See "Autoimmune hepatitis variants: Definitions and treatment" and "Primary sclerosing cholangitis in adults: Clinical manifestations and diagnosis".)

Other causes of hepatitis — Some clinical features of autoimmune hepatitis (eg, elevated transaminases) may be found in patients who present with inflammatory liver disease from a different etiology.

- **Viral hepatitis** – In the acute setting, it is necessary to distinguish autoimmune hepatitis from acute viral hepatitis (hepatitis A, B, C, D, E; herpes simplex virus; varicella zoster virus; Epstein-Barr virus; cytomegalovirus); other viral infections; or an acute exacerbation of chronic viral hepatitis (hepatitis B). The laboratory evaluation for a patient with acute hepatitis is discussed in more detail elsewhere. (See "Approach to the patient with abnormal liver biochemical and function tests", section on 'Elevated serum aminotransferases'.)

  With older testing methods, a nonspecific antibody response seen in some patients with autoimmune hepatitis made it difficult to distinguish between autoimmune disease and

chronic hepatitis C virus infection. A false positive hepatitis C antibody can easily be confirmed by obtaining a hepatitis C virus RNA level in these patients. (See "Screening and diagnosis of chronic hepatitis C virus infection".)

- **Drug-induced liver injury** – Some forms of drug-induced liver disease (DILI) can resemble autoimmune hepatitis histologically, so a liver biopsy is often indicated when this diagnosis is suspected as certain histologic features (eg, portal neutrophils, which are more common in DILI) can help distinguish between the two [65]. The clinical presentation and diagnosis of DILI is discussed separately. (See "Drug-induced liver injury".)

- **Nonalcoholic steatohepatitis** – Establishing the diagnosis of autoimmune hepatitis in patients with underlying nonalcoholic steatohepatitis may be difficult, especially in those with a positive antinuclear antibody (ANA) [66]. Antibodies that are more specific for autoimmune hepatitis (eg, anti-smooth muscle antibody [ASMA], liver/kidney microsomal-1 [LKM-1]) are not present in patients with liver disease due to nonalcoholic steatohepatitis. In addition, fatty infiltration and the presence of polymorphonuclear leukocytes and central fibrosis on histology points to steatohepatitis, which is discussed separately. (See "Epidemiology, clinical features, and diagnosis of nonalcoholic fatty liver disease in adults".)

- **Systemic lupus erythematosus (SLE)-associated liver disease** – Autoantibodies may help to distinguish between autoimmune hepatitis and liver disease associated with SLE. Although ANA can be seen in both conditions, ASMA and AMA are rarely present in patients with SLE. Thus, either antibody suggests that the patient has autoimmune hepatitis. On the other hand, there is a form of hepatitis that occurs in SLE which is distinct from autoimmune hepatitis. Its pathogenesis may be related to antiribosomal P protein antibodies, which are discussed separately. (See "Antiribosomal P protein antibodies".)

- **Acute liver failure** – Various autoantibodies (eg, AMA, anti-soluble liver/liver pancreas [SLA/LP]) have been described in patients with acute liver failure [67,68]. Thus, autoantibodies alone in such patients does not establish autoimmune hepatitis as the cause. The diagnostic evaluation of patients with acute liver failure is discussed separately. (See "Acute liver failure in adults: Etiology, clinical manifestations, and diagnosis", section on 'Diagnosis'.)

- **Iron overload** – On occasion, an elevated serum ferritin, sometimes accompanied by elevated transferrin saturation, occurs in autoimmune hepatitis. Iron overload from genetic hemochromatosis can be excluded by testing for common mutations for hereditary hemochromatosis (*HFE* C282Y and H63D) and by assessing hepatic iron content

with magnetic resonance imaging or liver biopsy. (See "Approach to the patient with suspected iron overload", section on 'Sequence and interpretation of testing'.)

TREATMENT AND PROGNOSIS

The initial treatment for autoimmune hepatitis typically includes a glucocorticoid, with or without azathioprine or 6-mercaptopurine (algorithm 1). Induction therapy, subsequent therapy, and prognosis are discussed in detail separately. (See "Management of autoimmune hepatitis".)

SPECIAL POPULATIONS

Children — The diagnostic evaluation for children with suspected autoimmune hepatitis is similar to the evaluation in adults, although we obtain magnetic resonance cholangiopancreatography in all children to exclude autoimmune sclerosing cholangitis. In addition, antibody titers of 1:20 or greater (for all antibodies) are regarded as positive in children. The median age at presentation in a cohort of 52 children was 10 years (age range, 2 to 15 years), while children with anti-liver/kidney microsomal-1 (LKM-1) antibodies (ie, type-2 autoimmune hepatitis) presented at a younger age [45].

For children with any serum aminotransferase abnormality, we initially measure the following serologic markers:

- Antinuclear antibody (ANA).
- Anti-smooth muscle antibody (ASM) [45].
- Anti-liver-kidney microsomal-1 antibodies (anti-LKM-1).
- Anti-mitochondrial antibody (AMA).
- IgG or gamma-globulin level. Low IgA levels can be seen in children with type 1 and, more frequently, type 2 disease [14].

For children who are negative for these autoantibodies, we obtain additional autoantibodies:

- Anti-soluble liver antigen/liver pancreas antibody (anti-SLA/LP; commonly found in children with type 2 disease).
- Atypical perinuclear anti-neutrophil cytoplasmic antibodies.

- Anti-liver cytosol antibody-1 (ALC-1).

In a study of 39 children and 14 adults with type 2 autoimmune hepatitis, ALC-1 antibodies were present more often in children compared with adults (59 versus 29 percent) [25]. In addition, ALC-1 antibodies were the sole autoantibody detected in 14 children (36 percent) with type 2 autoimmune hepatitis.

Almost exclusively a disease of children, Wilson disease can present as a chronic hepatitis or as fatty liver disease that resembles autoimmune hepatitis. Approximately 85 to 90 percent of patients with Wilson disease have low serum ceruloplasmin levels (<20 mg/dL or 200 mg/L) which can distinguish it from autoimmune hepatitis. (See "Wilson disease: Epidemiology and pathogenesis".)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Autoimmune hepatitis".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Beyond the Basics topics (see "Patient education: Autoimmune hepatitis (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Background** – Autoimmune hepatitis is a chronic, inflammatory disease of the liver that occurs predominantly in females and may present at any age. It is generally characterized by circulating autoantibodies and elevated serum globulin levels (table 2). The disease may start as acute hepatitis and may progress to chronic liver disease and cirrhosis. (See 'Introduction' above.)

- **Patterns of clinical presentation** – Autoimmune hepatitis has a heterogeneous and fluctuating nature, leading to marked variability in its clinical manifestations. Its spectrum ranges from asymptomatic patients to those with considerable and sometimes debilitating symptoms, and even to those with acute liver failure. (See 'Patterns of clinical presentation' above.)

- **Diagnostic evaluation** – Diagnosis is based upon characteristic serologic and histologic findings and exclusion of other forms of chronic liver disease. It can often be strongly suspected based upon clinical and laboratory features, and thus a liver biopsy is not always necessary in patients with typical findings on noninvasive testing (see 'Diagnostic evaluation' above):

  - For adults with compatible clinical or laboratory features, we obtain serum antinuclear antibodies (ANA), anti-smooth muscle antibodies (ASMA), anti-mitochondrial antibodies (AMA), anti-liver/kidney microsomal-1 antibodies (anti-LKM-1), and either an immunoglobulin G (IgG) or gamma globulin level. For patients who are negative for these autoantibodies, we obtain anti-soluble liver antigen/liver pancreas antibody (anti-SLA/LP), anti-actin antibodies, and atypical perinuclear anti-neutrophil cytoplasmic antibodies.

    We prefer to obtain a liver biopsy in all patients in whom autoimmune hepatitis is suspected because histologic assessment can confirm the diagnosis and help guide treatment. Histologic evaluation is particularly useful as part of the diagnostic evaluation for patients who have few or atypical findings, negative autoantibodies and/or normal IgG levels.

  - The diagnostic evaluation for children with suspected autoimmune hepatitis is similar to the evaluation in adults, although we obtain magnetic resonance cholangiopancreatography in all children to exclude autoimmune sclerosing cholangitis. In addition, antibody titers of 1:20 or greater are regarded as positive in children. (See 'Children' above.)

- **Treatment** – The initial treatment for autoimmune hepatitis typically includes a glucocorticoid, with or without azathioprine or 6-mercaptopurine (algorithm 1).

Induction therapy, subsequent therapy, and prognosis are discussed in detail separately. (See "Management of autoimmune hepatitis".)

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Topic 3665 Version 39.0

GRAPHICS

Extrahepatic disorders associated with autoimmune hepatitis

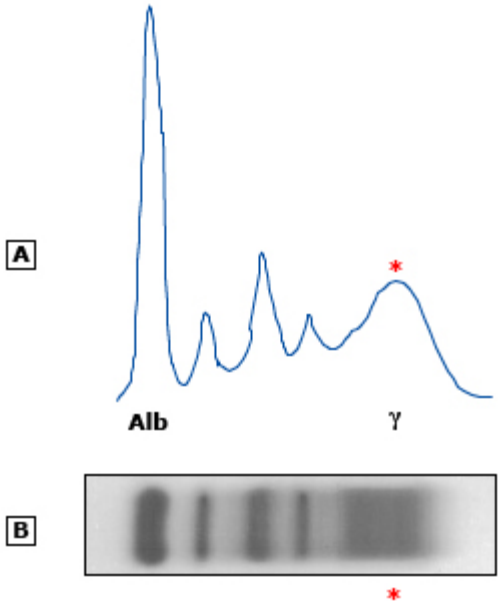
Extrahepatic diseases		Frequency among patients with AIH (%)
Pulmonary disorders	Fibrosing alveolitis	<1
	Pulmonary fibrosis	<1
	Sarcoidosis	<1
	Asthma	1 to 4
Hematological disorders	Immune thrombocytopenia	<1
	Autoimmune hemolytic anemia	<1
	Pernicious anemia	1
	Antiphospholipid syndrome	1
Neurologic disorders	Multiple sclerosis	<1
	Mononeuritis multiplex	<1
Miscellaneous	Primary amenorrhoea	4
	Glomerulonephritis	1
	Cryoglobulinemia	<1
	Uveitis	<1
	Polyglandular autoimmune syndrome	<1
Endocrine disorders	Autoimmune thyroiditis	8 to 23
	Diabetes (type 1)	1 to 10
Gastrointestinal disorders	IBD (ulcerative colitis)	2 to 8
	Celiac disease +/– IgA deficiency	1 to 6
Connective tissue disorders	Rheumatoid arthritis	2 to 4
	Sjögren's syndrome	1 to 7
	Mixed connective tissue disease	1 to 2.5
	Systemic lupus erythematosus	1 to 2.6
	Systemic sclerosis/scleroderma/CREST	<1
	Polymyalgia rheumatica	<1

	Polymyositis	<1
	Dermatomyositis	<1
Skin disorders	Psoriasis	3
	Vitiligo	1 to 2
	Pyoderma gangrenosum	<1
	Acne	<1
	Urticaria	<1
	Lichen planus	<1
	Erythema nodosum	<1
	Dermatitis herpetiformis	<1

AIH: autoimmune hepatitis; IBD: inflammatory bowel disease; CREST: calcinosis cutis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia.

Graphic 59606 Version 2.0

Polyclonal gammopathy



(A) Densitometer tracing of these findings reveals a broad-based peak of gamma mobility. This pattern is most often due to the presence of an inflammatory or reactive process, such as chronic liver disease, connective tissue disease, chronic infection, or a lymphoproliferative disorder.

(B) A polyclonal pattern is seen on serum protein electrophoresis on agarose gel (anode on left). The band at the right (red asterisk) is broad, and extends throughout the gamma mobility area.

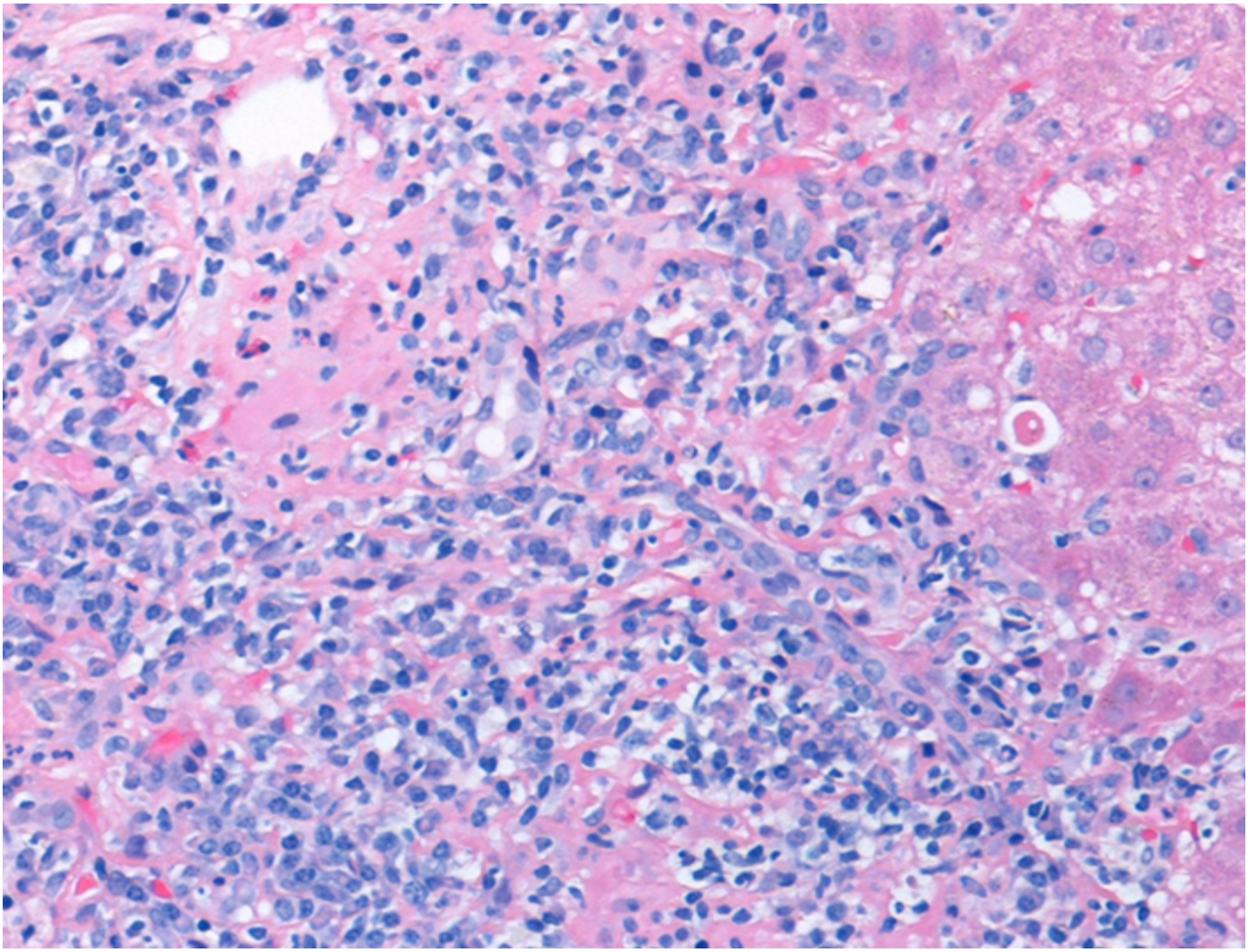
Graphic 74708 Version 4.0

Classification of autoantibodies in autoimmune hepatitis

Antibody	Disease subtype	Additional features
Antinuclear antibody (ANA)	Type 1	Most common antibodies in type 1 disease
Antismooth muscle antibody (ASMA)	Type 1	ASMA titers of 1:320 or greater generally reflect the presence of AAA
Antiactin antibody (AAA)	Type 1	Not routinely measured in North American laboratories
Antimitochondrial antibody (AMA)	Type 1	More specific for primary biliary cholangitis
Atypical perinuclear antineutrophil cytoplasmic antibody (p-ANCA)	Type 1	Also found in patients with primary sclerosing cholangitis
Anti-soluble liver antigen/liver pancreas antibodies (anti-SLA/LP)	Type 1 and type 2	More common in children with type 2 disease
Anti-DNA antibodies (single stranded DNA [ssDNA] and double-stranded DNA [dsDNA])	Type 1 and type 2	Anti-dsDNA antibody is commonly associated with systemic lupus erythematosus
Anti-liver kidney microsomal-1 antibody (ALKM-1)	Type 2	Occurs mostly in type 2 disease
Anti-liver cytosol-1 antibody (ALC-1)	Type 2	May occur in conjunction with ALKM-1
Anti-liver kidney microsomal-3 antibody (ALKM-3)	Type 2	Rarely present

Graphic 65135 Version 6.0

Autoimmune hepatitis

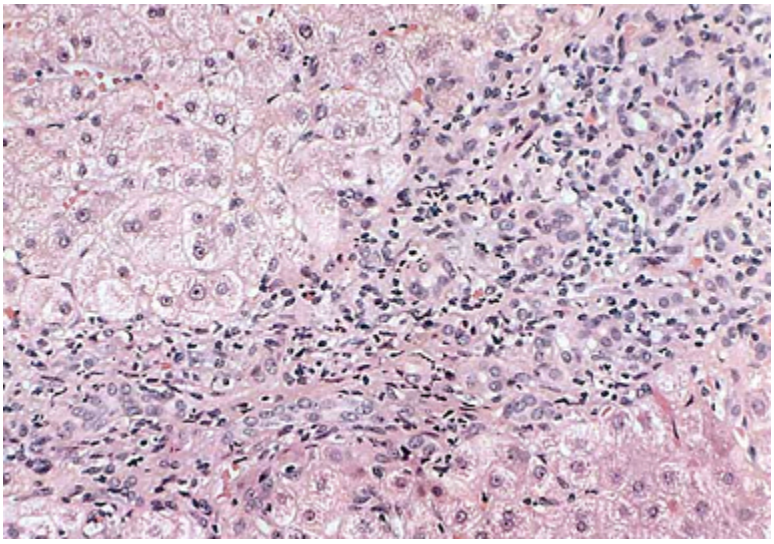


Liver biopsy in a patient with autoimmune hepatitis shows a portal tract with prominent plasma cell infiltration along with interface hepatitis.

Courtesy of Maria Isabel Fiel, MD, FAASLD.

Graphic 67909 Version 2.0

Interface hepatitis

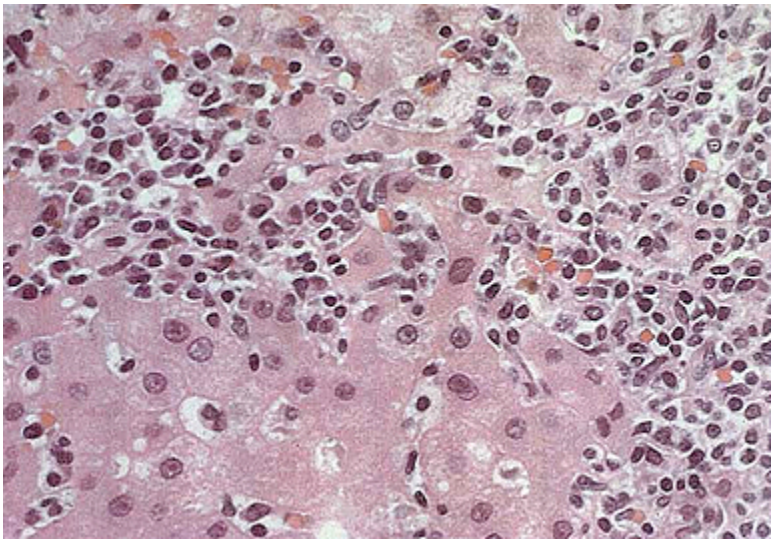


The portal tract is expanded by a mononuclear infiltrate; the limiting plate is disrupted; and the inflammatory process extends into the acinus. Staining by hematoxylin-eosin; original magnification x 200.

Reproduced with permission from the American Association for the Study of Liver Diseases. Hepatology 2002; 36:479.

Graphic 67959 Version 1.0

Plasma cell infiltrate



Plasma cells are identified by their eccentric, clock-face nucleus and pale perinuclear cytoplasmic crescent. They are characteristic of autoimmune hepatitis, but neither pathognomonic of the disease or required for its diagnosis. Staining by hematoxylin-eosin; original magnification x 400.

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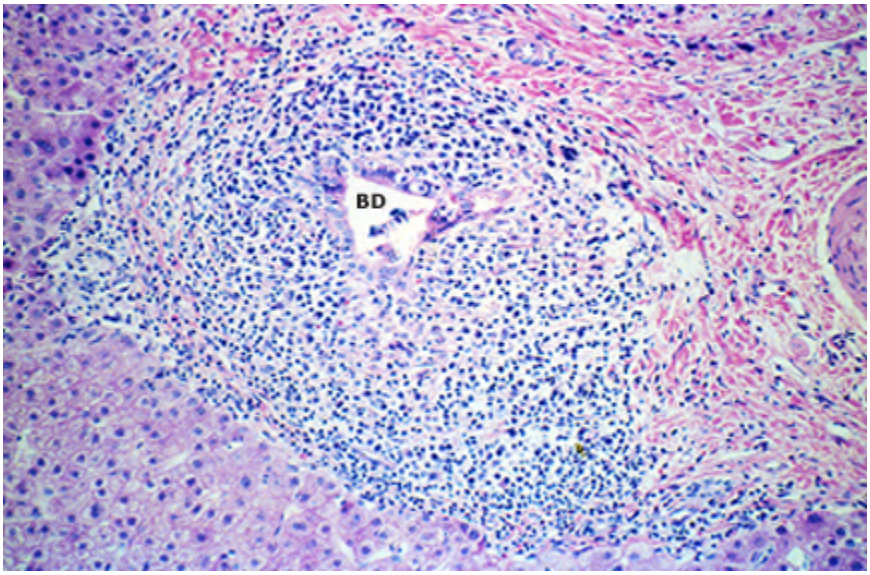
Graphic 69850 Version 1.0

Primary biliary cholangitis

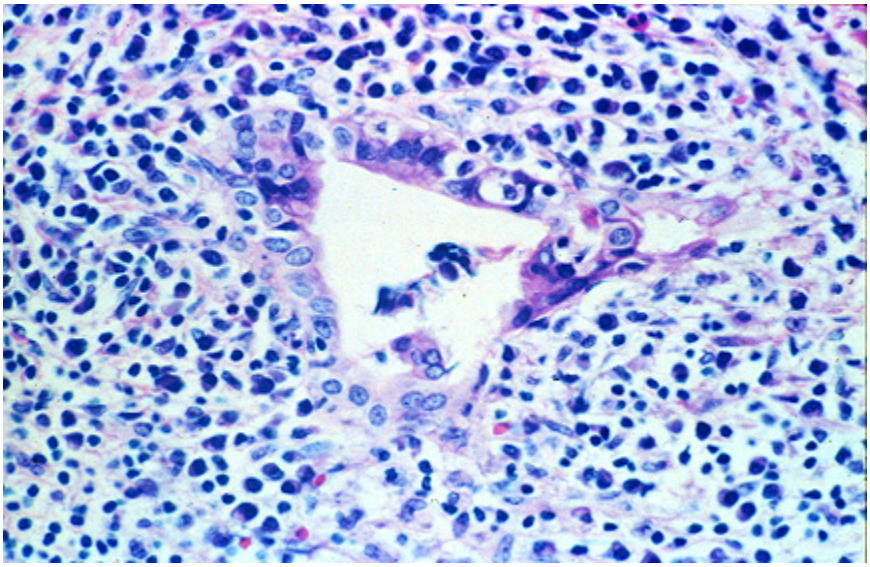


Low power view of liver biopsy in primary biliary cholangitis. A damaged bile duct (BD) is visible in the center of an intense inflammatory cell reaction in an enlarged portal triad. The bile duct appears to be the target of this inflammatory reaction.

Courtesy of Sanjiv Chopra, MD.

Graphic 54128 Version 2.0

Primary biliary cholangitis

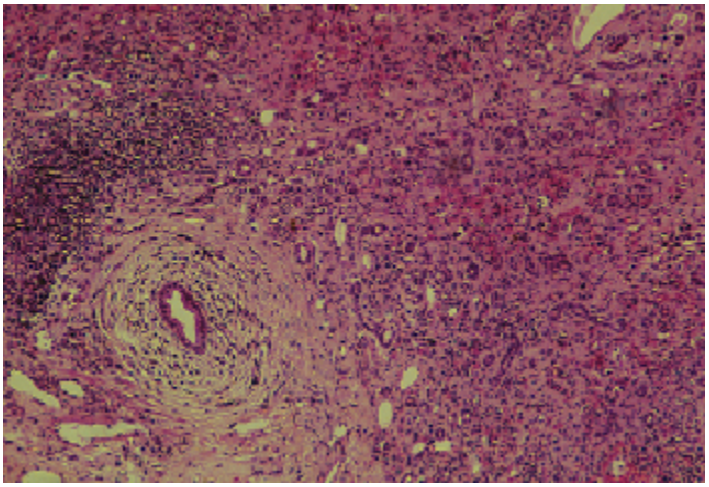


High power view of liver biopsy in primary biliary cholangitis in the same patient showing a marked mononuclear cell infiltrate surrounding and destroying a bile duct.

Courtesy of Sanjiv Chopra, MD.

Graphic 66904 Version 2.0

Primary sclerosing cholangitis

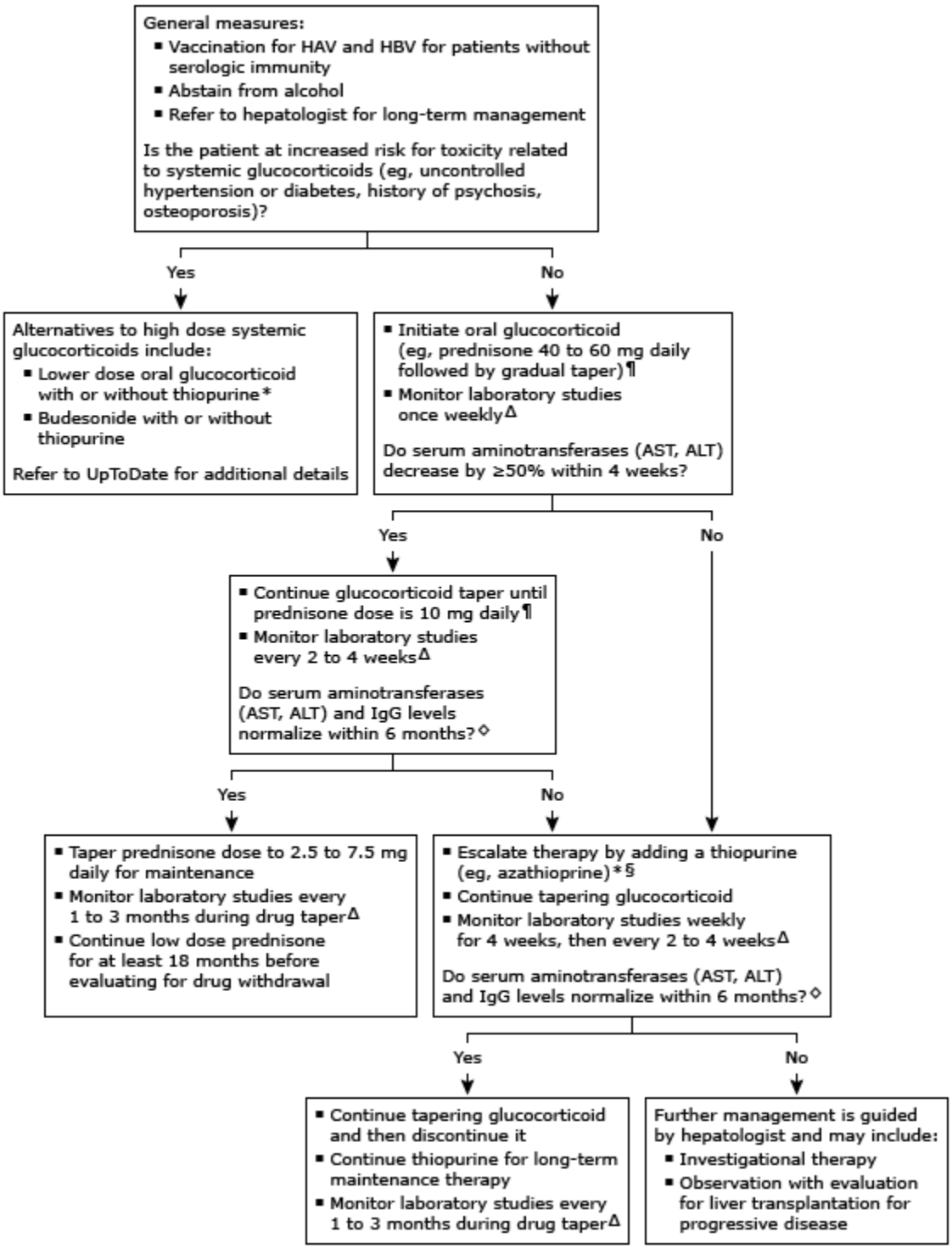


Medium power view of a liver biopsy in primary sclerosing cholangitis showing mononuclear cell infiltration and charactertistic concentric fibrosis around a small bile duct.

Courtesy of Edward L Krawitt, MD.

Graphic 81040 Version 1.0

Initial management of adults with autoimmune hepatitis who do not have acute liver failure or cirrhosis



This figure summarizes the general approach to initial therapy for adults with autoimmune hepatitis in the absence of acute liver failure or cirrhosis. This algorithm is intended for use in conjunction with other UpToDate content. Refer to UpToDate content on management of autoimmune hepatitis including the evidence supporting the efficacy of these therapies.

ALT: alanine aminotransferase; AST: aspartate aminotransferase; HAV: hepatitis A virus; HBV: hepatitis B virus; IgG: immunoglobulin G; TPMT: thiopurine methyltransferase.

* For thiopurine therapy, we typically use azathioprine. For patients with mild adverse effects (eg, gastrointestinal disturbances) related to azathioprine, we may switch to 6-mercaptopurine at one-half of the azathioprine dose.

¶ For most adults, we initiate prednisone 40 to 60 mg daily. After one to two weeks, we taper prednisone by 5 to 10 mg every one to two weeks to a dose of 20 mg daily. Next, we taper prednisone by 5 mg every one to two weeks to a target dose of 10 mg daily. Patients usually remain at this dose until achieving complete biochemical response. Oral prednisolone may be substituted for prednisone using the same dosing regimen. For patients with mild disease (asymptomatic patients with aminotransferase levels <10 times the upper limit of normal), we typically initiate prednisone at a lower dose (20 to 30 mg per day).

Δ For all patients, laboratory monitoring includes aminotransferases (AST, ALT), IgG level, and total bilirubin. For patients on a thiopurine, complete blood count and amylase are also measured.

◇ Complete biochemical response is the normalization of serum aminotransferases (AST, ALT) and IgG (ie, levels below the upper limit of normal).

§ For patients with normal or intermediate TPMT enzyme activity, we initiate azathioprine at 50 mg, orally, once daily. The azathioprine dose can be gradually increased up to 2 mg/kg daily (maximum daily dose, 200 mg). We do not use thiopurines in patients with low or absent TPMT enzyme activity.

Graphic 141356 Version 2.0

Contributor Disclosures

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Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

Conflict of interest policy

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