Diagnosis and Management of Autoimmune Hepatitis

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This guideline has been approved by the American Association for the Study of Liver Diseases (AASLD) and represents the position of the Association.

1. Preamble

Clinical practice guidelines are defined as "systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances." These guidelines on autoimmune hepatitis provide a data-supported approach to the diagnosis and management of this disease. They are based on the following: (1) formal review and analysis of the recently-published world literature on the topic [Medline search]; (2) American College of Physicians Manual for Assessing Health Practices and Designing Practice Guidelines; (3) guideline policies, including the AASLD Policy on the Development and Use of Practice Guidelines and the American Gastroenterological Association Policy Statement on Guidelines; and (4) the experience of the authors in the specified topic.

These recommendations, intended for use by physicians, suggest preferred approaches to the diagnostic, therapeutic and preventive aspects of care. They are intended to be flexible, in contrast to standards of care, which are inflexible policies to be followed in every case. Specific recommendations are based on relevant published information. To more fully characterize the quality of evidence supporting the recommendations, the Practice Guidelines Committee of the AASLD requires a class (reflecting benefit versus risk) and level (assessing strength or certainty) of evidence to be assigned and reported with each recommendation.4 The grading system applied to the recommendations has been adapted from the American College of Cardiology and the American Heart Association Practice Guidelines, and it is given below (Table 1).

2. Introduction

Autoimmune hepatitis (AIH) is a generally unresolving inflammation of the liver of unknown cause. A working model for its pathogenesis postulates that environmental triggers, a failure of immune tolerance mechanisms, and a genetic predisposition collaborate to induce a T cell–mediated immune attack upon liver antigens, leading to a progressive necroinflammatory and fibrotic process in the liver.5,6 Onset is frequently insidious with nonspecific symptoms such as fatigue, jaundice, nausea, abdominal pain, and arthralgias at presentation,7 but the clinical spectrum is wide, ranging from an asymptomatic presentation8,9 to an acute severe disease.10,11 The diagnosis is based on histologic abnormalities, characteristic clinical and laboratory findings, abnormal levels of serum globulins, and the presence of one or more characteristic autoantibodies.12-16 Women are affected more frequently than men (sex ratio, 3.6:1);17-19 and the disease is seen in all ethnic groups20-34 and at all ages.21,35-44 There are no robust epidemiological data on AIH in the United States. In Norway and Sweden, the mean incidence is 1 to 2 per 100,000 persons per year, and its point prevalence is 11 to 17 per 100,000 persons per year.45,46 A similar incidence and prevalence can be
Table 1. Description of Grading System Used to Assign Class and Level of Evidence

<table>
<thead>
<tr>
<th>Classification</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Conditions for which there is evidence and/or general agreement that a given diagnostic evaluation, procedure or treatment is beneficial, useful, and effective</td>
</tr>
<tr>
<td>Class II</td>
<td>Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a diagnostic evaluation, procedure or treatment</td>
</tr>
<tr>
<td>Class IIa</td>
<td>Weight of evidence/opinion is in favor of usefulness/efficacy</td>
</tr>
<tr>
<td>Class IIb</td>
<td>Usefulness/efficacy is less well established by evidence/opinion</td>
</tr>
<tr>
<td>Class III</td>
<td>Conditions for which there is evidence and/or general agreement that a diagnostic evaluation/procedure/treatment is not useful/effective and in some cases may be harmful</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Level of Evidence</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level A</td>
<td>Data derived from multiple randomized clinical trials or meta analyses</td>
</tr>
<tr>
<td>Level B</td>
<td>Data derived from a single randomized trial, or nonrandomized studies</td>
</tr>
<tr>
<td>Level C</td>
<td>Only consensus opinion of experts, case studies, or standard of care</td>
</tr>
</tbody>
</table>

3. Diagnosis: Criteria and Methods

The diagnostic criteria for AIH and a diagnostic scoring system were codified by an international panel in 199375 and revised in 199913 (Table 2). The clinical criteria for the diagnosis are sufficient to make or exclude definite or probable AIH in the majority of patients. The revised original scoring system was developed as a research tool by which to ensure the comparability of study populations in clinical trials (Table 3),13 and can also be applied in diagnostically challenging cases not readily captured by the descriptive criteria.13 The treatment response is graded in the revised original scoring system, and a score can be rendered both before and after treatment (Table 3).13 A pretreatment score of 10 points or higher, or a posttreatment score of 12 points or higher, indicate “probable” AIH at presentation. A pretreatment score of 10 points has a sensitivity of 100%, a specificity of 73%, and diagnostic accuracy of 67%.76 A pretreatment score of 15 points, indicative of “definite AIH” has a sensitivity of 95%, a specificity of 97%, and a diagnostic accuracy of 94%.76 A retrospective study supports the usefulness of the revised original system in children with AIH.77

A simplified scoring system has been proposed recently to ease clinical application78 and is based on the presence and level of autoantibody expression by indirect immunofluorescence, serum immunoglobulin G (IgG) concentration, compatible or typical histological features, and the absence of viral markers (Table 3).78 In three recent retrospective studies, the simplified scoring system performed with high sensitivity and specificity in the diagnosis of AIH, but it has yet to be validated in prospective studies.76,79,80

3.1. Clinical, Laboratory, and Histological Assessment

The diagnosis of AIH requires the presence of characteristic clinical and laboratory features, and the exclusion of other conditions that cause chronic hepatitis and cirrhosis (Table 2).13 The clinical assessment should include an evaluation of alcohol consumption and the use of drugs known to be hepatotoxic. The laboratory assessment should include determinations of the levels of serum alanine (ALT) or aspartate (AST) aminotransferases, alkaline phosphatase (AP), albumin, total or γ-globulin, IgG, and bilirubin (conjugated and unconjugated). AIH can be asymptomatic in 34%-45% of patients.3,9,269 Typically, these patients are men and have significantly lower serum ALT levels at presentation than do symptomatic patients.89 Histological findings, including the frequency of cirrhosis, are similar...
between asymptomatic patients and symptomatic patients. Because as many as 70% of asymptomatic patients become symptomatic during the course of their disease, asymptomatic patients must be followed lifelong, preferably by an expert, to monitor for changes in disease activity.

In children, the gamma glutamyl transferase level may be a better discriminator of biliary disease.

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**Table 2. Codified Diagnostic Criteria of the International Autoimmune Hepatitis Group**

<table>
<thead>
<tr>
<th>Features</th>
<th>Definite</th>
<th>Probable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver histology</td>
<td>Interface hepatitis of moderate or severe activity with or without lobular hepatitis or central portal bridging necrosis, but without biliary lesions or well defined granulomas or other prominent changes suggestive of a different etiology.</td>
<td>Same as for “definite”</td>
</tr>
<tr>
<td>Serum biochemistry</td>
<td>Any abnormality in serum aminotransferases, especially if the serum alkaline phosphatase is not markedly elevated. Normal serum concentrations of alpha antitrypsin, copper and ceruloplasmin.</td>
<td>Same as for “definite” but patients with abnormal serum concentrations of copper or ceruloplasmin may be included, provided that Wilson disease has been excluded by appropriate investigations</td>
</tr>
<tr>
<td>Serum immunoglobulins</td>
<td>Total serum globulin or γ globulin or IgG concentrations greater than 1.5 times the upper normal limit.</td>
<td>Any elevation of serum globulin or γ globulin or IgG concentrations above the upper normal limit</td>
</tr>
<tr>
<td>Serum autoantibodies</td>
<td>Seropositivity for ANA, SMA, or anti LKM 1 antibodies at titers greater than 1:80. Lower titers (particularly of anti LKM 1) may be significant in children. Seronegativity for AMA.</td>
<td>Same as for “definite” but at titers of 1:40 or greater. Patients who are seronegative for these antibodies but who are seropositive for other antibodies specified in the text may be included.</td>
</tr>
<tr>
<td>Viral markers</td>
<td>Seronegativity for markers of current infection with hepatitis A, B, and C viruses.</td>
<td>Same as for “definite”</td>
</tr>
<tr>
<td>Other etiological factors</td>
<td>Average alcohol consumption less than 25 g/day. No history of recent use of known hepatotoxic drugs.</td>
<td>Alcohol consumption less than 50 g/day and no recent use of known hepatotoxic drugs. Patients who have consumed larger amounts of alcohol or who have recently taken potentially hepatotoxic drugs may be included, if there is clear evidence of continuing liver damage after abstinence from alcohol or withdrawal of the drug.</td>
</tr>
</tbody>
</table>

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**Table 3. Revised Original Scoring System of the International Autoimmune Hepatitis Group**

<table>
<thead>
<tr>
<th>Features</th>
<th>Score</th>
<th>Definite</th>
<th>Probable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Female</td>
<td>+2</td>
<td>DR3 or DR4</td>
</tr>
<tr>
<td>AP:AST (or ALT) ratio</td>
<td>&gt;3</td>
<td>2</td>
<td>Immune Disease</td>
</tr>
<tr>
<td>&lt;1.5</td>
<td>&lt;1.5</td>
<td>+2</td>
<td>Thyroiditis, colitis, others</td>
</tr>
<tr>
<td>γ globulin or IgG level above normal</td>
<td>&gt;2.0</td>
<td>+3</td>
<td>Other markers</td>
</tr>
<tr>
<td>1.5</td>
<td>1.5</td>
<td>+2</td>
<td>Plasmacytic</td>
</tr>
<tr>
<td>1.0</td>
<td>1.0</td>
<td>+1</td>
<td>Rosettes</td>
</tr>
<tr>
<td>&lt;1.0</td>
<td>&lt;1.0</td>
<td>0</td>
<td>None of above</td>
</tr>
<tr>
<td>ANA, SMA, or anti LKM1 titers</td>
<td>&gt;1:80</td>
<td>+3</td>
<td>Histological features</td>
</tr>
<tr>
<td>1:40</td>
<td>1:40</td>
<td>+1</td>
<td>Plasmacytic</td>
</tr>
<tr>
<td>&lt;1:40</td>
<td>&lt;1:40</td>
<td>0</td>
<td>Rosettes</td>
</tr>
<tr>
<td>AMA</td>
<td>Positive</td>
<td>4</td>
<td>Other features</td>
</tr>
<tr>
<td>Viral markers</td>
<td>Positive</td>
<td>3</td>
<td>Biliary changes</td>
</tr>
<tr>
<td>Drugs</td>
<td>Yes</td>
<td>4</td>
<td>Other features</td>
</tr>
<tr>
<td>Alcohol</td>
<td>&lt;25 g/day</td>
<td>+2</td>
<td>Pretreatment aggregate score:</td>
</tr>
<tr>
<td>No</td>
<td>No</td>
<td>+1</td>
<td>Definite diagnosis &gt;15</td>
</tr>
<tr>
<td>Posttreatment aggregate score:</td>
<td>&lt;60 g/day</td>
<td>2</td>
<td>Probable diagnosis 10 15</td>
</tr>
</tbody>
</table>


AMA, antimitochondrial antibody; anti LC1, antibody to liver cytosol type 1; anti LKM1, antibody to liver/kidney microsomes type 1; anti SLA, antibody to soluble liver antigen; ANA, antinuclear antibody; AP:AST (or ALT) ratio, ratio of alkaline phosphatase level to aspartate or alanine aminotransferase level; HLA, human leukocyte antigen; IgG, immunoglobulin G; pANCA, perinuclear anti neutrophil cytoplasmic antibody; SMA, smooth muscle antibody.
specifically primary sclerosing cholangitis (PSC), than the AP level, which can be elevated due to bone activity in the growing child. Neither the gamma glutamyl transferase nor AP levels, however, discriminate between the presence or absence of cholangiopathy in children with AIH. The conventional serologic markers of AIH should also be assessed, including antinuclear antibody (ANA), smooth muscle antibody (SMA), antibody to liver/kidney microsome type 1 (anti-LKM1), and anti-liver cytosol type 1 (anti-LC1) (Table 4). Diagnostic evaluations should be undertaken to exclude hereditary diseases (Wilson disease and alpha 1 antitrypsin deficiency), viral hepatitis, steatohepatitis, and other autoimmune liver diseases that may resemble AIH specifically primary biliary cirrhosis (PBC) and PSC.

Liver biopsy examination at presentation is recommended to establish the diagnosis and to guide the treatment decision. In acute presentation unavailability of liver biopsy should not prevent from start of therapy. Interface hepatitis is the histological hallmark (Fig. 1), and plasma cell infiltration is typical (Fig. 2). Neither pathological finding is specific for AIH, and the absence of plasma cells in the infiltrate does not preclude the diagnosis. Eosinophils, lobular inflammation, bridging necrosis, and multiacinar necrosis may be present. Granulomas rarely occur. The portal lesions generally spare the bile ducts. In all but the mildest forms, fibrosis is present and, with advanced disease, bridging fibrosis or cirrhosis is seen. Occasionally, centrilobular (zone 3) lesions exist (Fig. 3), and sequential liver tissue examinations have demonstrated transition of this pattern to interface hepatitis in some patients. The histological findings differ depending on the kinetics of the disease. Compared to patients with an insidious onset, patients with acute severe hepatic failure exhibit more interface and lobular hepatitis, lobular disarray, hepatocyte necrosis, central necrosis and submassive necrosis, but less fibrosis and cirrhosis.

**Table 4. Autoantibodies in the Diagnosis of Autoimmune Hepatitis**

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Target Antigen(s)</th>
<th>Liver Disease</th>
<th>Value in AIH</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANA*</td>
<td>Multiple targets including:</td>
<td>AIH</td>
<td>Diagnosis of type 1 AIH</td>
</tr>
<tr>
<td></td>
<td>• chromatin,ribonucleoproteinsribonucleoprotein complexes</td>
<td>PBC</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SMA*</td>
<td>Microfilaments (filamentous actin) and intermediate filaments (vimentin, desmin)</td>
<td>Same as ANA</td>
</tr>
<tr>
<td>LKM 1*</td>
<td>Cytochrome P450 206 (CYP2D6)</td>
<td>Type 2 AIH</td>
<td>Diagnosis of type 2 AIH</td>
</tr>
<tr>
<td>LC 1*</td>
<td>Formiminotransferase cyclo deaminase (FTCD)</td>
<td>Type 2 AIH</td>
<td>Diagnosis of type 2 AIH</td>
</tr>
<tr>
<td>pANCA (atypical)</td>
<td>Nuclear lamina proteins</td>
<td>AIH</td>
<td>Diagnosis of type 1 AIH</td>
</tr>
<tr>
<td>SLA</td>
<td>tRNA&lt;sup&gt;(5E8)&lt;/sup&gt;Sec</td>
<td>AIH</td>
<td>Diagnosis of type 1 AIH</td>
</tr>
<tr>
<td>LKM 3</td>
<td>family 1 UDP glucuronosyl transferases (UGT1A)</td>
<td>Type 2 AIH</td>
<td>Diagnosis of type 2 AIH</td>
</tr>
<tr>
<td>ASGPR</td>
<td>Asialoglycoprotein receptor</td>
<td>AIH</td>
<td>Prognostic implications</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Drug induced hepatitis</td>
<td>Severe disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chronic hepatitis B, C, D</td>
<td>Histological activity</td>
</tr>
<tr>
<td>LKM2</td>
<td>Cytochrome P450 2C9</td>
<td>Ticrynafen induced hepatitis</td>
<td>None, does not occur after withdrawal of ticrynafen</td>
</tr>
<tr>
<td>LM</td>
<td>Cytochrome P450 1A2</td>
<td>Dihydralazine induced hepatitis</td>
<td>Diagnosis of APECED hepatitis</td>
</tr>
</tbody>
</table>

*Antibodies highlighted as bold letters indicate the conventional serological repertoire for the diagnosis of AIH. The other autoantibodies may be useful in patients who lack the conventional autoantibody markers.

AIH, autoimmune hepatitis; ANA, antinuclear antibody; APECED, autoimmune polyendocrinopathy candidiasis ectodermal dystrophy; ASGPR, antibody to asialoglycoprotein receptor; LC1, liver cytosol type 1; LKM, liver kidney/microsome; LM, liver microsome antibody; pANCA, perinuclear anti-neutrophil cytoplasmic antibody; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; SLA, soluble liver antigen; SMA, smooth muscle antibody; UGT, uridine diphosphate glucuronosyltransferase.
Some patients exhibit features of both AIH and another disorder such as PSC, PBC, or autoimmune cholangitis, a variant syndrome. Certain histologic changes such as ductopenia or destructive cholangitis may indicate the presence of one of these variant types. In these cases, the revised original scoring system can be used to assist in diagnosis (Table 3). The findings of steatosis or iron overload may suggest alternative or additional diagnoses, such as nonalcoholic fatty liver disease, Wilson disease, chronic hepatitis C, drug toxicity, or hereditary hemochromatosis.

Differences between a definite and probable diagnosis of AIH by the diagnostic scoring system relate mainly to the magnitude of serum IgG elevation, titers of autoantibodies, and extent of exposures to alcohol, medications, or infections that could cause liver injury. There is no time requirement to establish chronicity, and cholestatic clinical, laboratory, and histologic changes generally preclude the diagnosis. If the conventional autoantibodies are not detected, a probable diagnosis can be supported by the presence of other autoantibodies such as atypical perinuclear antineutrophil cytoplasmic antibody (atypical pANCA) or those directed against soluble liver antigen (anti-SLA).32

3.2. Serological Assessment

ANA, SMA, anti-LKM1, and anti-LC1 constitute the conventional serological repertoire for the diagnosis of AIH (Table 4). In North American adults, 96% of patients with AIH have ANA, SMA, or both, and 4% have anti-LKM1 and/or anti-LC1. Anti-LKM1 are deemed more frequent in European AIH patients and are typically unaccompanied by ANA or SMA. They are possibly underestimated in the United States. Anti-LKM1 are detected by indirect immunofluorescence, but because they may be confused with antimitochondrial antibody (AMA) using this technique, they can be assessed by measuring antibodies to cytochrome P4502D6, the major molecular target of anti-LKM1, using commercial enzyme-linked immunosorbent assays (ELISA). Autoantibodies are not specific to AIH and their expressions can vary during the course of the disease. Furthermore, low autoantibody titers do not exclude the diagnosis of AIH, nor do high titers (in the absence of other supportive findings) establish the diagnosis. Seronegative individuals may express...
conventional antibodies later in the disease or exhibit nonstandard autoantibodies. Autoantibody titers in adults only roughly correlate with disease severity, clinical course, and treatment response. In pediatric populations (patients aged ≤18 years), titers are useful biomarkers of disease activity and can be used to monitor treatment response.

When tested on rodent tissues, an autoantibody titer of 1:40 is significant in adults, whereas in children titers of 1:20 for ANA and SMA, and 1:10 for anti-LKM1, are clinically relevant, because autoantibody reactivity is infrequent in healthy children. If present in high titer, anti-LKM1 strongly support the diagnosis of AIH, even if liver biopsy is precluded by other clinical considerations.

The mainstay technique for autoantibody screening is indirect immunofluorescence on composite sections of freshly frozen rodent stomach, kidney and liver. This technique not only permits the detection of ANA, SMA, anti-LKM1, and AMA but also suggests the presence of other autoantibodies of an evolving clinical importance, such as antibody to liver cytosol type 1 (anti-LC1) and antibody to liver kidney microsome type 3 (anti LKM-3). Confirmation of the presence of the latter autoantibody is obtained with assays detecting antibodies to their molecular targets, formiminotransferase cyclo-deaminase (FTCD) and family 1 UDP-glucuronosyl-transferases (UGT1A), respectively (Table 4).

Other autoantibodies that may be useful in classifying patients who lack the conventional serological findings are anti-SLA and atypical pANCA. Atypical pANCA, originally considered specific for PSC and inflammatory bowel disease (IBD), are frequently present in patients with AIH, and occasionally can be the only autoantibodies detected (Table 4). ANCA typically do not coexist with anti-LKM1. Recent evidence indicates that the target of atypical pANCA is located within the nuclear membrane. For this reason, a more suitable designation may be peripheral anti-neutrophil nuclear antibody (pANNA) (Table 4).

Anti-SLA and anti-liver-pancreas (anti-LP), originally described as separate autoantibodies in AIH, were later found to target the same antigen and to represent a single serological entity. These antibodies are now referred to as anti-SLA or anti-SLA/LP. Their molecular target is a transfer ribonucleoprotein (Table 4). SLA has recently been renamed SEPSECS (Sep [O-phosphoserine] tRNA synthase) Selenocysteine Synthase. Anti-SLA are occasionally found in patients with AIH who are negative for ANA, SMA, and anti-LKM1, but are more commonly found in association with the conventional autoantibodies, especially if sensitive immunoassays are used. Anti-SLA are highly specific for the diagnosis of autoimmune liver disease, and their detection may identify patients with more severe disease and worse outcome.

Commercial ELISAs are available for their detection. The conventional and nonstandard autoantibodies described in AIH are shown in Table 4. Figure 4 provides an algorithm for the use of autoantibodies in the diagnosis of AIH.

### 3.3. Genetic Considerations

Multiple genetic associations with AIH have been described in different ethnic groups. The primary genetic association is with the major histocompatibility complex locus, and associations of HLA alleles with disease predisposition, clinical phenotype, response to therapy, and outcome have been studied. AIH is a complex polygenic disorder unlikely to be transmitted to subsequent generations; thus, routine screening of patients or family members for genetic markers is not recommended.

AIH may be present in patients with multiple endocrine organ failure, mucocutaneous candidiasis, and ectodermal dystrophy. Such patients have the rare genetic disorder autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), caused by a single-gene mutation located on chromosome 21q22.3 that affects the generation of the autoimmune regulator (AIRE) protein. AIRE is a transcription factor expressed in epithelial and dendritic cells within the thymus that regulates clonal deletion of autoreactive T cells (i.e., negative selection). APECED has an autosomal recessive pattern of inheritance and lacks HLA DR associations and female predilection. The liver autoantigens associated with APECED are cytochrome P450 1A2 (CYP1A2), CYP2A6 in addition to CYP2D6. Antibodies to cytochrome P450 1A2 were previously called anti liver microsomal (anti-LM) antibodies (Table 4). This is the only syndrome involving AIH that exhibits a Mendelian pattern of inheritance, and genetic counseling for the patient and family members are warranted.

**Recommendations:**

1. The diagnosis of AIH should be made when compatible clinical signs and symptoms, laboratory abnormalities (serum AST or ALT, and increased serum total IgG or γ-globulin), serological (ANA, SMA, anti-LKM 1, or anti-LC1), and histological (interface hepatitis) findings are present; and other
conditions that can cause chronic hepatitis, including viral, hereditary, metabolic, cholestatic, and drug-induced diseases, have been excluded (Table 2). (Class I, Level B)

2. Diagnostically challenging cases that have few or atypical clinical, laboratory, serological or histological findings should be assessed by the diagnostic scoring systems (Table 3). (Class IIa, Level B)

3. In patients negative for conventional autoantibodies in whom AIH is suspected, other serological markers, including at least anti-SLA and atypical pANCA, should be tested. (Table 4; Fig. 4). (Class I, Level B)

4. In patients with AIH and multiple endocrine disorders, the APECED syndrome must be excluded by testing for the typical mutations in the AIRE gene. (Class I, Level C)

4. Autoantibody Classification

Two types of AIH (type 1 and type 2) have been recognized based on serological markers but have not been established as valid clinical or pathological entities. A proposed third type (type 3) has been abandoned, as its serologic marker (anti-SLA) is also found in type 1 AIH and in type 2 AIH. Type 1 AIH is characterized by the presence of ANA, SMA or both, and constitutes 80% of AIH cases. Seventy percent of patients are female, with a peak incidence between ages 16 and 30 years. Associations with other autoimmune diseases are common (15%-34%); these include autoimmune thyroid disease, synovitis, celiac disease, and ulcerative colitis. At the time of diagnosis, cirrhosis is present in ~25% of patients. Antibodies to SLA have emerged as possible prognostic markers that may identify patients with severe AIH who are prone to relapse after corticosteroid withdrawal. Type 2 AIH is characterized by the presence of anti-LKM1 and/or anti-LC1 and/or anti-LKM-3. Most patients with type 2 AIH are children, and serum immunoglobulin levels are usually elevated except for the concentration of IgA, which may be reduced. Concurrent immune diseases are

Fig. 4. The use of serological tests assisting in the diagnosis of AIH. Serological tests in the evaluation of acute or chronic hepatitis of undetermined cause. The initial serological battery includes assessments for antinuclear antibodies (ANA), smooth muscle antibodies (SMA), antibodies to liver/kidney microsome type 1 (LKM-1), and antimitochondrial antibodies (AMA). The results of these conventional tests then direct the diagnostic effort. If one or more tests are positive, the diagnosis of autoimmune hepatitis (AIH) or primary biliary cirrhosis (PBC) should be pursued. If these tests are negative, other serological assessments are appropriate, including tests for antibodies to actin (F-actin), soluble liver antigen/liver pancreas (SLA/LP), liver cytosol type 1 (LC-1), UDP-glucuronosyltransferases (LKM-3), the E2 subunits of the pyruvate dehydrogenase complex (PDH-E2), perinuclear anti-neutrophil cytoplasmic antibodies (pANCA). The results of these supplemental tests may suggest other diagnoses, including primary sclerosing cholangitis (PSC), or cryptogenic chronic hepatitis.
common, progression to cirrhosis occurs, and an acute severe presentation is possible.

**Recommendations:**

5. Classification of autoimmune hepatitis into two types based on the presence of ANA and SMA (type 1 AIH) or anti-LKM1 and anti-LC1 (type 2 AIH) can be used to characterize the clinical syndrome or to indicate serological homogeneity in clinical investigations. Anti-LKM1 antibodies should be routinely investigated to avoid overlooking type 2 AIH. (Class IIa, Level C)

5. Diagnostic Difficulties

5.1. Mixed Clinical and Histological Features

PSC and PBC can have clinical, laboratory, histological, and genetic findings that resemble those of AIH. and AIH can have features that resemble each of these cholestatic syndromes. These nonspecific shared features can confound the codified diagnostic scoring system. The prevalence of AIH among patients with PSC was determined to be 21%-54% using the original scoring system, but this prevalence decreased to 8% in PSC when the revised original scoring system was applied. Application of the original scoring system in a retrospective review of 141 patients with PBC showed that 19% and 0% scored as probable and definite AIH, respectively. Clinical judgment is required to determine the predominant phenotype of the disease and to manage the process appropriately.

5.2. Serological Overlap

AIH patients may demonstrate serological features that suggest another diagnosis. AMA occur in about 5% of AIH patients in the absence of other biliary features ("serological overlap"), and their presence may confound the clinical diagnosis. AMA may disappear or persist as long as 27 years without an evolution into PBC. The revised original scoring system can render a diagnosis of “probable AIH” in these patients, if other features of AIH are sufficiently strong.

Other acute and chronic liver diseases of diverse etiologies that can have serological features of AIH include alcoholic and nonalcoholic fatty liver disease, acute and chronic viral hepatitis, and drug-induced hepatitis. Drugs such as minocycline, diclofenac, infliximab, propylthiouracil, atorvastatin, nitrofurantoin, methyl dopa, and isoniazid can cause a syndrome that resembles AIH replete with autoantibodies that generally disappear after discontinuation of the drug. Similarly, an AIH-like clinical syndrome has been associated with various herbal medications and with vaccination.

5.3. Ethnic Differences

Manifestations of AIH vary among ethnic groups. African-American patients have a greater frequency of cirrhosis at presentation than do white Americans. Alaskan natives exhibit a higher frequency of acute icteric disease than non-native counterparts, whereas Middle Eastern patients commonly have cholestatic features. Asian patients typically present with late onset, mild disease, whereas South American patients are commonly children with severe liver inflammation. Aboriginal North Americans have a disproportionately high frequency of immune-mediated disorders, cholestatic features, and advanced disease at presentation, and Somali patients are frequently men with rapidly progressive disease.

Socioeconomic status, healthcare access, and quality of care are additional factors that must be considered when assessing nonclassical disease manifestations within racial groups.

5.4. Acute Severe Presentation

AIH can have an acute severe presentation that can be mistaken for a viral or toxic hepatitis. Sometimes autoimmune hepatitis may present as acute liver failure. Corticosteroid therapy can be effective in suppressing the inflammatory activity in 36%-100% of patients, whereas delay in treatment can have a strong negative impact on outcome. In addition, unrecognized chronic disease can exhibit a spontaneous exacerbation and appear acute. If extrahepatic endocrine autoimmune features are present in children with severe acute presentation the APECED syndrome must be excluded.

5.5. Concurrent Immune Diseases

Concurrent immune disorders may mask the underlying liver disease. Autoimmune thyroiditis, Graves’ disease, synovitis and ulcerative colitis are the most common immune-mediated disorders associated with AIH in North American adults, whereas type I diabetes mellitus, vitiligo, and autoimmune thyroiditis are the most common concurrent disorders in European anti-LKM1 AIH patients. In children with AIH, autoimmune sclerosing cholangitis can be present, with or without IBD. In adults with both AIH and IBD, contrast cholangiography showing biliary changes suggestive of PSC are present in 44% of patients. In adults with AIH but not IBD, magnetic resonance imaging indicating biliary...
changes are observed in 8% of patients.\textsuperscript{82} Unless bile duct changes are present, concurrent immune diseases typically do not affect the prognosis of AIH.\textsuperscript{81} Cholangiographic studies should be performed in patients with both AIH and IBD, as well as in children and adults refractory to 3 months of conventional corticosteroid treatment. In a prospective pediatric study, 50% of patients with clinical, serological and histological characteristics of AIH type 1 had bile duct abnormalities compatible with early sclerosing cholangitis on cholangiogram.\textsuperscript{36}

**Recommendations:**

6. The diagnosis of AIH should be considered in all patients with acute or chronic hepatitis of undetermined cause, including patients with acute severe hepatitis. (Class I, Level C)

7. Cholangiographic studies should be considered to exclude PSC in adults if there has been no response to corticosteroid therapy after 3 months. (Class IIb, Level C)

8. All children with AIH and all adults with both AIH and IBD should undergo cholangiographic studies to exclude PSC. (Class I, Level C)

### 6. Treatment Indications

#### 6.1. Absolute Indications for Treatment

Three randomized, controlled trials have demonstrated that patients with serum AST levels of at least 10-fold the upper limit of the normal range (ULN) or more than five-fold ULN in conjunction with a serum γ-globulin level more than two-fold ULN have a high mortality (60% at 6 month) if untreated. Furthermore, histological findings of bridging necrosis or multilobular necrosis at presentation progress to cirrhosis in 82% of untreated patients and are associated with a 5-year mortality of 45%.\textsuperscript{55,86,87} These laboratory and histological findings of disease severity at presentation are absolute indications for corticosteroid treatment (Tables 4 and 5).\textsuperscript{274,275} Incapacitating symptoms associated with hepatic inflammation, such as fatigue and arthralgia, are also absolute indications for treatment regardless of other indices of disease severity (Table 5).

#### 6.2. Uncertain Indications for Treatment

The natural history of autoimmune hepatitis is uncertain in patients who have no or only mild symptoms and in those who have mild laboratory and histological findings. Prospective, randomized, controlled treatment trials have not been performed in these patients, and their indications for treatment remain uncertain and highly individualized (Table 5).\textsuperscript{269,276} Asymptomatic individuals with inactive cirrhosis may have an excellent immediate survival without corticosteroid treatment.\textsuperscript{8,9} Other asymptomatic patients who do not have cirrhosis may have inactive disease, and their natural 10-year survival may exceed 80%.\textsuperscript{9} There are no guidelines that reliably identify this “safe” population who require no therapy. Spontaneous resolution is possible in some asymptomatic patients with mild disease, but these patients improve less commonly (12% versus 63%, \(P < 0.006\)) and more slowly than treated patients.\textsuperscript{269} Furthermore, untreated asymptomatic patients with mild disease have a lower 10-year survival than treated counterparts (67% versus 98%, \(P < 0.01\)).\textsuperscript{269} The frequency of spontaneous improvement must be counterbalanced against the frequency of serious drug-related complications when making the treatment decision (12% versus 14%).\textsuperscript{269} Since the mild autoimmune hepatitis can progress and a rapid and complete response to a normal end point can be anticipated, corticosteroid therapy is favored in asymptomatic patients with mild disease.

<table>
<thead>
<tr>
<th><strong>Table 5. Indications for Immunosuppressive Treatment</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Absolute</strong></td>
</tr>
<tr>
<td>Serum AST ≥ 10 fold ULN</td>
</tr>
<tr>
<td>Symptoms (fatigue, arthralgia, jaundice)</td>
</tr>
<tr>
<td>Asymptomatic with normal or near normal serum AST and γ globulin levels</td>
</tr>
<tr>
<td>Serum AST ≥ 5 fold ULN and γ globulin level ≥ 2 fold ULN</td>
</tr>
<tr>
<td>Interface hepatitis</td>
</tr>
<tr>
<td>Severe cytopenia (white blood cell counts &lt;2.5 × 10^9/L or platelet counts &lt;50 × 10^9/L)</td>
</tr>
<tr>
<td>Osteopenia, emotional instability, hypertension, diabetes, or cytopenia (white blood cell counts ≤2.5 × 10^9/L or platelet counts ≤50 × 10^9/L)</td>
</tr>
<tr>
<td><strong>Relative</strong></td>
</tr>
<tr>
<td>Serum AST and/or γ globulin less than absolute criteria</td>
</tr>
<tr>
<td>Inactive cirrhosis or mild portal inflammation (portal hepatitis)</td>
</tr>
<tr>
<td>Severe cytopenia (white blood cell counts &lt;2.5 × 10^9/L or platelet counts &lt;50 × 10^9/L) or known complete deficiency of TPMT activity precludes treatment with azathioprine</td>
</tr>
<tr>
<td>Osteopenia, emotional instability, hypertension, diabetes, or cytopenia (white blood cell counts ≤2.5 × 10^9/L or platelet counts ≤50 × 10^9/L)</td>
</tr>
<tr>
<td><strong>None</strong></td>
</tr>
<tr>
<td>Inactive cirrhosis or mild portal inflammation (portal hepatitis)</td>
</tr>
<tr>
<td>Severe cytopenia (white blood cell counts &lt;2.5 × 10^9/L or platelet counts &lt;50 × 10^9/L) or known complete deficiency of TPMT activity precludes treatment with azathioprine</td>
</tr>
<tr>
<td>Osteopenia, emotional instability, hypertension, diabetes, or cytopenia (white blood cell counts ≤2.5 × 10^9/L or platelet counts ≤50 × 10^9/L)</td>
</tr>
</tbody>
</table>

AST, serum aspartate aminotransferase level; ULN, upper limit of normal range.
mild disease, especially in young individuals who are likely to tolerate the medication satisfactorily. Patients likely to have a poor outcome are those at increased risk for drug intolerance, and they include individuals with advanced inactive cirrhosis, post-menopausal osteopenia or vertebral compression, emotional instability or psychosis, poorly controlled hypertension, low thiopurine methyltransferase activity, and brittle diabetes (Table 5).

6.3. No Indications for Treatment
Corticosteroid therapy is effective only in patients who have clinical, laboratory or histological features of active liver inflammation. Patients with inactive or “burned out cirrhosis” cannot benefit from therapy, and they have an increased risk of drug-induced side effects because their associated hypoalbuminemia, hyperbilirubinemia, and portosystemic shunting can affect protein-binding and disposition of free prednisolone. Patients with brittle diabetes, vertebral compression, psychosis, or severe osteoporosis must be critically assessed for a treatment benefit before administering corticosteroids, and azathioprine should be avoided in patients with severe pretreatment cytopenia (white blood cell counts below 2.5 × 10^9/L or platelet counts below 50 × 10^9/L) or known complete deficiency of thiopurine methyltransferase activity (Table 5).

6.4. Treatment Indications in Children
The indications for treatment in children are similar to those in adults (Table 5). The disease process in children appears to be more severe at presentation than commonly seen in adults, perhaps because of delays in diagnosis or other concurrent immune diseases, such as autoimmune sclerosing cholangitis. More than 50% of children have cirrhosis at accession, and the milder forms of the disease described in adults are not typically seen in children. The perceived aggressive course in most children and reports that delays in diagnosis and treatment adversely affect the long-term outcome have justified drug therapy at the time of diagnosis. Only those children with advanced cirrhosis without evidence of inflammatory activity are unlikely to benefit. Therefore, all children in which the diagnosis of AIH has been established should be treated.

If the diagnosis of autoimmune hepatitis or the indications for the treatment are in doubt in children or adults, the patient should be referred to a hepatologist before starting corticosteroid therapy.

Recommendations:
9. Immunosuppressive treatment should be instituted in patients with serum AST or ALT levels greater than 10-fold ULN, at least five-fold ULN in conjunction with a serum γ-globulin level at least 2-fold ULN, and/or histological features of bridging necrosis or multilobular necrosis (Table 5). (Class I, Level A)

10. Immunosuppressive treatment may be considered in adult patients without symptoms and mild laboratory and histological changes, but the decision must be individualized and balanced against the possible risks of therapy. Consider referral to a hepatologist prior to starting therapy (Table 5). (Class IIa, Level C)

11. Immunosuppressive treatment should not be instituted in patients with minimal or no disease activity or inactive cirrhosis, but these patients must continue to be followed closely, i.e., 3-6 months (Table 5). (Class IIa, Level C)

12. Immunosuppressive treatment should not be instituted in patients with serious pre-existent comorbid conditions (vertebral compression, psychosis, brittle diabetes, uncontrolled hypertension), or previous known intolerances to prednisone unless the disease is severe and progressive and adequate control measures for the comorbid conditions can be instituted (Table 5). (Class III, Level C)

13. Azathioprine treatment should not be started in patients with a severe pretreatment cytopenia (white blood cell counts below 2.5 × 10^9/L or platelet counts below 50 × 10^9/L) or known complete deficiency of thiopurine methyltransferase activity (Table 5). (Class III, Level C)

14. Immunosuppressive treatment should be instituted in children at the time of diagnosis regardless of symptom status. (Class I, Level C)

7. Treatment Regimens
7.1. Treatment Regimens in Adults
Two treatment regimens are equally effective in severe AIH (Table 6). Prednisone alone (60 mg daily) or a lower dose of prednisone (30 mg daily) in conjunction with azathioprine (50 mg is usually used in the United States or 1-2 mg/kg body weight, which is widely used daily in Europe) (Table 6). Prednisone may be tapered down to an individual level sufficient to maintain a remission from 20 mg daily onward, reduction should be done by 5 mg every week until 10 mg/day are achieved and even further
reduction by 2.5 mg/week have been considered up to 5 mg daily. The maintenance regimen is then continued until resolution of the disease, treatment failure, or drug-intolerance.282-285 The combination regimen of prednisone and azathioprine is associated with a lower occurrence of corticosteroid-related side effects than the higher dose prednisone regimen (10% versus 44%), and it is the preferred treatment.273 Advanced cirrhosis can significantly impair the conversion of prednisone to prednisolone, but this impairment is insufficient to alter treatment response or mandate the administration of prednisolone.272 In Europe, prednisolone is preferred over prednisone,272 Prednisone is appropriate as the sole medication in individuals with severe cytopenia,288-292 those undergoing a short treatment trial (duration of therapy, <6 months),273,278 individuals who are pregnant or contemplating pregnancy,293-295 patients with some active malignancies,296,297 and individuals with known complete thiopurine methyltransferase deficiency (Table 6).291,292,298 The combination regimen is appropriate in patients who will be treated continuously for at least 6 months or who are at increased risk for drug-related complications, including postmenopausal women and individuals with emotional instability, osteoporosis, brittle diabetes, labile hypertension, or obesity (Table 6).43,44,277,282-287,299,300 Patients receiving prednisone should undergo eye examinations for cataracts and glaucoma periodically during treatment, and those receiving azathioprine in any dose should be monitored at 6 month intervals for leukopenia and thrombocytopenia.277,282-284,301

Adjunctive therapies should be based on an awareness of possible complications of the medication, and they should be introduced as appropriate to the individual’s perceived risk.277,282-284 Such therapies should include a regular weight baring exercise program, vitamin D and calcium supplementation. The administration of bone active agents such as bisphosphonates may be appropriate for individual patients.277,282,302 Patients on long-term corticosteroid treatment should be monitored for bone disease by baseline and annual bone mineral densitometry of the lumbar spine and hip.277,282,300,303 Like other patients suffering from chronic liver disease patients with AIH should be protected against hepatitis B virus (HBV) and hepatitis A virus (HAV). Vaccination should be done as early as possible even before immunosuppression is started because of lower response rates.

7.2. Treatment Regimes in Children

Treatment regimens have been less rigorously established in children than in adults and to some extent, they reflect the preferences of individual centers.35,36,120,279-281,283,305-309 There have been no randomized, controlled, treatment trials in children with autoimmune hepatitis, but several reports of 17 or more children have documented the efficacy of regimens similar to those used in adults (Table 7).35,36,279-281 Despite the severe disease at presentation, the response to treatment with corticosteroids with or without azathioprine is generally excellent in children. Normalization of liver tests is noted after 6-9 months of therapy in 75%-90%.

Prednisone is the mainstay in virtually all reported regimens for children, and it is usually administered initially in a dose of 1-2 mg/kg daily (up to 60 mg daily) (Table 7).35,36,279-281 Tapering schedules vary
widely. In some centers, a rapid switch to alternate day regimens has been advocated, whereas in other centers, maintenance of a low dose daily schedule is considered essential. Because of the significant deleterious effects of long-term intermediate or high dose corticosteroid therapy on linear growth, bone development, and physical appearance, early use of azathioprine (1-2 mg/kg daily) or 6-mercaptopurine (1.5 mg/kg daily) for all children without contraindications is usually recommended. Experience with azathioprine alone as maintenance therapy has been limited in children, but the drug appears to hold some promise for those who do not tolerate complete cessation of treatment. Regimens incorporating cyclosporin A as initial treatment for children with autoimmune hepatitis do not appear to confer a significant advantage over more traditional therapies, and they should be considered investigational. Pretreatment evidence of susceptibility to HAV or HBV would justify vaccination against these viruses in children.

Recommendations:

15. Treatment should be instituted with prednisone (starting with 30 mg daily and tapering down to 10 mg daily within 4 weeks) in combination with azathioprine (50 mg daily or 1-2 mg/kg body weight as widely used in Europe) or a higher dose of prednisone alone (starting with 40-60 mg daily and tapering down to 20 mg daily within 4 weeks) in adults with AIH. The combination regimen is preferred, and prednisolone in equivalent dose can be used instead of prednisone (Table 6). (Class I, Level A)

16. Treatment should be instituted with prednisone (1-2 mg/kg daily; maximum dose 60 mg daily) in children in combination with azathioprine (1-2 mg/kg daily) or 6-mercaptopurine (1.5 mg/kg daily) (Table 7). (Class I, Level B)

17. Patients on long-term corticosteroid treatment should be monitored for bone disease at baseline and then annually. (Class IIa, Level C)

18. Adjunctive therapies for bone disease include a regular weight bearing exercise program, vitamin D, calcium and where appropriate bone active agents such as bisphosphonates. (Class IIa, Level A)

19. Pretreatment vaccination against HAV and HBV should be performed if there has been no previous vaccination or susceptibility to these viruses has been shown. (Class IIa, Level C)

8. Treatment-Related Side Effects

The nature and frequency of the side effects associated with each treatment regimen must be explained to the patient prior to the institution of therapy (Table 8).

8.1. Corticosteroid-Related Side Effects

Cosmetic changes, including facial rounding, dorsal hump formation, striae, weight gain, acne, alopecia and facial hirsutism, occur in 80% of patients after 2 years of corticosteroid treatment regardless of the regimen (Table 8). Severe side effects include osteopenia with vertebral compression, brittle diabetes, psychosis, pancreatitis, opportunistic infection, labile hypertension, and malignancy. Severe complications are uncommon, but if they occur, it is usually after protracted therapy (more than 18 months) with prednisone alone (20 mg daily).

Corticosteroid-related side effects are the most common causes for premature drug withdrawal in autoimmune hepatitis. Treatment is discontinued in 13% of patients because of complications, and 47% of these have intolerable cosmetic changes or obesity. Twenty-seven percent have osteoporosis with vertebral compression, and 20% have brittle diabetes.

8.2. Azathioprine-Related Side Effects

Complications of azathioprine therapy in autoimmune hepatitis include cholestatic hepatitis, pancreatitis, nausea, emesis, rash, opportunistic infection, bone marrow suppression and malignancy (Table 8). Five percent of patients treated with
azathioprine develop early adverse reactions (nausea, vomiting, arthralgias, fever, skin rash or pancreatitis), which warrants its discontinuation. The overall frequency of azathioprine-related side effects in patients with autoimmune hepatitis is 10%, and the side effects typically improve after the dose of azathioprine is reduced or the therapy is discontinued. An important but rare complication of azathioprine treatment is a diarrheal syndrome associated with malabsorption and small intestinal villus atrophy that improves after azathioprine withdrawal. The sinusoidal obstruction syndrome ("veno-occlusive disease") described after renal transplantation has not been reported in azathioprine-treated autoimmune hepatitis, nor has the nodular regenerative hyperplasia described in azathioprine-treated patients with inflammatory bowel disease.

The principal side effect of azathioprine is cytopenia, and the most dire consequence is bone marrow failure (Table 8). The frequency of cytopenia in azathioprine-treated patients with autoimmune hepatitis is 46%, and the occurrence of severe hematological abnormalities is 6%. These toxicities are not predictable by either genotyping or phenotyping for thiopurine methyltransferase activity, and the most common cause of cytopenia in these patients is hypersplenism associated with underlying cirrhosis. Patients undergoing azathioprine therapy should have blood leukocyte and platelet counts assessed at 6-month intervals.

Chronic immune suppression in autoimmune hepatitis has been associated with an increased risk of malignancy (Table 8). The incidence of extrahepatic neoplasm in treated autoimmune hepatitis is 1 per 194 patient-years, and the probability of tumor occurrence is 3% after 10 years. Tumors do not have a predominant cell type, and they are not related to age, sex, treatment regimen or cumulative duration of treatment. The low but increased risk of malignancy associated with chronic low dose azathioprine therapy (1.4-fold greater than normal) must be counterbalanced against the beneficial actions of the drug as a corticosteroid-sparing agent.

8.3. Special Populations at Risk for Drug Toxicity

8.3.1. Patients with Cirrhosis. Individuals with cirrhosis at presentation have a higher frequency of drug-related complications than those without cirrhosis.

### Table 8. Frequency and Nature of Side Effects Associated with Treatment in Adults with Autoimmune Hepatitis

<table>
<thead>
<tr>
<th>Prednisone-Related Side Effects</th>
<th>Frequency</th>
<th>Azathioprine-Related Side Effects</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type</strong></td>
<td><strong>Frequency</strong></td>
<td><strong>Type</strong></td>
<td><strong>Frequency</strong></td>
</tr>
<tr>
<td>Cosmetic (usually mild)</td>
<td>80% (after 2 years)</td>
<td>Hematologic (mild)</td>
<td>46% (especially with cirrhosis)</td>
</tr>
<tr>
<td>Facial rounding</td>
<td></td>
<td>Cytopenia</td>
<td></td>
</tr>
<tr>
<td>Weight gain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dorsal hump striae</td>
<td></td>
<td>Leucopenia</td>
<td>6% (treatment ending)</td>
</tr>
<tr>
<td>Hirsutism</td>
<td></td>
<td>Thrombocytopenia</td>
<td></td>
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<tr>
<td>Alopecia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somatic (usually mild)</td>
<td>13% (treatment ending)</td>
<td>Neoplastic</td>
<td>5%</td>
</tr>
<tr>
<td>Emotional instability</td>
<td></td>
<td>Nonhepatic cell types</td>
<td>3% (after 10 years)</td>
</tr>
<tr>
<td>Glucose intolerance</td>
<td></td>
<td>Hematologic/enteric</td>
<td>Rare (treatment ending)</td>
</tr>
<tr>
<td>Cataracts</td>
<td></td>
<td>Bone marrow failure</td>
<td></td>
</tr>
<tr>
<td>Somatic (severe)</td>
<td></td>
<td>Villous atrophy</td>
<td></td>
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<tr>
<td>Osteopenia</td>
<td></td>
<td>Malabsorption</td>
<td></td>
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<tr>
<td>Vertebral compression</td>
<td></td>
<td>Teratogenic during pregnancy</td>
<td>Rare (theoretical)</td>
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<tr>
<td>Diabetes (brittle)</td>
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<tr>
<td>Psychosis</td>
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<td></td>
<td></td>
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<tr>
<td>Hypertension (labile)</td>
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<tr>
<td>Inflammatory/neoplastic</td>
<td>Rare</td>
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<tr>
<td>Pancreatitis</td>
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<tr>
<td>Opportunistic infection</td>
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</tr>
<tr>
<td>Malignancy</td>
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<td></td>
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</table>
|                             | Adapted from Czaia AJ. Expert Opin Drug Saf 2008;7:319 333.
(25% versus 8%). Patients with cirrhosis must be closely monitored during therapy, and those individuals with cytopenia should be assessed for thiopurine methyltransferase activity prior to the administration of azathioprine.

### 8.3.2. Pregnant Patients

Most experiences indicate that pregnancy and the medication are well tolerated by the mother and the neonate. The major risk is prematurity, and infant mortality relates directly to the degree of prematurity. Fetal loss is higher than in normal mothers, but no greater than in mothers with other chronic illnesses. Fetal mortality has been reported as high as 19% with deliveries usually before the 20th week. Perinatal mortality is 4%; maternal mortality is 3%. The frequency of serious maternal complications is 9%; and the occurrence of an adverse outcome of any type is 26%. Outcomes in autoimmune hepatitis are similar to those in the general population where the frequencies of fetal loss, caesarian section, and still births are 21%, 17%, and 5%, respectively. Furthermore, mothers with autoimmune hepatitis have better outcomes than women with diabetes in whom the frequency of fetal loss ranges from 24%-29%.

Preconceptional counseling is advised and termination of immunosuppressive therapy should be attempted where possible. Azathioprine has a category D pregnancy rating by the FDA. It has been associated with congenital malformations in pregnant mice, and low levels of the 6-thioguanine nucleotides are detectable in the newborns of mothers treated for Crohn’s disease (Table 8). Teratogenicity associated with azathioprine therapy therefore is a theoretical consideration, but increased birth defects have not been reported in mothers receiving this treatment, nor have there been apparent adverse consequences of breast feeding by treated mothers. Nevertheless, these human experiences have been anecdotal, and there has not been a comprehensive human study establishing the safety of azathioprine in pregnant women. Exacerbations of disease commonly follow delivery as blood estrogen levels fall. The frequency of exacerbation after delivery has been variously reported between 12%-86%. Its occurrence must be anticipated, and conventional therapy must be resumed pre-emptively 2 weeks before anticipated delivery and maintained throughout the postpartum period. Contraception should be advised in women with advanced liver disease and features of portal hypertension because they are at risk for variceal hemorrhage during pregnancy.

### 8.3.4. Patients with Low Thiopurine Methyltransferase Activity

Patients with near-zero erythrocyte concentrations of thiopurine methyltransferase activity are at risk for myelosuppression during azathioprine treatment. Only 0.3%-0.5% of the population has a severe enzyme deficiency, and not all patients with a deficiency of this degree experience bone marrow failure. Individuals with abnormally decreased but not extreme reductions in thiopurine methyltransferase activity (heterozygous state) tolerate azathioprine satisfactorily at the low dose of 50 mg, and the level of enzyme activity may actually increase with continued administration of the drug. The rarity of severe azathioprine-induced myelosuppression, the low dose of azathioprine used in conventional treatment (50 mg-150 mg daily), and the inability to reliably predict risk by phenotypic and genotypic assessments have not supported routine screening for thiopurine methyltransferase activity in AIH. Pretreatment cytopenia, cytopenia developing during therapy, or the administration of higher than conventional doses of azathioprine (>150 mg daily) justifies determination of enzyme activity.

### Recommendations:

20. The possible side effects of therapy with corticosteroids must be reviewed with the patient prior to treatment (Table 8). (Class Ia, Level C)

21. Patients must be counseled regarding the uncertain risk of azathioprine in pregnancy, and azathioprine should be discontinued, if possible, in patients during pregnancy. (Class III, Level C)

22. Azathioprine has a category D pregnancy rating by the FDA, and it should be discontinued, if possible, in patients during pregnancy. (Class III, Level C)

23. Postpartum exacerbation of AIH must be anticipated by resuming standard therapy 2 weeks prior to anticipated delivery and by closely monitoring serum AST or ALT levels at 3-week intervals for at least 3 months after delivery. (Class Ia, Level C)

24. Blood thiopurine methyltransferase activity should be assessed in patients with cytopenia before or during azathioprine therapy. (Class Ia, Level C)
9. Treatment Endpoints and Courses of Action

Conventional therapy in adults is continued until remission, treatment failure, incomplete response, or drug toxicity (Table 9).283-284 There is no prescribed minimum or maximum duration of treatment. The length of therapy can be based on a fixed minimum duration that is usually associated with a complete response344 or on a variable duration that is individualized to the desired result and tolerance.345

9.1. Remission

All adult patients should be given the opportunity to enter a sustained remission that is free of medication (Table 9).282-285,345-347 Ninety percent of adults have improvements in the serum AST, bilirubin, and γ-globulin levels within 2 weeks.266 Adults rarely achieve resolution of their laboratory and liver tissue abnormalities in less than 12 months, and the probability of remission during therapy diminishes after 2 years.346-348 Histological improvement lags behind clinical and laboratory improvement by 3-8 months.49,349

Resolution of the laboratory indices (normal serum AST or ALT, γ-globulin, and IgG levels) and tissue manifestations of active liver inflammation (normal liver tissue examination) is the ideal treatment endpoint and the goal of initial therapy (Table 9).345,350-353 The average duration of treatment is 18-24 months.283-285,345 Normal laboratory indices before termination of treatment reduce the relative risk of relapse after drug withdrawal by 3-fold to 11-fold compared to patients who do not achieve these results, and 87% of patients who achieve long-term remission have normal laboratory indices prior to the termination of therapy.345 Therefore, the biochemical endpoint in previous studies of <2 times the upper limit of normal should not be accepted in future studies as endpoint or goal of treatment because relapse after termination of therapy in those patients is universal. However, the normalization of tests and tissue does not protect against relapse, and 60% of patients who relapse do so despite disappearance of inflammatory features.345 The frequency that corticosteroid treatment can achieve full resolution of the laboratory tests and liver tissue abnormalities is unclear, and whereas pursuit of an ideal treatment endpoint is desirable, it must be tempered by the realization that not all patients can achieve this result or tolerate the required treatment.345 Daily maintenance doses of medication should remain fixed in adults until the goal of therapy is achieved. Titrations in dose are associated with delayed or incomplete histological improvement, and it can prolong the durations of therapy.273 Alternate day schedules of prednisone can induce symptomatic and laboratory improvement, but not histological resolution.273

Liver biopsy assessment prior to termination of treatment is the only method by which to ensure full resolution of the disease and an optimal endpoint of therapy. Interface hepatitis is found in 55% of patients with normal serum AST and γ-globulin levels during therapy,349 and these individuals typically relapse after cessation of treatment.311,347 Their recognition by liver biopsy examination prior to drug withdrawal can justify an extension of treatment. Therefore, a liver biopsy is recommended before termination of

### Table 9. Endpoints of Initial Immunosuppressive Treatment and Courses of Action in Autoimmune Hepatitis

<table>
<thead>
<tr>
<th>Treatment Endpoint</th>
<th>Criteria</th>
<th>Courses of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remission</td>
<td>Disappearance of symptoms, normal serum aminotransferases, bilirubin and γ globulin levels, normal hepatic tissue or inactive cirrhosis</td>
<td>Gradual withdrawal of prednisone over 6 week period Serum AST or ALT, total bilirubin, and γ globulin levels determined at 3 week intervals during and for 3 months after drug withdrawal</td>
</tr>
<tr>
<td>Treatment failure</td>
<td>Worsening clinical, laboratory, and histological features despite compliance with therapy Development of jaundice, ascites or hepatic encephalopathy</td>
<td>Repeat laboratory assessments thereafter every 6 months for at least 1 year and then every year lifelong Prednisone, 60 mg daily, or prednisone, 30 mg daily, and azathioprine, 150 mg daily, for at least 1 month Dose reduction of prednisone by 10 mg and azathioprine by 50 mg for each month of improvement until standard treatment doses are achieved</td>
</tr>
<tr>
<td>Incomplete response</td>
<td>Some or no improvement in clinical, laboratory, and histological features despite compliance with therapy after 2 3 years</td>
<td>Reduction in doses of prednisone by 2.5 mg/month until lowest level possible (≤10 mg daily) to prevent worsening of serum AST or ALT abnormalities Indefinite azathioprine therapy (2 mg/kg daily) as an alternative treatment if corticosteroid intolerance</td>
</tr>
<tr>
<td>Drug toxicity</td>
<td>Development of intolerable cosmetic changes, symptomatic osteopenia, emotional instability, poorly controlled hypertension, brittle diabetes or progressive cytopenia</td>
<td>Reduction in dose or discontinuation of offending drug Maintenance on tolerated drug in adjusted dose</td>
</tr>
</tbody>
</table>

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immunosuppressive treatment in AIH. Termination of therapy should be considered after at least 2-year treatment, when liver function tests and immunoglobulin levels have been repeatedly normal.

Termination of therapy after induction of remission requires a gradual, well-monitored dose reduction over a 6-week period of close surveillance (Table 9).\textsuperscript{282-285} Patients who are on a protracted course of steroid therapy need to be assessed for adrenal insufficiency. The activity of the disease during and after drug withdrawal is assessed by the appearance of symptoms (fatigue, arthralgias, and anorexia) and the behavior of the laboratory indices of liver inflammation (serum AST and γ-globulin concentrations). Laboratory tests are performed at 3-week intervals during drug withdrawal and for 3 months after termination of therapy. Thereafter, they are repeated at 3 months and then every 6 months for 1 year,\textsuperscript{282-284} and then annually life-long.

9.2. Treatment Failure

Treatment failure connotes clinical, laboratory, and histological worsening despite compliance with conventional treatment schedules; it occurs in at least 9% of patients and may be observed within 3-6 weeks. (Table 9).\textsuperscript{354,355} Patients who will later fail treatment, die of liver failure or require liver transplantation can be identified early by applying the model of end-stage liver disease (MELD).\textsuperscript{355} Early recognition of individuals who are likely to fail corticosteroid therapy may improve their outcome by prompting treatment modifications, including timely liver transplantation.\textsuperscript{11,266,356}

Treatment failure justifies the discontinuation of conventional treatments, and institution of high dose therapy with prednisone alone (60 mg daily) or prednisone (30 mg daily) in conjunction with azathioprine (150 mg daily) (Table 9).\textsuperscript{282-285,357} Doses at this level are maintained for at least 1 month. Thereafter, the doses of prednisone and azathioprine are reduced each month after improvement in the serum AST level until conventional maintenance doses of medication (original schedule) are reached.\textsuperscript{290,291}

Seventy percent of patients improve their clinical and laboratory findings within 2 years, and survival is preserved.\textsuperscript{354,355,357} Histological remission is achieved in only 20%, and most patients remain on therapy and at risk for drug-related side effects and/or disease progression.\textsuperscript{354,355,357} The development of hepatic encephalopathy, ascites, and/or variceal hemorrhage during therapy for treatment failure is an indication for liver transplantation.\textsuperscript{11,73}

9.3. Incomplete Response

Protracted therapy that has improved the clinical, laboratory, and histological indices but not induced complete resolution constitutes an incomplete response (Table 8).\textsuperscript{282-285} Thirteen percent of patients fail to enter remission after 36 months of treatment, and they are classified as incomplete responders. In these instances, alternative strategies must be considered. Long-term low dose corticosteroid therapy involves a gradual decrease in the prednisone dose by 2.5 mg per month until the lowest level (≤10 mg daily) is achieved, and the serum AST or ALT level remains stable.\textsuperscript{282-285,329} Long-term azathioprine (2 mg/kg daily) can also be used to stabilize the serum AST and ALT levels in corticosteroid intolerant individuals who require continuous treatment.\textsuperscript{282-285,327}

9.4. Drug Toxicity

Drug toxicity justifies premature discontinuation or alteration of conventional therapy in 13% of patients (Table 8).\textsuperscript{277,282-285} In these instances, therapy with the tolerated agent (prednisone or azathioprine) can be maintained in adjusted dose to prevent worsening in the clinical and laboratory features.\textsuperscript{282-285}

9.5. Treatment Endpoints for Children

The treatment endpoints for children are similar to those of adults. Almost all children demonstrate improvement in liver tests within the first 2-4 weeks of treatment with either prednisone or prednisone and azathioprine.\textsuperscript{35,36,279-281,283,305,358-361} Some 80%-90% achieve laboratory remission in 6-12 months. In most treatment protocols, high-dose prednisone (1-2 mg/kg daily) is administered for up to 2 weeks, at which time a gradual decrease in dose is undertaken to reach a maintenance level (usually 0.1-0.2 mg/kg daily or 5 mg daily) in 6-8 weeks.\textsuperscript{35,36,279-281,283,305,358-361} Clinical and laboratory parameters are usually sufficient to determine the adequacy of response. Flares in disease activity, as assessed by an increase in serum AST or ALT level, are treated with a temporary increase in corticosteroid dose.

The goal of treatment in children is to have minimal or no serum AST or ALT abnormality on the lowest dose of medication possible.\textsuperscript{35, 36, 279-281, 283, 305, 358-361} Long-term, low-dose therapy is anticipated and emotional, cosmetic, and growth-related side effects temper treatment in an individualized fashion. Long-term monotherapy with azathioprine is generally well tolerated, and it is a strategy by which to suppress inflammatory activity and discontinue corticosteroids.\textsuperscript{305}
Routine monitoring of conventional liver tests and blood counts and amylase are performed at 4 to 6 week intervals. The decision to terminate therapy in children is based on laboratory evidence of prolonged inactivity, and it is a consideration in only 20%-30% of patients. After 2-3 years of treatment, drug withdrawal is considered in children if liver function tests and IgG are repeatedly normal, and autoantibodies negative or $\leq 1:20$, for at least 1 year on low-dose corticosteroids. At that time, a liver biopsy examination should be performed and therapy withdrawn only if there is no histological evidence of inflammation. Relapse after drug withdrawal occurs in 60%-80% of children, and parents and patients must be informed that the probability of retreatment is high.35,36,279-281,283,305,358-361

Recommendations:

25. Improvements in the serum AST or ALT level, total bilirubin concentration, and $\gamma$-globulin or IgG level should be monitored at 3-6 month intervals during treatment. (Class IIa, Level C)

26. Treatment should be continued until normal serum AST or ALT level, total bilirubin concentration, $\gamma$-globulin or IgG level, and normal liver histology not exhibiting inflammatory activity is achieved. (Table 9). (Class IIa, Level C)

27. Patients should experience a minimum duration of biochemical remission before immunosuppression is terminated after at least 24 months of therapy. (Class II a, Level C)

28. Worsening symptoms, laboratory tests or histological features during conventional therapy (treatment failure) compel the institution of high dose prednisone alone (60 mg daily) or prednisone (30 mg daily) in combination with azathioprine (150 mg daily) (Table 9). (Class IIa, Level C)

29. Clinical, laboratory and histological improvement which is insufficient to satisfy criteria for a treatment endpoint after continuous therapy for at least 36 months (incomplete response) should be treated with long-term prednisone therapy or azathioprine maintenance in doses adjusted to ensure absence of symptoms and stable laboratory abnormalities (Table 9). (Class IIa, Level C)

30. Intolerance to the medication (drug toxicity) should be managed by reducing the dose of the offending agent or discontinuing its use (Table 9). (Class IIa, Level C)

10. Relapse After Drug Withdrawal

Relapse connotes recrudescence of disease activity after induction of remission and termination of therapy.345,347,348,362 It is characterized by an increase in the serum AST level to more than three-fold the ULN and/or increase in the serum $\gamma$-globulin level to more than 2 g/dL.349 Laboratory changes of this degree are invariably associated with the re-appearance of interface hepatitis in the liver tissue, and they preclude the need for a liver biopsy examination to document relapse.349

Progression to cirrhosis (38% versus 4%, $P = 0.004$) and death from liver failure or requirement for liver transplantation (20% versus 0%, $P = 0.008$) are more common in the patients who relapse multiply than in those who sustain remission after their first treatment.363 Furthermore, the number of relapse episodes correlates with disease progression and an adverse clinical outcome. Patients who relapse and require re-treatment also have a higher occurrence of drug-related side-effects than those who sustain their remission after drug withdrawal (54% versus 26%, $P = 0.05$).346 Relapse occurs in approximately 80% of patients who enter remission, depending in part on the laboratory and histological findings prior to drug withdrawal.311,345-348,352,362 The optimal time to prevent the consequences of repeated relapse and re-treatment is after the first relapse.363

The preferred management of relapse is to reinstitute therapy with prednisone and azathioprine until clinical and laboratory resolution is again achieved and then to eliminate the prednisone while increasing the dose of azathioprine.282,283,327,364 The dose of azathioprine is increased to 2 mg/kg daily as the dose of prednisone is gradually withdrawn. Azathioprine is then continued indefinitely as a chronic maintenance therapy.

Eighty-seven percent of adult patients managed by the indefinite azathioprine maintenance strategy remain in remission during a median observation interval of 67 months.327,364 Follow-up liver biopsy assessments show inactive or minimal histological disease in 94%; corticosteroid-related side effects improve or disappear in most patients; and the drug is generally well tolerated. The most common side effect is withdrawal arthralgia, which is encountered in 63% of patients. Myelosuppression occurs in 7%; lymphopenia occurs in 57%; and diverse malignancies of uncertain relationship to the therapy develop in 8%. The major advantage of the azathioprine regimen is the avoidance of corticosteroids and its possible side effects.

An alternative strategy is to administer prednisone in the lowest dose possible to maintain the serum AST
level within normal limits or at least below three-fold the ULN. \(^{329}\) Suppression of the serum AST level to less than three-fold the ULN decreases the likelihood of interface hepatitis on histological examination, \(^{349,365}\) and a dose of prednisone less than 10 mg daily is generally well tolerated long-term. \(^{282,283,329}\) Eighty-seven percent of patients can be managed long-term on 10 mg of prednisone daily or less (median dose, 7.5 mg daily). \(^{329}\) Observation intervals for up to 149 months have indicated satisfactory outcomes that have justified continued application of the strategy. Side effects associated with the earlier conventional treatments improve or disappear in 85% of patients maintained on low dose prednisone; new side effects do not develop; and survival is unaffected when compared with patients receiving standard dose therapy after relapse. \(^{329}\) The major advantages of the low dose prednisone schedule are avoidance of long-term azathioprine therapy in fertile young adults and elimination of the theoretical risks of oncogenicity and teratogenicity. Furthermore the topical steroid budesonide is now being evaluated as an alternative to prednisone or prednisolone in order to achieve or maintain remission with less steroid specific side effects. \(^{366-369}\)

Retrospective analyses have indicated that the long-term maintenance therapies need not be life-long. \(^{347}\) Twelve percent of patients treated with these schedules are able to be permanently withdrawn from medication after 69 ± 8 months of follow-up, and the probability of a sustained remission after total withdrawal is 13% after 5 years. \(^{347}\) These observations justify periodic attempts at drug withdrawal in all patients with longstanding (≥12 months) inactive disease. The inability to discontinue azathioprine mandates indefinite treatment.

Relapse in children is characterized by any manifestation of recrudescent hepatic inflammation after drug withdrawal. \(^{35,36,279-281,283,305,358-361}\)

Its frequency in children is the same or higher than that observed in adults. Relapse is often associated with nonadherence to treatment. \(^{370}\) The occurrence of relapse in children justifies reinstatement of the original treatment regimen. Indefinite low-dose therapy can then be instituted after suppression of disease activity using prednisone in combination with azathioprine or 6-mercaptopurine. Maintenance therapy with azathioprine alone is a management option for children who have relapsed. \(^{395}\)

**Recommendations:**

**31. The first relapse after drug withdrawal should be retreated with a combination of prednisone plus azathioprine at the same treatment regimen as with the initial course of therapy and then tapered to monotherapy with either azathioprine (2 mg/kg daily) as a long-term maintenance therapy or with indefinite low dose prednisone (≤10 mg daily) in patients intolerant of azathioprine. (Class IIa, Level C)**

**32. Gradual withdrawal from long-term azathioprine or low-dose prednisone maintenance therapy should be attempted after at least 24 months of treatment and continued normal serum AST or ALT level only after careful benefit risk evaluation in patients who had previously relapsed. (Class IIa, Level C)**

**11. Alternative Drug Therapies for Suboptimal Responses**

Treatment failure should be managed with high dose prednisone (60 mg daily) or prednisone (30 mg daily) in combination with azathioprine (150 mg daily) before considering other drugs such as cyclosporine, tacrolimus, or mycophenolate mofetil.

Alternative medications that have been used empirically for treatment failure in adults have included cyclosporine, \(^{308,371-376}\) tacrolimus, \(^{377,379}\) ursodeoxycholic acid, \(^{380}\) budesonide, \(^{381}\) 6-mercaptopurine, \(^{382}\) methotrexate, \(^{383}\) cyclophosphamide, \(^{384}\) and mycophenolate mofetil. \(^{357,385-391}\) In each instance, experiences have been small and anecdotal. Only ursodeoxycholic acid has been evaluated by randomized controlled clinical trial \(^{380}\) and it and budesonide are the only salvage therapies in which the reported experiences have been negative. \(^{380,381}\) This is, however, understandable, because Ursodeoxycholic acid is not a major immunosuppressive agent and budesonide is a steroid that acts via the corticosteroid receptor like conventional steroids. Its benefit might come from the 90% first pass elimination in the liver that might lead to less steroid specific side effects while still maintaining long term remission. \(^{366-369}\)

None of the empiric salvage therapies has been incorporated into a standard management algorithm. Mycophenolate mofetil and cyclosporine have had the most empiric use, and mycophenolate mofetil is the most promising current agent. \(^{357,385-392}\) Improvement occurs in 39%-84% of patients who tolerate mycophenolate mofetil, but the intention to treat is thwarted in 34%-78% of patients because of intolerances to the drug (nausea, vomiting, pancreatitis, rash, alopecia, deep venous thrombosis, diarrhea and failure to normalize liver tests). \(^{357,390,391}\) The target populations,
dosing regimens, and monitoring schedules for the nonstandard medications are imprecise, and additional studies are required to ensure the safety of these drugs in AIH and to demonstrate that the incremental improvements in outcome that they promise are cost-effective.393

Doses of prednisone and azathioprine should be increased in children who worsen despite compliance with their original therapy. As alternative medications mycophenolate mofetil, cyclosporine and tacrolimus have been used in children. Children with persistent treatment failure may become candidates for liver transplantation.

Recommendations:

33. Treatment failure in adults should be managed with high dose prednisone (60 mg daily) or prednisone (30 mg daily) in combination with azathioprine (150 mg daily) before considering other drugs such as cyclosporine, tacrolimus, or mycophenolate mofetil. (Class IIa, Level B)

34. In treatment failure mycophenolate mofetil or cyclosporine have had the most empiric use as alternative medications. Mycophenolate mofetil (2 g daily orally) is the most promising current agent. (Class IIa, Level C)

35. Doses of prednisone and azathioprine should be increased in children who worsen despite compliance with their original therapy, and they may become candidates for liver transplantation. (Class IIa, Level C)

12. Hepatocellular Carcinoma

Hepatocellular carcinoma occurs in 4% of patients with type 1 AIH, and the 10-year probability of developing this neoplasm is 2.9%.394-397 In North American patients, the risk of HCC is related to male sex, portal hypertension manifested by ascites, esophageal varices, or thrombocytopenia, immunosuppressive treatment for at least 3 years, and cirrhosis of at least 10 years duration.396 A focused surveillance strategy based on hepatic ultrasonography at 6-month intervals is recommended for these individuals.396-399

Recommendations:

36. Patients with AIH cirrhosis should undergo hepatic ultrasonography at 6 months intervals to detect HCC as in other causes of liver cirrhosis. (Class IIa, Level C)

13. Transplantation for Autoimmune Hepatitis

13.1. Indications and Outcomes

AIH is the indication for liver transplantation (LT) in approximately 2%-3% of pediatric and 4%-6% of adult recipients in the United States and Europe.69,73,400,401 LT is indicated for patients presenting with acute liver failure, and it is the treatment of choice for patients progressing to decompensated cirrhosis with a MELD score of ≥15 or those with hepatocellular carcinoma meeting transplant criteria. Need for LT may result from a failure to diagnose and treat AIH as an etiology of cirrhosis, inadequate response or intolerance to immunosuppressive therapy or noncompliance with treatment.394,395 Untreated patients have a 10-year survival of <30%,69-73 and treatment failure requiring LT is often associated with the HLA genotype DRB1*0301.155,158 LT for AIH is very successful with 5-year and 10-year patient survivals of approximately 75%.69,73,402-404 A combination of prednisone and a calcineurin inhibitor (tacrolimus more frequently than cyclosporine) is the most common immunosuppression regimen after LT.402-404

13.2. Recurrent AIH in Allografts

Recurrent AIH in transplant allografts occurs in approximately 30% of adult and pediatric patients (range 12%-46%) with an average time to recurrence of 4.6 years.404-413 The incidence increases with time after LT and accelerates after discontinuation of steroids.404 Diagnostic criteria for recurrence include: (1) elevation of serum AST or ALT levels; (2) persistence of autoantibodies; (3) hypergammaglobulinemia and/or elevation of IgG level; (4) compatible histopathological findings; (5) exclusion of alternative etiologies; and (6) responsiveness to steroids.404,412,413 Histopathological abnormalities compatible with recurrent AIH may precede laboratory or clinical evidence of recurrence.414 There is no prospectively validated scoring system for the diagnosis of recurrent AIH. Reported risk factors for recurrence included inadequate dosing of immunosuppression (especially discontinuation of prednisone), type 1 AIH and a recipient positive for either HLA-DRB1*03 or DRB1*04.412,414-421 The risk for recurrence has been associated with the HLA genotypes DRB1*03 or DRB1*04 in the recipients of some series, but not in all.412,414-421 Primary immunosuppression with either tacrolimus or cyclosporine does not influence the risk of recurrence.

Treatment of recurrent AIH has been empiric, and no controlled trials have been reported. Reintroduction of prednisone or prednisolone and optimization of
calcineurin inhibitor levels is usually successful.\textsuperscript{403,419} A combination of prednisone and azathioprine has also been successful.\textsuperscript{419} Occasionally, substituting tacrolimus for cyclosporine may be useful.\textsuperscript{422} Sirolimus may also benefit patients unresponsive to steroids and calcineurin inhibitors.\textsuperscript{423} Based on these reports, recurrent AIH should be treated with prednisone and azathioprine in adjusted doses to suppress serum AST or ALT levels or increased doses of corticosteroids and optimization of calcineurin inhibitor levels (preferably, tacrolimus). Failure to normalize the serum AST or ALT levels justifies the addition of mycophenolate (2 g daily) to the regimen of corticosteroids and calcineurin inhibitor. If the response continues to be inadequate, tacrolimus should be replaced with cyclosporine or calcineurin inhibitors replaced with sirolimus. Discontinuation of steroids after successful treatment of recurrent AIH is inadvisable because of the risk of allograft loss.

The prognosis of patients treated for recurrent AIH is comparable to patients transplanted for AIH who do not experience recurrence.\textsuperscript{419} Even though only a small minority of patients progress to cirrhosis and require retransplantation,\textsuperscript{407,411,414,420,421} retransplantation must be considered for patients with refractory recurrent AIH that is progressing to allograft loss.

13.3. De novo AIH After Liver Transplantation (LT)

AIH can occur \textit{de novo} after LT in both pediatric and adult recipients.\textsuperscript{424-438} The risk of \textit{de novo} AIH appears to be unrelated to the original disease indication for LT. In children with \textit{de novo} AIH, the indications for LT have included biliary atresia, \( \alpha \)-1-antitrypsin deficiency, Alagille syndrome, primary familial intrahepatic cholestasis, primary sclerosing cholangitis and acute liver failure. In adults, the original indications for LT have included PBC, PSC, alcoholic cirrhosis, hepatitis C cirrhosis, Wilson disease and acute liver failure. Thus, \textit{de novo} AIH must be considered in the differential diagnosis of all pediatric and adult patients with allograft dysfunction after LT, regardless of whether the original indication for LT was AIH or another disease. Treatment has been empiric and has usually involved addition of prednisone, with or without azathioprine,\textsuperscript{424,437} to a regimen of tacrolimus,\textsuperscript{438,439} cyclosporine,\textsuperscript{425,426} or sirolimus.\textsuperscript{423} The contributions of calcineurin inhibitors or sirolimus are unclear. Treatment with prednisone alone or a combination of prednisone and azathioprine was successful in 100% of patients with \textit{de novo} AIH in five case series,\textsuperscript{424,425,429,440,441} whereas two other series reported progression resulting in allograft loss in more than 30%.\textsuperscript{426,427} Based on these data, \textit{de novo} AIH after LT should be treated with reintroduction of corticosteroids or an increased dosage of corticosteroids along with optimization of calcineurin inhibitor levels. If the response is incomplete, azathioprine (1.0-2.0 mg/kg daily) or mycophenolate mofetil (2 g daily) should be added to the regimen of corticosteroid and calcineurin inhibitor.

Recommendations:

37. Liver transplantation should be considered in patients with AIH and acute liver failure, decompensated cirrhosis with a MELD score \( \geq 15 \), or hepatocellular carcinoma meeting criteria for transplantation. (Class I, Level C)

38. Recurrent AIH should be treated with prednisone and azathioprine in adjusted doses to suppress serum AST or ALT levels or increased doses of corticosteroids and optimization of calcineurin inhibitor levels (preferably, tacrolimus). (Class IIa, Level C)

39. Continued inability to normalize the serum AST or ALT levels following recurrent disease justifies the addition of mycophenolate (2 g daily) to the regimen of corticosteroids and calcineurin inhibitor. (Class IIa, Level C)

40. If treatment response continues to be inadequate in recurrent disease, tacrolimus should be replaced with cyclosporine or the calcineurin inhibitors replaced with sirolimus. (Class IIa, Level C)

41. Retransplantation must be considered for patients with refractory recurrent AIH that is progressing to allograft loss.

42. Consider \textit{de novo} AIH in all pediatric and adult patients with allograft dysfunction after liver transplantation regardless of whether the original indication for LT was AIH or another disease. (Class IIa, Level C)

42a. Treatment for \textit{de novo} AIH should be instituted with the reintroduction of corticosteroids or the dose of corticosteroids increased and calcineurin inhibitor levels optimized. Class IIa, Level C

42b. An incomplete response in \textit{de novo} AIH should be treated by adding azathioprine (1.0-2.0 mg/kg daily) or mycophenolate mofetil (2 g daily) to the regimen of corticosteroid and calcineurin inhibitor. (Class IIa, Level C)

43. Tacrolimus should be replaced with cyclosporine or either calcineurin inhibitor replaced with sirolimus if the response continues to be incomplete. (Class IIa, Level C)

44. Retransplantation should be considered for patients with refractory \textit{de novo} AIH that is progressing to allograft failure. (Class IIa, Level C)

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