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 heath care for specific clinical circumstances."[1] 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;[2] (3) guideline policies, including the AASLD Policy on the Development and Use of Practice Guidelines and the American Gastroenterological Association Policy Statement on Guidelines;[3] 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 presentation[8,9] 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 groups[20-34] 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

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Abbreviations: AASLD, American Association for the Study of Liver Diseases; AIH, autoimmune hepatitis; ALT, alanine aminotransferase; ANA, antinuclear antibody; AST, aspartate aminotransferase; CYP1A2, cytochrome P450 1A2; HCV, hepatitis C virus; IBD, inflammatory bowel disease; IgG, immunoglobulin G; LKM-1, liver/kidney microsome type 1; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; SMA, smooth muscle antibodies.

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Table 1. Description of Grading System Used to Assign Class and Level of Evidence

Classification	Description
Class I	Conditions for which there is evidence and/or general agreement that a given diagnostic evaluation, procedure or treatment is beneficial, useful, and effective
Class II	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a diagnostic evaluation, procedure or treatment
Class IIa	Weight of evidence/opinion is in favor of usefulness/efficacy
Class IIb	Usefulness/efficacy is less well established by evidence/opinion
Class III	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
Level of Evidence	**Description**
Level A	Data derived from multiple randomized clinical trials or meta analyses
Level B	Data derived from a single randomized trial, or nonrandomized studies
Level C	Only consensus opinion of experts, case studies, or standard of care

assumed for the Caucasian population of North America.

Data on the natural progression of untreated disease are derived principally from experiences published prior to the widespread use of immunosuppressive agents for AIH and before the detection of the hepatitis C virus (HCV).[47-54] These studies showed that as many as 40% of patients with untreated severe disease died within 6 months of diagnosis,[47,49] and that survivors frequently developed cirrhosis, esophageal varices and subsequent hemorrhage.[47,49,50,55] An acute onset of illness is common (~40%),[56-63] and an acute severe presentation, characterized by hepatic encephalopathy within 8 weeks of clinical symptoms, is sometimes seen.[10,11,58,64-68]

Three randomized, controlled treatment trials established that prednisone alone or in combination with azathioprine improved symptoms, laboratory tests, histological findings, and immediate survival.[48-50] These studies led to the acceptance of immunosuppressive regimens as the standard in treatment, and supported an autoimmune pathogenesis of the disease. However, these studies were completed decades ago before the discovery of HCV. Therefore, HCV infection could not be excluded in these studies and one can assume that several of these patients were indeed infected with HCV. Liver transplantation has also evolved as an effective treatment for the decompensated patient, and the 5-year patient and graft survivals now exceed 80%.[69-74]

3. Diagnosis: Criteria and Methods

The diagnostic criteria for AIH and a diagnostic scoring system were codified by an international panel in 1993[75] and revised in 1999[13] (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 application[78] 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.[8,9,269] Typically, these patients are men and have significantly lower serum ALT levels at presentation than do symptomatic patients.[8] Histological findings, including the frequency of cirrhosis, are similar

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

Features	Definite	Probable
Liver histology	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	Same as for "definite"
Serum biochemistry	Any abnormality in serum aminotransferases, especially if the serum alkaline phosphatase is not markedly elevated. Normal serum concentrations of alpha antitrypsin, copper and ceruloplasmin.	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
Serum immunoglobulins	Total serum globulin or γ globulin or IgG concentrations greater than 1.5 times the upper normal limit	Any elevation of serum globulin or γ globulin or IgG concentrations above the upper normal limit
Serum autoantibodies	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.	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.
Viral markers	Seronegativity for markers of current infection with hepatitis A, B, and C viruses	Same as for "definite"
Other etiological factors	Average alcohol consumption less than 25 g/day. No history of recent use of known hepatotoxic drugs.	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.

Adapted from Alvarez F, Berg PA, Bianchi FB, et al. J Hepatol 1999;31:929 938.

between asymptomatic patients and symptomatic patients. Because as many as 70% of asymptomatic patients become symptomatic during the course of their disease,[8,9] asymptomatic patients must be followed life-long, 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,

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

Sex	Female	+2	**HLA**	DR3 or DR4	+1
AP:AST (or ALT) ratio	>3	2	**Immune Disease**	Thyroiditis, colitis, others	+2
	<1.5	+2			
γ globulin or IgG level above normal	>2.0	+3	**Other markers**	Anti SLA, anti actin, anti LC1, pANCA	+2
	1.5 2.0	+2			
	1.0 1.5	+1			
	<1.0	0			
ANA, SMA, or anti LKM1 titers	>1:80	+3	**Histological features**	Interface hepatitis	+3
	1:80	+2		Plasmacytic	+1
	1:40	+1		Rosettes	+1
	<1:40	0		None of above	5
				Biliary changes	3
				Other features	3
AMA	Positive	4	**Treatment response**	Complete	+2
				Relapse	+3
Viral markers	Positive	3			
	Negative	+3			
Drugs	Yes	4	**Pretreatment aggregate score:**		
	No	+1	**Definite diagnosis >15**		
			Probable diagnosis 10 15		
Alcohol	<25 g/day	+2	**Posttreatment aggregate score:**		
	>60 g/day	2	**Definite diagnosis >17**		
			Probable diagnosis 12 17		

Adapted from Alvarez F, Berg PA, Bianchi FB, et al. J Hepatol 1999;31:929 938.

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 leuko cyte antigen; IgG, immunoglobulin G; pANCA, perinuclear anti neutrophil cytoplasmic antibody; SMA, smooth muscle antibody.

Table 4. Autoantibodies in the Diagnosis of Autoimmune Hepatitis

Antibody	Target Antigen(s)	Liver Disease	Value in AIH
ANA*	Multiple targets including: • chromatin, • ribonucleoproteins • ribonucleoprotein complexes	AIH PBC PSC Drug induced Chronic hepatitis C Chronic hepatitis B Nonalcoholic fatty liver disease	Diagnosis of type 1 AIH
SMA*	Microfilaments (filamentous actin) and intermediate filaments (vimentin, desmin)	Same as ANA	Diagnosis of type 1 AIH
LKM 1*	Cytochrome P450 2D6 (CYP2D6)	Type 2 AIH Chronic hepatitis C	Diagnosis of type 2 AIH
LC 1*	Formiminotransferase cyclo deaminase (FTCD)	Type 2 AIH Chronic hepatitis C	Diagnosis of type 2 AIH Prognostic implications Severe disease
pANCA (atypical)	Nuclear lamina proteins	AIH PSC	Diagnosis of type 1 AIH Re classification of cryptogenic chronic hepatitis as type 1 AIH
SLA	$tRNP^{(SER)}Sec$	AIH Chronic hepatitis C	Diagnosis of AIH Prognostic implications Severe disease Relapse Treatment dependence
LKM 3	family 1 UDP glucuronosyl transferases (UGT1A)	Type 2 AIH Chronic hepatitis D	Diagnosis of type 2 AIH
ASGPR	Asialoglycoprotein receptor	AIH PBC Drug induced hepatitis Chronic hepatitis B, C, D	Prognostic implications Severe Disease Histological activity Relapse
LKM2	Cytochrome P450 2C9	Ticrynafen induced hepatitis	None, does not occur after withdrawal of ticrynafen
LM	Cytochrome P450 1A2	Dihydralazine induced hepatitis APECED hepatitis	Diagnosis of APECED hepatitis

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

AIH, autoimmune hepatitis; ANA, antinuclear antibody; APECED, autoimmune polyendocrinopathy candidias 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 bili ary cirrhosis; PSC, primary sclerosing cholangitis; SLA, soluble liver antigen; SMA, smooth muscle antibody; UGT, uridine diphosphate glucuronosyltransferase.

specifically primary sclerosing cholangitis (PSC), than the AP level, which can be elevated due to bone activity in the growing child.[77] Neither the gamma glutamyl transferase nor AP levels, however, discriminate between the presence or absence of cholangiopathy in children with AIH.[36] 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).[12-16] 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.[12,13,36,81,82]

Liver biopsy examination at presentation is recommended to establish the diagnosis and to guide the treatment decision.[12,13,15,16] 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).[83-87] Neither histological finding is specific for AIH, and the absence of plasma cells in the infiltrate does not preclude the diagnosis.[84] Eosinophils, lobular inflammation, bridging necrosis, and multiacinar necrosis may be present.[55,86,87] 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.[55,83-85] Occasionally, centrizonal (zone 3) lesions exist (Fig. 3),[10,60-62,88-91] and sequential liver tissue examinations have demonstrated transition of this pattern to interface hepatitis in some patients.[62] 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.[10,92,93]

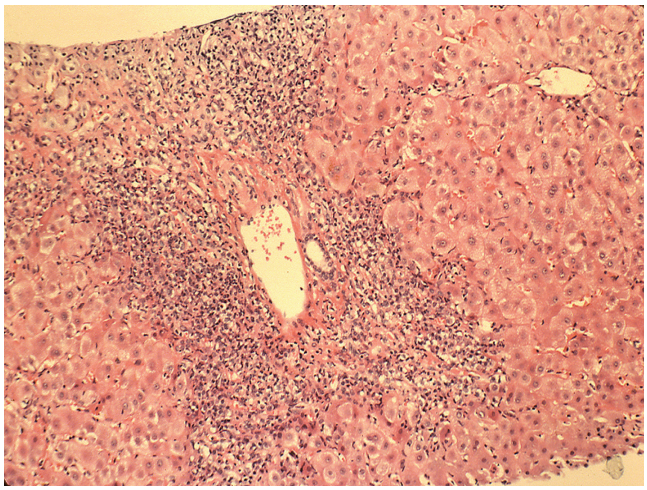

Fig. 1. Interface hepatitis. The limiting plate of the portal tract is disrupted by a lymphoplasmacytic infiltrate. Hematoxylin and eosin stain; magnification, ×200.

Some patients exhibit features of both AIH and another disorder such as PSC, PBC, or autoimmune cholangitis, a variant syndrome.[94-100] Certain histologic changes such as ductopenia or destructive cholangitis may indicate the presence of one of these variant types.[101] In these cases, the revised original scoring system can be used to assist in diagnosis (Table 3).[13,76] 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.[84,85,101]

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.[13,76,78] 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).[102,103]

3.2. Serological Assessment

ANA, SMA, anti-LKM1, and anti-LC1 constitute the conventional serological repertoire for the diagnosis of AIH (Table 4).[12-16,104-109] In North American adults, 96% of patients with AIH have ANA, SMA, or both,[110] and 4% have anti-LKM1 and/or anti-LC1.[111] Anti-LKM1 are deemed more frequent in European AIH patients and are typically unaccompanied by ANA or SMA.[112] They are possibly underestimated in the United States.[113] 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[104-109] and their expressions can vary during the course of the disease.[110] 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.[110] Seronegative individuals may express

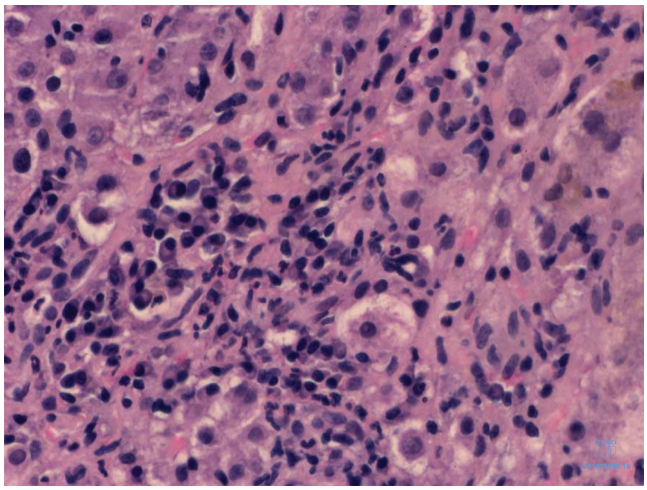

Fig. 2. Plasma cell infiltration. Plasma cells, characterized by cytoplasmic halo about the nucleus, infiltrate the hepatic parenchyma. Hematoxylin and eosin stain; magnification, ×400.

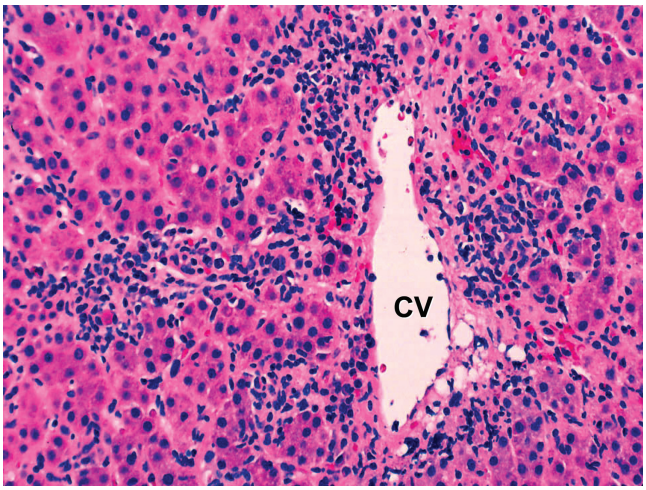

Fig. 3. Median centrilobular zone 3 necrosis. Centrilobular zone 3 necrosis associated with a mononuclear inflammatory infiltrate. Hematoxylin and eosin stain; original magnification, ×200.

conventional antibodies later in the disease[114-118] or exhibit nonstandard autoantibodies.[104-109,119] Autoantibody titers in adults only roughly correlate with disease severity, clinical course, and treatment response.[110] In pediatric populations (patients aged $\leq$18 years), titers are useful biomarkers of disease activity and can be used to monitor treatment response.[120]

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.[13] 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.[14] 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)[111,121] and antibody to liver kidney microsome type 3 (anti LKM-3).[122,123] 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[124-128] and atypical pANCA.[119,129,130,131-139] Atypical pANCA, originally considered specific for PSC and inflammatory bowel disease (IBD),[124,125] are frequently present in patients with AIH,[126,127] and occasionally can be the only autoantibodies detected (Table 4).[128] ANCA typically do not coexist with anti-LKM1.[127] 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).[102,103]

Anti-SLA[129] and anti–liver-pancreas (anti-LP),[130] 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).[119,131,132] 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,[133] but are more commonly found in association with the conventional autoantibodies, especially if sensitive immunoassays are used.[133-136] Anti-SLA are highly specific for the diagnosis of autoimmune liver disease,[133] and their detection may identify patients with more severe disease and worse outcome.[137-140] 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.[29,141-154] 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.[18,155-168] AIH is a complex polygenic disorder[169] 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.[170] 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.[171-174] 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

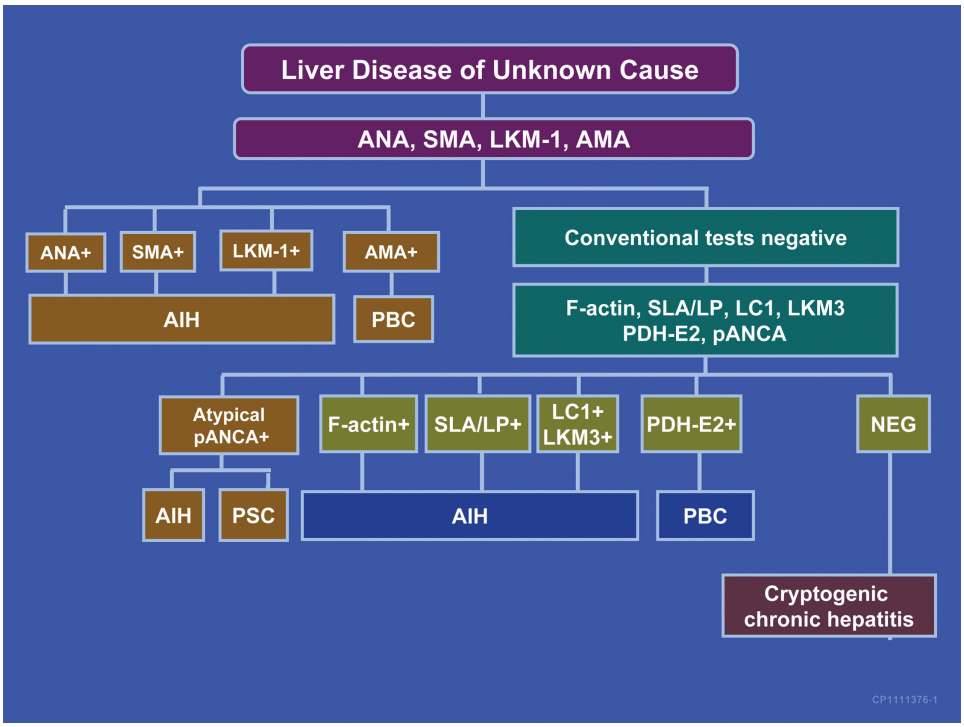

Fig. 4. The use of serological tests assisting in the diagnosis of AIH. Serological tests in the evaluation of acute or chronic hepatitis of undetermined cause. The initial serological battery includes assessments for antinuclear antibodies (ANA), smooth muscle antibodies (SMA), antibodies to liver/kidney 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.

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[112,129,130,175] but have not been established as valid clinical or pathological entities.[13] 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.[176-179] Type 1 AIH is characterized by the presence of ANA, SMA or both, and constitutes 80% of AIH cases.[175] Seventy percent of patients are female, with a peak incidence between ages 16 and 30 years.[180,181] Fifty percent of patients are older than 30 years, and 23% are at least 60 years old.[38,43,44,181] Associations with other autoimmune diseases are common (15%-34%); these include autoimmune thyroid disease, synovitis, celiac disease, and ulcerative colitis.[43,44,182] At the time of diagnosis, cirrhosis is present in ~25% of patients.[183,184] Antibodies to SLA have emerged as possible prognostic markers that may identify patients with severe AIH who are prone to relapse after corticosteroid withdrawal.[134,137-140,179,185] Type 2 AIH is characterized by the presence of anti-LKM1[112] 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.[112] Concurrent immune diseases are

common,[112] progression to cirrhosis occurs,[112] and an acute severe presentation is possible.[58,64]

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,[95,206-212] and AIH can have features that resemble each of these cholestatic syndromes.[36,81,82,213-217] These nonspecific shared features can confound the codified diagnostic scoring system.[13,76,78] The prevalence of AIH among patients with PSC was determined to be 21%-54% using the original scoring system,[218,219] but this prevalence decreased to 8% in PSC when the revised original scoring system was applied.[206,220,221] 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.[222] Clinical judgment is required to determine the predominant phenotype of the disease and to manage the process appropriately.[95,223]

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"),[178,224-228] and their presence may confound the clinical diagnosis. AMA may disappear[226] or persist as long as 27 years without an evolution into PBC.[227] The revised original scoring system can render a diagnosis of "probable AIH" in these patients, if other features of AIH are sufficiently strong.[229,230]

Other acute and chronic liver diseases of diverse etiologies that can have serological features of AIH include alcoholic[231] and nonalcoholic fatty liver disease,[232,233] acute[234] and chronic[54,235-241] viral hepatitis, and drug-induced hepatitis.[242,243] Drugs such as minocycline,[244-246] diclofenac,[247,248] infliximab,[249] propylthiouracil,[250] atorvastatin,[251] nitrofurantoin,[252] methyl dopa,[253] and isoniazid[254] 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[255-258] and with vaccination.[259-261]

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.[26,31,32] Alaskan natives exhibit a higher frequency of acute icteric disease than non-native counterparts,[27] whereas Middle Eastern patients commonly have cholestatic features.[28] Asian patients typically present with late onset, mild disease,[20,262] whereas South American patients are commonly children with severe liver inflammation.[21,22] Aboriginal North Americans have a disproportionately high frequency of immune-mediated disorders, cholestatic features, and advanced disease at presentation,[33,34] and Somali patients are frequently men with rapidly progressive disease.[30] Socioeconomic status, healthcare access, and quality of care are additional factors that must be considered when assessing nonclassical disease manifestations within racial groups.[31,32,263,264]

5.4. Acute Severe Presentation

AIH can have an acute severe presentation that can be mistaken for a viral or toxic hepatitis.[10,11,58,64,65,67,68,265] Sometimes autoimmune hepatitis may present as acute liver failure. Corticosteroid therapy can be effective in suppressing the inflammatory activity in 36%-100% of patients,[11] whereas delay in treatment can have a strong negative impact on outcome.[265-267] In addition, unrecognized chronic disease can exhibit a spontaneous exacerbation and appear acute.[92] If extrahepatic endocrine autoimmune features are present in children with severe acute presentation the APECED syndrome must be excluded.[268]

5.5. Concurrent Immune Diseases

Concurrent immune disorders may mask the underlying liver disease.[16,17,38,43,44,182] Autoimmune thyroiditis, Graves' disease, synovitis and ulcerative colitis are the most common immune-mediated disorders associated with AIH in North American adults,[43,44,180,270] whereas type I diabetes mellitus, vitiligo, and autoimmune thyroiditis are the most common concurrent disorders in European anti-LKM1$^+$ AIH patients.[112] In children with AIH, autoimmune sclerosing cholangitis can be present, with or without IBD.[36] In adults with both AIH and IBD, contrast cholangiography showing biliary changes suggestive of PSC are present in 44% of patients.[81] In adults with AIH but not IBD, magnetic resonance imaging indicating biliary

Table 5. Indications for Immunosuppressive Treatment

Absolute	Relative	None
Serum AST $\geq$ 10 fold ULN	Symptoms (fatigue, arthralgia, jaundice)	Asymptomatic with normal or near normal serum AST and γ globulin levels
Serum AST $\geq$ 5 fold ULN and γ globulin level $\geq$ 2 fold ULN	Serum AST and/or γ globulin less than absolute criteria	Inactive cirrhosis or mild portal inflammation (portal hepatitis)
Bridging necrosis or multiacinar necrosis on histological examination	Interface hepatitis	Severe cytopenia (white blood cell counts $<2.5 \times 10^9$/L or platelet counts $<50 \times 10^9$/L) or known complete deficiency of TPMT activity precludes treatment with azathioprine
Incapacitating symptoms	Osteopenia, emotional instability, hypertension, diabetes, or cytopenia (white blood cell counts $\leq 2.5 \times 10^9$/L or platelet counts $\leq 50 \times 10^9$/L)	Vertebral compression, psychosis, brittle diabetes, uncontrolled hypertension, known intolerances to prednisone or azathioprine

AST, serum aspartate aminotransferase level; ULN, upper limit of normal range.

changes are observed in 8% of patients.[82] Unless bile duct changes are present, concurrent immune diseases typically do not affect the prognosis of AIH.[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.[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%.[55,86,87] These laboratory and histological findings of disease severity at presentation are absolute indications for corticosteroid treatment (Tables 4 and 5).[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).[269,276] Asymptomatic individuals with inactive cirrhosis may have an excellent immediate survival without corticosteroid treatment.[8,9] Other asymptomatic patients who do not have cirrhosis may have inactive disease, and their natural 10-year survival may exceed 80%.[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.[269] Furthermore, untreated asymptomatic patients with mild disease have a lower 10-year survival than treated counterparts (67% versus 98%, $P < 0.01$).[269] The frequency of spontaneous improvement must be counterbalanced against the frequency of serious drug-related complications when making the treatment decision (12% versus l4%).[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

mild disease, especially in young individuals who are likely to tolerate the medication satisfactorily.[269] Patients likely to have a poor outcome are those at increased risk for drug intolerance, and they include individuals with advanced inactive cirrhosis, postmenopausal osteopenia or vertebral compression, emotional instability or psychosis, poorly controlled hypertension, low thiopurine methyltransferase activity, and brittle diabetes (Table 5).[277]

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,[9] 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.[278] 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).[277]

6.4. Treatment Indications in Children

The indications for treatment in children are similar to those in adults (Table 5).[35] 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.[35,36,279-281] 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.[35,36,279-281] 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.[35,36,279-281] 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).[273,282-287] 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

Table 6. Immunosuppressive Treatment Regimens for Adults in Autoimmune Hepatitis

	Monotherapy	Combination Therapy		
			Azathioprine	
	Prednisone only* (mg/day)	Prednisone* (mg/day)	USA (mg/day)	EU (mg/kg/day)
Week 1	60	30	50	1 2
Week 2	40	20	50	1 2
Week 3	30	15	50	1 2
Week 4	30	15	50	1 2
Maintenance until endpoint	20 and below	10	50	1 2
Reasons for Preference	Cytopenia		Postmenopausal state	
	Thiopurine methyltransferase deficiency		Osteoporosis	
			Brittle diabetes	
			Obesity	
	Pregnancy		Acne	
	Malignancy		Emotional lability	
	Short course ($\leq$6 months)		Hypertension	

*Prednisolone can be used in place of prednisone in equivalent doses.

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

Table 7. Immunosuppressive Treatment Regimens for Children in Autoimmune Hepatitis

Initial Regimen	Maintenance Regimen	Endpoint
Prednisone, 1 2 mg/kg daily (up to 60 mg/day), for two weeks either alone or in combination with azathioprine, 1 2 mg/kg daily	Prednisone taper over 6 8 weeks to 0.1 0.2 mg/kg daily or 5 mg daily	Normal liver tests for 1 2 years during treatment
	Azathioprine at constant dose if added initially	No flare during entire interval
	Continue daily prednisone dose with or without azathioprine or switch to alternate day prednisone dose adjusted to response with or without azathioprine	Liver biopsy examination discloses no inflammation

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.[35,36,279-281,305] 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.[305] 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.[306-309] Pretreatment evidence of susceptibility to HAV or HBV would justify vaccination against these viruses in children.[304]

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 baring exercise program, vitamin D, calcium and where appropriate bone active agents such as bisphosphonates. (Class IIa, Level C)

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).[284]

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).[273,277,278] Severe side effects include osteopenia with vertebral compression, brittle diabetes, psychosis, pancreatitis, opportunistic infection, labile hypertension, and malignancy.[273,277,282,299,300,310] Severe complications are uncommon, but if they occur, it is usually after protracted therapy (more than 18 months) with prednisone alone (20 mg daily).[273,277,278]

Corticosteroid-related side effects are the most common causes for premature drug withdrawal in autoimmune hepatitis.[277,311] Treatment is discontinued in 13% of patients because of complications, and 47% of these have intolerable cosmetic changes or obesity.[277,311] Twenty-seven percent have osteoporosis with vertebral compression, and 20% have brittle diabetes.[277,311]

8.2. Azathioprine-Related Side Effects

Complications of azathioprine therapy in autoimmune hepatitis include cholestatic hepatitis,[312] pancreatitis,[313,314] nausea,[277] emesis,[277] rash,[277] opportunistic infection,[310] bone marrow suppression and malignancy (Table 8).[288-292] Five percent of patients treated with

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

Prednisone-Related Side Effects		Azathioprine-Related Side Effects	
Type	**Frequency**	**Type**	**Frequency**
Cosmetic (usually mild)	80% (after 2 years)	Hematologic (mild)	46% (especially with cirrhosis)
Facial rounding		Cytopenia	
Weight gain			
Dorsal hump striae			
Hirsutism			
Alopecia			
Somatic (usually mild)			
Emotional instability			
Glucose intolerance			
Cataracts			
Somatic (severe)	13% (treatment ending)	Hematologic (severe)	6% (treatment ending)
Osteopenia		Leucopenia	
Vertebral compression		Thrombocytopenia	
Diabetes (brittle)			
Psychosis			
Hypertension (labile)			
Inflammatory/neoplastic	Rare	Somatic (usually mild)	5%
Pancreatitis		Nausea	
Opportunistic infection		Emesis	
Malignancy		Rash	
		Fever	
		Arthralgias	
		Neoplastic	3% (after 10 years)
		Nonhepatic cell types	
		Hematologic/enteric	Rare (treatment ending)
		Bone marrow failure	
		Villous atrophy	
		Malabsorption	
		Teratogenic during pregnancy	Rare (theoretical)

Adapted from Czaja AJ. Expert Opin Drug Saf 2008;7:319 333.

azathioprine develop early adverse reactions (nausea, vomiting, arthralgias, fever, skin rash or pancreatitis), which warrants its discontinuation.[315] The overall frequency of azathioprine-related side effects in patients with autoimmune hepatitis is 10%,[273] and the side effects typically improve after the dose of azathioprine is reduced or the therapy is discontinued.[277,282] 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.[316] The sinusoidal obstruction syndrome ("veno-occlusive disease") described after renal transplantation has not been reported in azathioprine-treated autoimmune hepatitis,[317,318] nor has the nodular regenerative hyperplasia described in azathioprine-treated patients with inflammatory bowel disease.[319]

The principal side effect of azathioprine is cytopenia, and the most dire consequence is bone marrow failure (Table 8).[277,289,292] The frequency of cytopenia in azathioprine-treated patients with autoimmune hepatitis is 46%, and the occurrence of severe hematological abnormalities is 6%.[320] These toxicities are not predictable by either genotyping or phenotyping for thiopurine methyltransferase activity,[320-322] and the most common cause of cytopenia in these patients is hypersplenism associated with underlying cirrhosis.[320,322] 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).[296,297,326,327] 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.[297] Tumors do not have a predominant cell type, and they are not related to age, sex, treatment regimen or cumulative duration of treatment.[297,327] 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.[297]

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

(25% versus 8%),[273,278,328] They also have a high frequency of cytopenia that may compromise their tolerance for azathioprine.[320,322] 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.[277,301,320]

8.3.2. Pregnant Patients. Most experiences indicate that pregnancy and the medication are well tolerated by the mother and the neonate.[294,323-325,327-333] 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.[294,323-325,330-333]

Fetal mortality has been reported as high as 19% with deliveries usually before the 20th week.[325] Perinatal mortality is 4%;[325] maternal mortality is 3%;[325] the frequency of serious maternal complications is 9%;[332] and the occurrence of an adverse outcome of any type is 26%.[332] 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.[324] Furthermore, mothers with autoimmune hepatitis have better outcomes than women with diabetes in whom the frequency of fetal loss ranges from 24%-29%.[324]

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,[293] and low levels of the 6-thioguanine nucleotides are detectable in the newborns of mothers treated for Crohn's disease (Table 8).[295] Teratogenicity associated with azathioprine therapy therefore is a theoretical consideration,[293] but increased birth defects have not been reported in mothers receiving this treatment,[323-325,330-333] nor have there been apparent adverse consequences of breast feeding by treated mothers.[333] Nevertheless, these human experiences have been anecdotal, and there has not been a comprehensive human study establishing the safety of azathioprine in pregnant women. These findings, however, do justify caution when using azathioprine during pregnancy.[323-325]

Autoimmune hepatitis can improve during pregnancy, and this improvement may allow reductions in immunosuppressive therapy during pregnancy.[334,335] Intuitively, little or no treatment during pregnancy is a desirable protective measure for the mother and fetus.

Exacerbations of disease commonly follow delivery as blood estrogen levels fall.[334] The frequency of exacerbation after delivery has been variously reported between 12%-86%.[324,332,335] 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.[330]

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.[291,292] Only 0.3%-0.5% of the population has a severe enzyme deficiency,[336-340] and not all patients with a deficiency of this degree experience bone marrow failure.[341] Individuals with abnormally decreased but not extreme reductions in thiopurine methyltransferase activity (heterozygous state) tolerate azathioprine satisfactorily at the low dose of 50 mg[320] and the level of enzyme activity may actually increase with continued administration of the drug.[320,342,343] 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.[277]

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 IIa, Level C)

24. Blood thiopurine methyltransferase activity should be assessed in patients with cytopenia before or during azathioprine therapy. (Class IIa, Level C)

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

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

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 response[344] 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 reduces 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

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).[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,[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).[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).[355] Early recognition of individuals who are likely to fail corticosteroid therapy may improve their outcome by prompting treatment modifications, including timely liver transplantation.[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).[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.[290,291]

Seventy percent of patients improve their clinical and laboratory findings within 2 years, and survival is preserved.[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.[354,355,357] The development of hepatic encephalopathy, ascites, and/or variceal hemorrhage during therapy for treatment failure is an indication for liver transplantation.[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).[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 ($\leq$10 mg daily) is achieved, and the serum AST or ALT level remains stable.[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.[282-285,327]

9.4. Drug Toxicity

Drug toxicity justifies premature discontinuation or alteration of conventional therapy in 13% of patients (Table 8).[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.[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.[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.[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.(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.[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.[361] 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 γ-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, γ-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 γ-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 drug 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 reinstitution 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.[305]

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 $\geq$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.[354,355] 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.[403,419] A combination of prednisone and azathioprine has also been successful.[419] Occasionally, substituting tacrolimus for cyclosporine may be useful.[422] Sirolimus may also benefit patients unresponsive to steroids and calcineurin inhibitors.[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.[419] Even though only a small minority of patients progress to cirrhosis and require retransplantation,[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 *de novo* after LT in both pediatric and adult recipients.[424-438] The risk of *de novo* AIH appears to be unrelated to the original disease indication for LT. In children with *de novo* AIH, the indications for LT have included biliary atresia, α-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, *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,[424,437] to a regimen of tacrolimus,[438,439] cyclosporine[425,426] or sirolimus.[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 *de novo* AIH in five case series,[424,425,429,440,441] whereas two other series reported progression resulting in allograft loss in more than 30%.[426,427] Based on these data, *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. (Class, IIa, Level C)

42. Consider* 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* 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* 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* de novo *AIH that is progressing to allograft failure. (Class IIa, Level C)

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References

1. Committee to Advise the Public Health Service on Clinical Practice Guidelines, Institute of Medicine. Clinical Practice Guidelines: Direction of a New Program. Field MJ, Lohr KN, eds. Washington, DC: National Academy Press; 1990.
2. Eddy D. A Manual for Assessing Health Practices and Designing Practice Guidelines. Philadelphia: American College of Physicians; 1996.
3. American Gastroenterological Association policy statement on the use of medical practice guidelines by managed care organizations and insurance carriers. Gastroenterology 1995;108:925-926.
4. Shiffmann RN, Shekelle P, Overhage JM, Slutsky J, Grimshaw J, Deshpande AM. Standardized reporting of clinical practice guidelines: a proposal from the conference on guideline standardization. Ann Intern Med 2003;139:493-498.
5. Vergani D, Choudhuri K, Bogdanos DP, Mieli-Vergani G. Pathogenesis of autoimmune hepatitis. Clin Liver Dis 2002;6:727-737.
6. Czaja AJ. Autoimmune hepatitis. Part A: pathogenesis. Expert Rev Gastroenterol Hepatol 2007;1:113-128.
7. Czaja AJ. Diverse manifestations and evolving treatments of autoimmune hepatitis. Minerva Gastroenterol Dietol 2005;51:313-333.
8. Kogan J, Safadi R, Ashur Y, Shouval D, Ilan Y. Prognosis of symptomatic versus asymptomatic autoimmune hepatitis: a study of 68 patients. J Clin Gastroenterol 2002;35:75-81.
9. Feld JJ, Dinh H, Arenovich T, Marcus VA, Wanless IR, Heathcote EJ. Autoimmune hepatitis: effect of symptoms and cirrhosis on natural history and outcome. Hepatology 2005;42:53-62.
10. Kessler WR, Cummings OW, Eckert G, Chalasani N, Lumeng L, Kwo PY. Fulminant hepatic failure as the initial presentation of acute autoimmune hepatitis. Clin Gastroenterol Hepatol 2004;2:625-631.
11. Ichai P, Duclos-Vallee JC, Guettier C, Hamida SB, Antonini T, Delvart V, et al. Usefulness of corticosteroids for the treatment of severe and fulminant forms of autoimmune hepatitis. Liver Transpl 2007;13:996-1003.
12. Krawitt EL. Autoimmune hepatitis. N Engl J Med 2006;354:54-66.
13. Alvarez F, Berg PA, Bianchi FB, Bianchi L, Burroughs AK, Cancado EL, et al. International Autoimmune Hepatitis Group Report: review of criteria for diagnosis of autoimmune hepatitis. J Hepatol 1999;31:929-938.
14. Vergani D, Alvarez F, Bianchi FB, Cancado EL, Mackay IR, Manns MP, Nishioka M, et al. Liver autoimmune serology: a consensus statement from the committee for autoimmune serology of the International Autoimmune Hepatitis Group. J Hepatol 2004;41:677-683.
15. Manns MP, Vogel A. Autoimmune hepatitis, from mechanisms to therapy. Hepatology 2006;43:S132-S144.
16. Czaja AJ. Autoimmune hepatitis. Part B: diagnosis. Expert Rev Gastroenterol Hepatol 2007;1:129-143.
17. Czaja AJ, dos Santos RM, Porto A, Santrach PJ, Moore SB. Immune phenotype of chronic liver disease. Dig Dis Sci 1998;43:2149-2155.
18. Czaja AJ, Donaldson PT. Gender effects and synergisms with histocompatibility leukocyte antigens in type 1 autoimmune hepatitis. Am J Gastroenterol 2002;97:2051-2057.
19. Al-Chalabi T, Underhill JA, Portmann BC, McFarlane IG, Heneghan MA. Impact of gender on the long-term outcome and survival of patients with autoimmune hepatitis. J Hepatol 2008;48:140-147.
20. Seki T, Ota M, Furuta S, Fukushima H, Kondo T, Hino K, et al. HLA class II molecules and autoimmune hepatitis susceptibility in Japanese patients. Gastroenterology 1992;103:1041-1047.
21. Fainboim L, Marcos Y, Pando M, Cappuchio M, Reyes GB, Galoppo C, et al. Chronic active autoimmune hepatitis in children: strong association with a particular HLA-DR6 (DRB1*1301) haplotype. Hum Immunol 1994;41:146-150.
22. Czaja AJ, Souto EO, Bittencourt PL, Cancado EL, Porta G, Goldberg AC, et al. Clinical distinctions and pathogenic implications of type 1 autoimmune hepatitis in Brazil and the United States. J Hepatol 2002;37:302-308.
23. Bittencourt PL, Palacios SA, Cancado EL, Porta G, Drigo S, Carrilho FJ, et al. Autoimmune hepatitis in Brazilian patients is not linked to tumor necrosis factor alpha polymorphisms at position-308. J Hepatol 2001;35:24-28.
24. Gupta R, Agarwal SR, Jain M, Malhotra V, Sarin SK. Autoimmune hepatitis in the Indian subcontinent: 7 years experience. J Gastroenterol Hepatol 2001;16:1144-1148.
25. Gohar S, Desai D, Joshi A, Bhaduri A, Deshpande R, Balkrishna C, et al. Autoimmune hepatitis: a study of 50 patients. Indian J Gastroenterol 2003;22:140-142.
26. Lim KN, Casanova RL, Boyer TD, Bruno CJ. Autoimmune hepatitis in African Americans: presenting features and response to therapy. Am J Gastroenterol 2001;96:3390-3394.
27. Hurlburt KJ, McMahon BJ, Deubner H, Hsu-Trawinski B, Williams JL, Kowdley KV. Prevalence of autoimmune liver disease in Alaska Natives. Am J Gastroenterol 2002;97:2402-2407.
28. Zolfino T, Heneghan MA, Norris S, Harrison PM, Portmann BC, McFarlane IG. Characteristics of autoimmune hepatitis in patients who are not of European Caucasoid ethnic origin. Gut 2002;50:713-717.
29. Qiu DK, Ma X. Relationship between human leukocyte antigen-DRB1 and autoimmune hepatitis type I in Chinese patients. J Gastroenterol Hepatol 2003;18:63-67.
30. D'Souza R, Sinnott P, Glynn MJ, Sabin CA, Foster GR. An unusual form of autoimmune hepatitis in young Somalian men. Liver Int 2005;25:325-330.
31. Verma S, Torbenson M, Thuluvath PJ. The impact of ethnicity on the natural history of autoimmune hepatitis. Hepatology 2007;46:1828-1835.
32. Nguyen GC, Thuluvath PJ. Racial disparity in liver disease: Biological, cultural, or socioeconomic factors. Hepatology 2008;47:1058-1066.
33. Minuk GY, Liu S, Kaita K, Wong S, Renner E, Rempel J, et al. Autoimmune hepatitis in a North American Aboriginal/First Nations population. Can J Gastroenterol 2008;22:829-834.
34. Scott JD, Garland N. Chronic liver disease in Aboriginal North Americans. World J Gastroenterol 2008;14:4607-4615.
35. Gregorio GV, Portman B, Reid F, Donaldson PT, Doherty DG, McCartney M, et al. Autoimmune hepatitis in childhood: a 20-year experience. Hepatology 1997;25:541-547.
36. Gregorio GV, Portmann B, Karani J, Harrison P, Donaldson PT, Vergani D, et al. Autoimmune hepatitis/sclerosing cholangitis overlap syndrome in childhood: a 16-year prospective study. Hepatology 2001;33:544-553.
37. Parker DR, Kingham JG. Type I autoimmune hepatitis is primarily a disease of later life. Q J Med 1997;90:289-296.
38. Schramm C, Kanzler S, zum Buschenfelde KH, Galle PR, Lohse AW. Autoimmune hepatitis in the elderly. Am J Gastroenterol 2001;96:1587-1591.
39. Verslype C, George C, Buchel E, Nevens F, van Steenbergen W, Fevery J. Diagnosis and treatment of autoimmune hepatitis at age 65 and older. Aliment Pharmacol Ther 2005;21:695-699.
40. Granito A, Muratori L, Pappas G, Muratori P, Ferri S, Cassani F, et al. Clinical features of type 1 autoimmune hepatitis in elderly Italian patients. Aliment Pharmacol Ther 2005;21:1273-1277.

41. Miyake T, Miyaoka H, Abe M, Furukawa S, Shigematsu S, Furukawa E, et al. Clinical characteristics of autoimmune hepatitis in older aged patients. Hepatol Res 2006;36:139-142.
42. Al-Chalabi T, Boccato S, Portmann BC, McFarlane IG, Heneghan MA. Autoimmune hepatitis (AIH) in the elderly: a systematic retrospective analysis of a large group of consecutive patients with definite AIH followed at a tertiary referral centre. J Hepatol 2006;45:575-583.
43. Czaja AJ, Carpenter HA. Distinctive clinical phenotype and treatment outcome of type 1 autoimmune hepatitis in the elderly. HEPATOLOGY 2006;43:532-538.
44. Czaja AJ. Clinical features, differential diagnosis and treatment of autoimmune hepatitis in the elderly. Drugs Aging 2008;25:219-239.
45. Boberg KM, Aadland E, Jahnsen J, Raknerud N, Stiris M, Bell H. Incidence and prevalence of primary biliary cirrhosis, primary sclerosing cholangitis, and autoimmune hepatitis in a Norwegian population. Scand J Gastroenterol 1998;33:99-103.
46. Werner M, Prytz H, Ohlsson B, Almer S, Bjornsson E, Bergquist A, et al. Epidemiology and the initial presentation of autoimmune hepatitis in Sweden: a nationwide study. Scand J Gastroenterol 2008;43:1232-1240.
47. Mistilis SP, Skyring AP, Blackburn CR. Natural history of active chronic hepatitis. I. Clinical features, course, diagnostic criteria, morbidity, mortality and survival. Australas Ann Med 1968;17:214-223.
48. Cook GC, Mulligan R, Sherlock S. Controlled prospective trial of corticosteroid therapy in active chronic hepatitis. Q J Med 1971;40:159-185.
49. Soloway RD, Summerskill WH, Baggenstoss AH, Geall MG, Gitnick GL, Elveback IR, et al. Clinical, biochemical, and histological remission of severe chronic active liver disease: a controlled study of treatments and early prognosis. Gastroenterology 1972;63:820-833.
50. Murray-Lyon IM, Stern RB, Williams R. Controlled trial of prednisone and azathioprine in active chronic hepatitis. Lancet 1973;I:735-737.
51. De Groote J, Fevery J, Lepoutre L. Long-term follow-up of chronic active hepatitis of moderate severity. Gut 1978;19:510-513.
52. Fevery J, Desmet V, DeGroote J. Long-term follow-up and management of asymptomatic chronic active hepatitis. In: Cohen S, Soloway RD, eds. Chronic Active Liver Disease. Churchill Livingstone: New York. 1983:51-64.
53. Czaja AJ, Taswell HF, Rakela J, Schimek C. Frequency of antibody to hepatitis C virus in asymptomatic HBsAg-negative chronic active hepatitis. J Hepatol 1992;14:88-93.
54. Czaja AJ, Magrin S, Fabiano C, Fiorentino G, Diquattro O, Craxi A, et al. Hepatitis C virus infection as a determinant of behavior in type 1 autoimmune hepatitis. Dig Dis Sci 1995;40:33-40.
55. Schalm SW, Korman MG, Summerskill WH, Czaja AJ, Baggenstoss AH. Severe chronic active liver disease. Prognostic significance of initial morphologic patterns. Am J Dig Dis 1977;22:973-980.
56. Crapper RM, Bhathal PS, Mackay IR, Frazer IH. "Acute" autoimmune hepatitis. Digestion 1986;34:216-225.
57. Amontree JS, Stuart TD, Bredfeldt JE. Autoimmune chronic active hepatitis masquerading as acute hepatitis. J Clin Gastroenterol 1989;11:303-307.
58. Maggiore G, Porta G, Bernard O, Hadchouel M, Alvarez F, Homberg JC, et al. Autoimmune hepatitis with initial presentation as acute hepatic failure in young children. J Pediatr 1990;116:280-282.
59. Nikias GA, Batts KP, Czaja AJ. The nature and prognostic implications of autoimmune hepatitis with acute presentation. J Hepatol 1994;21:866-871.
60. Abe M, Hiasa Y, Masumoto T, Kumagi T, Akbar SM, Ninomiya T, et al. Clinical characteristics of autoimmune hepatitis with histological features of acute hepatitis. Hepatol Res 2001;21:213-219.
61. Singh R, Nair S, Farr G, Mason A, Perrillo R. Acute autoimmune hepatitis presenting with centrizonal liver disease: case report and review of the literature. Am J Gastroenterol 2002;97:2670-2673.
62. Okano N, Yamamoto K, Sakaguchi K, Miyake Y, Shimada N, Hakoda T, et al. Clinicopathological features of acute-onset autoimmune hepatitis. Hepatol Res 2003;25:263-270.
63. Kanda T, Yokosuka O, Hirasawa Y, Imazeki F, Nagao K, Suzuki Y, et al. Acute-onset autoimmune hepatitis resembling acute hepatitis: a case report and review of reported cases. Hepatogastroenterology 2005;52:1233-1235.
64. Porta G, Gayotto LC, Alvarez F. Anti-liver-kidney microsome antibody-positive autoimmune hepatitis presenting as fulminant liver failure. J Pediatr Gastroenterol Nutr 1990;11:138-140.
65. Herzog D, Rasquin-Weber AM, Debray D, Alvarez F. Subfulminant hepatic failure in autoimmune hepatitis type 1: an unusual form of presentation. J Hepatol 1997;27:578-582.
66. Viruet EJ, Torres EA. Steroid therapy in fulminant hepatic failure secondary to autoimmune hepatitis. P R Health Sci J 1998;17:297-300.
67. Aydogdu S, Ozgenc F, Yurtsever S, Akman SA, Tokat Y, Yagci RV. Our experience with fulminant hepatic failure in Turkish children: etiology and outcome. J Trop Pediatr 2003;49:367-370.
68. Santos RG, Alissa F, Reyes J, Teot L, Ameen N. Fulminant hepatic failure: Wilson's disease or autoimmune hepatitis? Implications for transplantation. Pediatr Transplant 2005;9:112-116.
69. Seaberg EC, Belle SH, Beringer KC, Schivins JL, Detre KM. Liver transplantation in the United States from 1987-1998: updated results from the Pitt-UNOS Liver Transplant Registry. Clin Transpl 1998:17-37.
70. Wiesner RH, Demetris AJ, Belle SH, Seaberg EC, Lake JR, Zetterman RK, et al. Acute hepatic allograft rejection: incidence, risk factors, and impact on outcome. HEPATOLOGY 1998;28:638-645.
71. Cross TJ, Antoniades CG, Muiesan P, Al-Chalabi T, Aluvihare V, Agarwal K, et al. Liver transplantation in patients over 60 and 65 years: an evaluation of long-term outcomes and survival. Liver Transpl 2007;13:1382-1388.
72. Khalaf H, Mourad W, El-Sheikh Y, Abdo A, Helmy A, Medhat Y, et al. Liver transplantation for autoimmune hepatitis: a single-center experience. Transplant Proc 2007;39:1166-1170.
73. Sanchez-Urdazpal L, Czaja AJ, van Hoek B, Krom RA, Wiesner RH. Prognostic features and role of liver transplantation in severe corticosteroid-treated autoimmune chronic active hepatitis. HEPATOLOGY 1992;15:215-221.
74. Campsen J, Zimmerman MA, Trotter JF, Wachs M, Bak T, Steinberg T, et al. Liver transplantation for autoimmune hepatitis and the success of aggressive corticosteroid withdrawal. Liver Transpl 2008;14:1281-1286.
75. Johnson PJ, McFarlane IG. Meeting report: International autoimmune hepatitis group. HEPATOLOGY 1993;18:998-1005.
76. Czaja AJ. Performance parameters of the diagnostic scoring systems for autoimmune hepatitis. HEPATOLOGY 2008;48:1540-1548.
77. Ebbeson RL, Schreiber RA. Diagnosing autoimmune hepatitis in children: is the International Autoimmune Hepatitis Group scoring system useful? Clin Gastroenterol Hepatol 2004;2:935-940.
78. Hennes EM, Zeniya M, Czaja AJ, Pares A, Dalekos GN, Krawitt EL, et al. Simplified criteria for the diagnosis of autoimmune hepatitis. HEPATOLOGY 2008;48:169-176.
79. Muratori P, Granito A, Pappas G, Muratori L. Validation of simplified diagnostic criteria for autoimmune hepatitis in Italian patients. HEPATOLOGY 2009;49:1782-1783; author reply, 1783.
80. Yeoman AD, Westbrook RH, Al-Chalabi T, Carey I, Heaton ND, Portmann BC, et al. Diagnostic value and utility of the simplified International Autoimmune Hepatitis Group (IAIHG) criteria in acute and chronic liver disease. HEPATOLOGY 2009;50:538-545.
81. Perdigoto R, Carpenter HA, Czaja AJ. Frequency and significance of chronic ulcerative colitis in severe corticosteroid-treated autoimmune hepatitis. J Hepatol 1992;14:325-331.
82. Abdalian R, Dhar P, Jhaveri K, Haider M, Guindi M, Heathcote EJ. Prevalence of sclerosing cholangitis in adults with autoimmune hepatitis: evaluating the role of routine magnetic resonance imaging. HEPATOLOGY 2008;47:949-957.

83. Dienes HP, Popper H, Manns M, Baumann W, Thoenes W, Meyer zum Büschenfelde K-H. Histologic features in autoimmune hepatitis. Z Gastroenterol 1989;27:327-330.
84. Czaja AJ, Carpenter HA. Sensitivity, specificity, and predictability of biopsy interpretations in chronic hepatitis. Gastroenterology 1993; 105:1824-1832.
85. Czaja AJ, Carpenter HA. Optimizing diagnosis from the medical liver biopsy. Clin Gastroenterol Hepatol 2007;5:898-907.
86. Baggenstoss AH, Soloway RD, Summerskill WH, Elveback LR, Schoenfield LJ. Chronic active liver disease. The range of histological lesions, their response to treatment and evaluation. Hum Pathol 1972; 3:183-198.
87. Cooksley WGE, Bradbear RA, Robinson W, Harrison M, Halliday JW, Powell LW, et al. The prognosis of chronic active hepatitis without cirrhosis in relation to bridging necrosis. HEPATOLOGY 1986;6: 345-348.
88. Pratt DS, Fawaz KA, Rabson A, Dellelis R, Kaplan MM. A novel histological lesion in glucocorticoid-responsive chronic hepatitis. Gastroenterology 1997;113:664-668.
89. Misdraji J, Thiim M, Graeme-Cook FM. Autoimmune hepatitis with centrilobular necrosis. Am J Surg Pathol 2004;28:471-478.
90. Zen Y, Notsumata K, Tanaka N, Nakanuma Y. Hepatic centrilobular zonal necrosis with positive antinuclear antibody: a unique subtype or early disease of autoimmune hepatitis? Hum Pathol 2007;38: 1669-1675.
91. Miyake Y, Iwasaki Y, Terada R, Onishi T, Okamoto R, Takaguchi K, et al. Clinical features of Japanese type 1 autoimmune hepatitis patients with zone III necrosis. Hepatol Res 2007;37:801-805.
92. Burgart LJ, Batts KP, Ludwig J, Nikias GA, Czaja AJ. Recent-onset autoimmune hepatitis. Biopsy findings and clinical correlations. Am J Surg Pathol 1995;19:699-708.
93. Iwai M, Jo M, Ishii M, Mori T, Harada Y. Comparison of clinical features and liver histology in acute and chronic autoimmune hepatitis. Hepatol Res 2008;38:784-789.
94. Czaja AJ. The variant forms of autoimmune hepatitis. Ann Intern Med 1996;125:588-598.
95. Czaja AJ. Frequency and nature of the variant syndromes of autoimmune liver disease. HEPATOLOGY 1998;28:360-365.
96. Czaja AJ. Variant forms of autoimmune hepatitis. Curr Gastroenterol Rep 1999;1:63-70.
97. Czaja AJ, Carpenter HA, Santrach PJ, Moore SB. Autoimmune cholangitis within the spectrum of autoimmune liver disease. HEPATOLOGY 2000;31:1231-1238.
98. Heathcote J. Variant syndromes of autoimmune hepatitis. Clin Liver Dis 2002;6:669-684.
99. Rust C, Beuers U. Overlap syndromes among autoimmune liver diseases. World J Gastroenterol 2008;14:3368-3373.
100. Al-Chalabi T, Portmann BC, Bernal W, McFarlane IG, Heneghan MA. Autoimmune hepatitis overlap syndromes: an evaluation of treatment response, long-term outcome and survival. Aliment Pharmacol Ther 2008;28:209-220.
101. Carpenter HA, Czaja AJ. The role of histologic evaluation in the diagnosis and management of autoimmune hepatitis and its variants. Clin Liver Dis 2002;6:685-705.
102. Terjung B, Herzog V, Worman HJ, Gestmann I, Bauer C, Sauerbruch T, et al. Atypical antineutrophil cytoplasmic antibodies with perinuclear fluorescence in chronic inflammatory bowel diseases and hepatobiliary disorders colocalize with nuclear lamina proteins. HEPATOLOGY 1998;28:332-340.
103. Terjung B, Spengler U, Sauerbruch T, Worman HJ. "Atypical p-ANCA" in IBD and hepatobiliary disorders react with a 50-kilodalton nuclear envelope protein of neutrophils and myeloid cell lines. Gastroenterology 2000;119:310-322.
104. Czaja AJ. Autoantibodies in autoimmune liver disease. Adv Clin Chem 2005;40:127-164.
105. Czaja. The role of autoantibodies as diagnostic markers of autoimmune hepatitis. Expert Rev Clin Immunol 2006;2:33-48.
106. Czaja AJ, Homburger HA. Autoantibodies in liver disease. Gastroenterology 2001;120:239-249.
107. Czaja AJ, Norman GL. Autoantibodies in the diagnosis and management of liver disease. J Clin Gastroenterol 2003;37:315-329.
108. Strassburg CP, Manns MP. Autoantibodies and autoantigens in autoimmune hepatitis. Semin Liver Dis 2002;22:339-352.
109. Bogdanos DP, Invernizzi P, Mackay IR, Vergani D. Autoimmune liver serology: current diagnostic and clinical challenges. World J Gastroenterol 2008;14:3374-3387.
110. Czaja AJ. Behavior and significance of autoantibodies in type 1 autoimmune hepatitis. J Hepatol 1999;30:394-401.
111. Martini E, Abuaf N, Cavalli F, Durand V, Johanet C, Homberg JC. Antibody to liver cytosol (anti-LC1) in patients with autoimmune chronic active hepatitis type 2. HEPATOLOGY 1988;8:1662-1666.
112. Homberg JC, Abuaf N, Bernard O, Islam S, Alvarez F, Khalil SH, et al. Chronic active hepatitis associated with anti liver/kidney microsome type 1: a second type of "autoimmune" hepatitis. HEPATOLOGY 1987;7:1333-1339.
113. Duchini A, McHutchison JG, Pockros PJ. LKM-positive autoimmune hepatitis in the western United States: a case series. Am J Gastroenterol 2000;95:3238-3241.
114. Czaja AJ, Rakela J, Hay JE, Moore SB. Clinical and prognostic implications of human leucocyte antigen B8 in corticosteroid-treated severe chronic active hepatitis. Gastroenterology 1990;98:1587-1593.
115. Provenzano G, Marino L, Craxi A. Features of autoimmunity in cryptogenic chronic hepatitis. Allergol Immunopathol (Madr) 1991;19:119-122.
116. Czaja AJ, Carpenter HA, Santrach PJ, Moore SB, Homburger HA. The nature and prognosis of severe cryptogenic chronic active hepatitis. Gastroenterology 1993;104:1755-1761.
117. Gassert DJ, Garcia H, Tanaka K, Reinus JF. Corticosteroid-responsive cryptogenic chronic hepatitis: evidence for seronegative autoimmune hepatitis. Dig Dis Sci 2007;52:2433-2437.
118. Potthoff A, Deterding K, Trautwein C, Flemming P, Strassburg CP, Manns MP, et al. Steroid treatment for severe acute cryptogenic hepatitis. Z Gastroenterol 2007;45:15-19.
119. Wies I, Brunner S, Henninger J, Herkel J, Kanzler S, Meyer zum Buschenfelde KH, et al. Identification of target antigen for SLA/LP autoantibodies in autoimmune hepatitis. Lancet 2000;355:1510-1515.
120. Gregorio GV, McFarlane B, Bracken P, Vergani D, Mieli-Vergani G. Organ and non-organ specific autoantibody titres and IgG levels as markers of disease activity: a longitudinal study in childhood autoimmune liver disease. Autoimmunity 2002;35:515-519.
121. Abuaf N, Johanet C, Chretien P, Martini E, Soulier E, Laperche S, et al. Characterization of the liver cytosol antigen type 1 reacting with autoantibodies in chronic active hepatitis. HEPATOLOGY 1992;16: 892-898.
122. Philipp T, Durazzo M, Trautwein C, Alex B, Straub P, Lamb JG, et al. Recognition of uridine diphosphate glucuronosyl transferases by LKM-3 antibodies in chronic hepatitis D. Lancet 1994;344:578-581.
123. Strassburg CP, Obermayer-Straub P, Alex B, Durazzo M, Rizzetto M, Tukey RH, et al. Autoantibodies against glucuronosyltransferases differ between viral hepatitis and autoimmune hepatitis. Gastroenterology 1996;111:1576-1586.
124. Duerr RH, Targan SR, Landers CJ, LaRusso NF, Lindsay KL, Wiesner RH. Neutrophil cytoplasmatc antibodies: a link between primary sclerosing cholangitis and ulcerative colitis. Gastroenterology 1991; 100:1385-1391.
125. Frenzer A, Fierz W, Rundler E, Hammer B, Binek J. Atypical, cytoplasmic and perinuclear anti-neutrophil cytoplasmic antibodies in patients with inflammatory bowel disease. J Gastroenterol Hepatol 1998;13:950-954.
126. Targan SR, Landers C, Vidrich A, Czaja AJ. High titer antineutrophil cytoplasmic antibodies in type-1 autoimmune hepatitis. Gastroenterology 1995;108:1159-1166.
127. Zauli D, Ghetti S, Grassi A, Descovich C, Cassani F, Ballardini G, et al. Anti-neutrophil cytoplasmic antibodies in type1 and 2 autoimmune hepatitis. HEPATOLOGY 1997;25:1105-1107.

128. LaBrecque DR, Phillips MJP, Ippolito LA, Mitros FA, Goeken JA. Antineutrophil cytoplasmic antibody and chronic liver disease [Abstract]. HEPATOLOGY 1999;30:428A.
129. Manns M, Gerken G, Kyriatsoulis A, Staritz M, Meyer zum Buschenfelde KH. Characterisation of a new subgroup of autoimmune chronic active hepatitis by autoantibodies against a soluble liver antigen. Lancet 1987;1:292-294.
130. Stechemesser E, Klein R, Berg PA. Characterization and clinical relevance of liver-pancreas antibodies in autoimmune hepatitis. HEPATOLOGY 1993;18:1-9.
131. Costa M, Rodriguez-Sanchez JL, Czaja AJ, Gelpi C. Isolation and characterization of cDNA encoding the antigenic protein of the human tRNP(Ser)Sec complex recognized by autoantibodies from patients withtype-1 autoimmune hepatitis. Clin Exp Immunol 2000; 121:364-374.
132. Volkmann M, Martin L, Baurle A, Heid H, Strassburg CP, Trautwein C, et al. Soluble liver antigen: isolation of a 35-kd recombinant protein (SLA-p35) specifically recognizing sera from patients with autoimmune hepatitis. HEPATOLOGY 2001;33:591-596.
133. Baeres M, Herkel J, Czaja AJ, Wies I, Kanzler S, Cancado EL, et al. Establishment of standardised SLA/LP immunoassays: specificity for autoimmune hepatitis, worldwide occurrence, and clinical characteristics. Gut 2002;51:259-264.
134. Ma Y, Bogdanos BP, Williams R, Mieli-Vergani G, Vergani D. Anti-SLA antibody is a marker of severity of liver damage in patients with autoimmune liver disease. J Hepatol 2001;34(Suppl. 1):212.
135. Vitozzi S, Djilali-Saiah I, Lapierre P, Alvarez F. Anti-soluble liver antigen/liver-pancreas (SLA/LP) antibodies in pediatric patients with autoimmune hepatitis. Autoimmunity 2002;35:485-492.
136. Torres-Collado AX, Czaja AJ, Gelpi C. Anti-tRNP(ser)sec/SLA/LP autoantibodies. Comparative study using in-house ELISA with a recombinant 48.8 kDa protein, immunoblot, and analysis of immunoprecipitated RNAs. Liver Int 2005;25:410-419.
137. Gelpi C, Sontheimer EJ, Rodriguez-Sanchez JL. Autoantibodies against a serine tRNA-protein complex implicated in cotranslational selenocysteine insertion. Proc Natl Acad Sci U S A 1992;89: 9739-9743.
138. Ma Y, Okamoto M, Thomas MG, Bogdanos DP, Lopes AR, Portmann B, et al. Antibodies to conformational epitopes of soluble liver antigen define a severe form of autoimmune liver disease. HEPATOLOGY 2002;35:658-664.
139. Czaja AJ, Donaldson PT, Lohse AW. Antibodies to soluble liver antigen/liver pancreas and HLA risk factors for type 1 autoimmune hepatitis. Am J Gastroenterol 2002;97:413-419.
140. Czaja AJ, Shums Z, Norman GL. Nonstandard antibodies as prognostic markers in autoimmune hepatitis. Autoimmunity 2004;37: 195-201.
141. Donaldson PT, Doherty DG, Hayllar KM, Mc Farlane IG, Johnson PJ, Williams R. Susceptibility to autoimmune chronic active hepatitis: human leukocyte antigens DR 4 and A1-B8-DR-3 are independent risk factors. HEPATOLOGY 1991;13:701-706.
142. Doherty DG, Donaldson PT, Underhill JA, Farrant JM, Duthie A, Mieli-Vergani G, et al. Allelic sequence variation in the HLA class II genes and proteins on patients with autoimmune hepatitis. HEPATOLOGY 1994;19:609-615.
143. Strettell MD, Donaldson PT, Thomson LJ, Santrach PJ, Moore SB, Czaja AJ, et al. Allelic basis for HLA-encoded susceptibility to type 1 autoimmune hepatitis. Gastroenterology 1997;112:2028-2035.
144. Yoshizawa K, Ota M, Katsuyama Y, Ichijo T, Matsumoto A, Tanaka E, et al. Genetic analysis of the HLA region of Japanese patients with type 1 autoimmune hepatitis. J Hepatol 2005;42:578-584.
145. Yokosawa S, Yoshizawa K, Ota M, Katsuyama Y, Kawa S, Ichijo T, et al. A genomewide DNA microsatellite association study of Japanese patients with autoimmune hepatitis type 1. HEPATOLOGY 2007;45: 384-390.
146. Pando M, Larriba J, Fernandez GC, Fainboim H, Ciocca M, Ramonet M, et al. Pediatric and adult forms of type I autoimmune hepatitis in Argentina: evidence for differential genetic predisposition. HEPATOLOGY 1999;30:1374-1380.
147. Fainboim L, Canero Velasco MC, Marcos CY, Ciocca M, Roy A, Theiler G, et al. Protracted, but not acute, hepatitis A virus infection is strongly associated with HLA-DRB*1301, a marker for pediatric autoimmune hepatitis. HEPATOLOGY 2001;33:1512-1517.
148. Vazquez-Garcia MN, Alaez C, Olivo A, Debaz H, Perez-Luque E, Burguete A, et al. MHC class II sequences of susceptibility and protection in Mexicans with autoimmune hepatitis. J Hepatol 1998;28: 985-990.
149. Bittencourt PL, Goldberg AC, Cancado EL, Porta G, Carrilho FJ, Farias AQ, et al. Genetic heterogeneity in susceptibility to autoimmune hepatitis types 1 and 2. Am J Gastroenterol 1999;94: 1906-1913.
150. Goldberg AC, Bittencourt PL, Mougin B, Cancado EL, Porta G, Carrilho F, et al. Analysis of HLA haplotypes in autoimmune hepatitis type 1: identifying the major susceptibility locus. Hum Immunol 2001;62:165-169.
151. Goldberg AC, Bittencourt PL, Oliveira LC, Ramasawmy R, Marin ML, Palacios SA, et al. Autoimmune hepatitis in Brazil: an overview. Scand J Immunol 2007;66:208-216.
152. Fortes Mdel P, Machado IV, Gil G, Fernandez-Mestre M, Dagher L, Leon RV, et al. Genetic contribution of major histocompatibility complex class II region to type 1 autoimmune hepatitis susceptibility in Venezuela. Liver Int 2007;27:1409-1416.
153. Lim YS, Oh HB, Choi SE, Kwon OJ, Heo YS, Lee HC, et al. Susceptibility to type 1 autoimmune hepatitis is associated with shared amino acid sequences at positions 70–74 of the HLA-DRB1 molecule. J Hepatol 2008;48:133-139.
154. Huang HC, Wu JC, Huang YS, Teh-Ia H, Lo JC, Li CP, et al. Genetic distinctions and clinical characteristics of type 1 autoimmune hepatitis in Taiwan. Hepatogastroenterology 2008;55:605-608.
155. Czaja AJ, Carpenter HA, Santrach PJ, Moore SB. Significance of HLA DR4 in type 1 autoimmune hepatitis. Gastroenterology 1993; 105:1502-1507.
156. Czaja AJ, Kruger M, Santrach PJ, Breanndan Moore S, Manns MP. Genetic distinctions between types 1 and 2 autoimmune hepatitis. Am J Gastroenterol 1997;92:2197-2200.
157. Jurado A, Cardaba B, Jara P, Cuadrado P, Hierro L, deAndres B, et al. Autoimmune hepatitis type 2 and hepatitis C virus infection: study of HLA antigens. J Hepatol 1997;26:983-991.
158. Czaja AJ, Strettell M, Thomson LJ, Santrach P, Moore SB, Donaldson PT, et al. Associations between alleles of the major histocompatibility complex and type 1 autoimmune hepatitis. HEPATOLOGY 1997;25: 317-323.
159. Cookson S, Constantini PK, Clare M, Underhill JA, Bernal W, Czaja AJ, et al. Frequency and nature of cytokine gene polymorphisms in type 1 autoimmune hepatitis. HEPATOLOGY 1999;30:851-856.
160. Czaja AJ, Cookson S, Constantini PK, Clare M, Underhill JA, Donaldson PT. Cytokine polymorphisms associated with clinical features and treatment outcome in type 1 autoimmune hepatitis. Gastroenterology 1999;117:645-652.
161. Manns MP, Jaeckel E. Searching for the needle in the haystack: another candidate needle in autoimmune hepatitis? Gastroenterology 1999;117:728-732.
162. Agarwal K, Jones DE, Daly AK, James OF, Vaidya B, Pearce S, et al. CTLA-4 gene polymorphism confers susceptibility to primary biliary cirrhosis. J Hepatol 2000;32:538-541.
163. Ma Y, Thomas MG, Okamoto M, Bogdanos DP, Nagl S, Kerkar N, et al. Key residues of a major cytochrome P4502D6 epitope are located on the surface of the molecule. J Immunol 2002;169:277-285.
164. Vogel A, Strassburg CP, Manns MP. Genetic association of vitamin D receptor polymorphisms with primary biliary cirrhosis and autoimmune hepatitis. HEPATOLOGY 2002;35:126-131.
165. Vogel A, Strassburg CP, Manns MP. 77 C/G mutation in the tyrosine phosphatase CD45 gene and autoimmune hepatitis: evidence for a genetic link. Genes Immun 2003;4:79-81.

166. Hiraide A, Imazeki F, Yokosuka O, Kanda T, Kojima H, Fukai K, et al. Fas polymorphisms influence susceptibility to autoimmune hepatitis. Am J Gastroenterol 2005;100:1322-1329.
167. Djilali-Saiah I, Fakhfakh A, Louafi H, Caillat-Zucman S, Debray D, Alvarez F. HLA class II influences humoral autoimmunity in patients with type 2 autoimmune hepatitis. J Hepatol 2006;45:844-850.
168. Agarwal K, Czaja AJ, Donaldson PT. A functional Fas promoter polymorphism is associated with a severe phenotype in type 1 autoimmune hepatitis characterized by early development of cirrhosis. Tissue Antigens 2007;69:227-235.
169. Czaja AJ. Genetic factors affecting the occurrence, clinical phenotype, and outcome of autoimmune hepatitis. Clin Gastroenterol Hepatol 2008;6:379-388.
170. Aaltonen J, Bjorses P, Sandkuijl L, Perheentupa J, Peltonen L. An autosomal locus causing autoimmune disease: autoimmune polyglandular disease type I assigned to chromosome 21. Nat Genet 1994;8:83-87.
171. Obermayer-Straub P, Perheentupa J, Braun S, Kayser A, Barut A, Loges S, et al. Hepatic autoantigens in patients with autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy. Gastroenterology 2001;121:668-677.
172. Clemente MG, Meloni A, Obermayer-Straub P, Frau F, Manns MP, De Virgiliis S. Two cytochromes P450 are major hepatocellular autoantigens in autoimmune polyglandular syndrome type 1. Gastroenterology 1998;114:324-328.
173. Clemente MG, Obermayer-Straub P, Meloni A, Strassburg CP, Arangino V, Tukey RH, et al. Cytochrome P450 1A2 is a hepatic autoantigen in autoimmune polyglandular syndrome type 1. J Clin Endocrinol Metab 1997;82:1353-1361.
174. Choudhuri K, Gregorio GV, Mieli-Vergani G, Vergani D. Immunological cross-reactivity to multiple autoantigens in patients with liver kidney microsomal type 1 autoimmune hepatitis. HEPATOLOGY 1998; 28:1177-1181.
175. Czaja AJ, Manns MP. The validity and importance of subtypes in autoimmune hepatitis: a point of view. Am JGastroenterol 1995;90: 1206-1211.
176. Ballot E. HJ, Johanet C. Antibodies to soluble liver antigen: an additional marker in type 1 auto-immune hepatitis. J Hepatol 2000;33: 208-215.
177. Vitozzi S, Lapierre P, Djilali-Saiah I, Marceau G, Beland K, Alvarez F. Anti-soluble liver antigen (SLA) antibodies in chronic HCV infection. Autoimmunity 2004;37:217-222.
178. Czaja AJ, Carpenter HA, Manns MP. Antibodies to soluble liver antigen, P450IID6, and mitochondrial complexes in chronic hepatitis. Gastroenterology 1993;105:1522-1528.
179. Czaja AJ, Shums Z, Norman GL. Frequency and significance of antibodies to soluble liver antigen/liver pancreas in variant autoimmune hepatitis. Autoimmunity 2002;35:475-483.
180. Czaja AJ, Carpenter HA, Santrach PJ, Moore B, Taswell HF, Homburger HA. Evidence against hepatitis viruses as important causes of severe autoimmune hepatitis in the United States. J Hepatol 1993;18: 342-352.
181. McFarlane IG. Autoimmune hepatitis: Clinical manifestations and diagnostic criteria. Can J Gastroenterol 2001;15:107-113.
182. Bittencourt PL, Farias AQ, Porta G, Cancado EL, Miura I, Pugliese R, et al. Frequency of concurrent autoimmune disorders in patients with autoimmune hepatitis: effect of age, gender, and genetic background. J Clin Gastroenterol 2008;42:300-305.
183. Davis GL, Czaja AJ, Ludwig J. Development and prognosis of histologic cirrhosis in corticosteroid-treated hepatitis B surface antigen-negative chronic active hepatitis. Gastroenterology 1984;87:1222-1227.
184. Roberts SK, Therneau TM, Czaja AJ. Prognosis of histological cirrhosis in type 1 autoimmune hepatitis. Gastroenterology 1996;110: 848-857.
185. Manns MP, Johnson EF, Griffin KJ, Tan EM, Sullivan KF. Major antigen of liver kidney microsomal antibodies in idiopathic autoimmune hepatitis is cytochrome P450db1. J Clin Invest 1989;83: 1066-1072.
186. Manns MP, Griffin KJ, Sullivan KF, Johnson EF. LKM-1 autoantibodies recognize a short linear sequence in P450IID6, a cytochrome P-450 monooxygenase. J Clin Invest 1991;88:1370-1378.
187. Alvarez F, Bernard O, Homberg JC, Kreibich G. Anti-liver-kidney microsome antibody recognizes a 50,000 molecular weight protein of the endoplasmic reticulum. J Exp Med 1985;161:1231-1236.
188. Guenguen M, Meunier-Rotival M, Bernard O, Alvarez F. Anti-liver-kidney microsome antibody recognizes a cytochrome P450 from the IID subfamily. J Exp Med 1988;168:801.
189. Zanger UM, Hauri HP, Loeper J, Homberg JC, Meyer UA. Antibodies against human cytochrome P-450db1 in autoimmune hepatitis type 2. Proc Natl Acad Sci U S A 1988;85:8256-8260.
190. Guenguen M, Boniface O, Bernard O, Clerc F, Cartwright T, Alvarez F. Identification of the main epitope on human cytochrome P450IID6 recognized by anti-liver kidney microsome antibody. J Autoimmun 1991;4:607-615.
191. Ma Y, Bogdanos DP, Hussain MJ, Underhill J, Bansal S, Longhi MS, et al. Polyclonal T-cell responses to cytochrome P450IID6 are associated with disease activity in autoimmune hepatitis type 2. Gastroenterology 2006;130:868-882.
192. Lunel F, Abuaf N, Lionel F, Grippon P, Perrin M, Coz YL, et al. Liver/kidney microsome antibody type 1 and hepatitis C virus infection. HEPATOLOGY 1992;16:630-636.
193. Yamamoto AM, Cresteil D, Homberg JC, Alvarez F. Characterization of anti-liver-kidney microsome antobody (anti-LKM1) from hepatitis C virus-positive and -negative sera. Gastroenterology 1993;104: 1762-1767.
194. Michitaka K, Durazzo M, Tillmann HL, Walker D, Philipp T, Manns MP. Analysis of hepatitis C virus genome in patients with autoimmune hepatitis type 2. Gastroenterology 1994;106:1603-1610.
195. Dalekos GN, Wedemeyer H, Obermayer-Straub P, Kayser A, Barut A, Frank H, et al. Epitope mapping of cytochrome P4502D6 autoantigen in patients with chronic hepatitis C during alpha-interferon treatment. J Hepatol 1999;30:366-375.
196. Todros L, Touscoz G, D'Urso N, Durazzo M, Albano E, Poli G, et al. Hepatitis C virus-related chronic liver disease with autoantibodies to liver-kidney microsomes (LKM). Clinical characterization from idiopathic LKM-positive disorders. J Hepatol 1991;13:128-131.
197. Giostra F, Manzin A, Lenzi M, Francesconi R, Solforosi L, Manotti P, et al. Low hepatitis C viremia levels in liver/kidney microsomal antibody type 1-positive chronic hepatitis. J Hepatol 1996;25:433-438.
198. Marceau G, Lapierre P, Beland K, Soudeyns H, Alvarez F. LKM1 autoantibodies in chronic hepatitis C infection: a case of molecular mimicry? HEPATOLOGY 2005;42:675-682.
199. Muratori P, Czaja AJ, Muratori L, Granito A, Guidi M, Ferri S, et al. Evidence of a genetic basis for the different geographic occurrences of liver/kidney microsomal antibody type 1 in hepatitis C. Dig Dis Sci 2007;52:179-184.
200. Muratori L, Lenzi M, Cataleta M, Giostra F, Ballardini G. Interferon therapy in liver/kidney microsomal antibody type 1-positive patients with chronic hepatitis C. J Hepatol 1994;21:199-203.
201. Durazzo M, Philipp T, Van Pelt FN, Luttig B, Borghesio E, Michel G, et al. Heterogeneity of liver-kidney microsomal autoantibodies in chronic hepatitis C and D virus infection. Gastroenterology 1995; 108:455-462.
202. Bogdanos DP, Choudhuri K, Vergani D. Molecular mimicry and autoimmune liver disease: virtuous intentions, malign consequences. Liver 2001;21:225-232.
203. Lapierre P, Hajoui O, Homberg J-C, Alvarez F. Formiminotransferase cyclodeaminase is an organ specific autoantigen recognized by sera of patients with autoimmune hepatitis. Gastroenterology 1999;116:643-649.
204. Muratori L, Sztul E, Muratori P, Gao Y, Ripalti A, Ponti C, et al. Distinct epitopes on formiminotransferase cyclodeaminase induce autoimmune liver cytosol antibody type 1. HEPATOLOGY 2001;34:494-501.
205. Lapierre P, Johanet C, Alvarez F. Characterization of the B cell response of patients with anti-liver cytosol autoantibodies in type 2 autoimmune hepatitis. Eur J Immunol 2003;33:1869-1878.

206. van Buuren HR, van Hoogstraten HJE, Terkivatan T, Schalm SW, Vleggaar FP. High prevalence of autoimmune hepatitis among patients with primary sclerosing cholangitis. J Hepatol 2000;33:543-548.
207. Czaja AJ, Santrach PJ, Breanndan Moore S. Shared genetic risk factors in autoimmune liver disease. Dig Dis Sci 2001;46:140-147.
208. Joshi S, Cauch-Dudek K, Wanless IR, Lindor KD, Jorgensen R, Batts K, et al. Primary biliary cirrhosis with additional features of autoimmune hepatitis: response to therapy with ursodeoxycholic acid. Hepatology 2002;35:409-413.
209. Chazouilleres O, Wendum D, Serfaty L, Montembault S, Rosmorduc O, Poupon R. Primary biliary cirrhosis-autoimmune hepatitis overlap syndrome: clinical features and response to therapy. Hepatology 1998;28:296-301.
210. Lohse AW, zum Buschenfelde KH, Franz B, Kanzler S, Gerken G, Dienes HP. Characterization of the overlap syndrome of primary biliary cirrhosis (PBC) and autoimmune hepatitis: evidence for it being a hepatitic form of PBC in genetically susceptible individuals. Hepatology 1999;29:1078-1084.
211. McNair AN, Moloney M, Portmann BC, Williams R, McFarlane IG. Autoimmune hepatitis overlapping with primary sclerosing cholangitis in five cases. Am J Gastroenterol 1998;93:777-784.
212. Chazouilleres O, Wendum D, Serfaty L, Rosmorduc O, Poupon R. Long term outcome and response to therapy of primary biliary cirrhosis-autoimmune hepatitis overlap syndrome. J Hepatol 2006;44:400-406.
213. Ludwig J, Czaja AJ, Dickson ER, LaRusso NF, Wiesner RH. Manifestations of nonsuppurative cholangitis in chronic hepatobiliary diseases: morphologic spectrum, clinical correlations and terminology. Liver 1984;4:105-116.
214. Czaja AJ, Carpenter HA. Autoimmune hepatitis with incidental histologic features of bile duct injury. Hepatology 2001;34:659-665.
215. Czaja AJ, Muratori P, Muratori L, Carpenter HA, Bianchi FB. Diagnostic and therapeutic implications of bile duct injury in autoimmune hepatitis. Liver Int 2004;24:322-329.
216. Floreani A, Rizzotto ER, Ferrara F, Carderi I, Caroli D, Blasone L, et al. Clinical course and outcome of autoimmune hepatitis/primary sclerosing cholangitis overlap syndrome. Am J Gastroenterol 2005; 100:1516-1522.
217. Czaja AJ. Overlap syndrome of primary biliary cirrhosis and autoimmune hepatitis: a foray across diagnostic boundaries. J Hepatol 2006; 44:251-252.
218. Czaja A, Carpenter HA. Validation of scoring system for diagnosis of autoimmune hepatitis. Dig Dis Sci 1996;41:305-314.
219. Boberg KM, Fausa O, Haaland T, Holter E, Mellbye OJ, Spurkland A, et al. Features of autoimmune hepatitis in primary sclerosing cholangitis: an evaluation of 114 primary sclerosing cholangitis patients according to a scoring system for the diagnosis of autoimmune hepatitis. Hepatology 1996;23:1369-1376.
220. Omagari K, Masuda J, Kato Y, Nakata K, Kanematsu T, Kusumoto Y, et al. Re-analysis of clinical features of 89 patients with autoimmune hepatitis using the revised scoring system proposed by the International Autoimmune Hepatitis Group. Intern Med 2000;39: 1008-1012.
221. Kaya M, Angulo P, Lindor KD. Overlap of autoimmune hepatitis and primary sclerosing cholangitis: an evaluation of a modified scoring system. J Hepatol 2000;33:537-542.
222. Talwalkar JA, Keach JC, Angulo P, Lindor KD. Overlap of autoimmune hepatitis and primary biliary cirrhosis: an evaluation of a modified scoring system. Am J Gastroenterol 2002;97:1191-1197.
223. Ben-Ari Z, Dhillon AP, Sherlock S. Autoimmune cholangiopathy: part of the spectrum of autoimmune chronic active hepatitis. Hepatology 1993;18:10-15.
224. Kenny RP, Czaja AJ, Ludwig J, Dickson ER. Frequency and significance of antimitochondrial antibodies in severe chronic active hepatitis. Dig Dis Sci 1986;31:705-711.
225. Nezu S, Tanaka A, Yasui H, Imamura M, Nakajima H, Ishida H, et al. Presence of antimitochondrial autoantibodies in patients with autoimmune hepatitis. J Gastroenterol Hepatol 2006;21:1448-1454.
226. Montano-Loza AJ, Carpenter HA, Czaja AJ. Frequency, behavior, and prognostic implications of antimitochondrial antibodies in type 1 autoimmune hepatitis. J Clin Gastroenterol 2008;42:1047-1053.
227. O'Brien C, Joshi S, Feld JJ, Guindi M, Dienes HP, Heathcote EJ. Long-term follow-up of antimitochondrial antibody-positive autoimmune hepatitis. Hepatology 2008;48:550-556.
228. Mishima S, Omagari K, Ohba K, Kadokawa Y, Masuda J, Mishima R, et al. Clinical implications of antimitochondrial antibodies in type 1 autoimmune hepatitis: a longitudinal study. Hepatogastroenterology 2008;55:221-227.
229. Farias AQ, Goncalves LL, Bittencourt PL, De Melo ES, Abrantes-Lemos CP, Porta G, et al. Applicability of the IAIHG scoring system to the diagnosis of antimitochondrial/anti-M2 seropositive variant form of autoimmune hepatitis. J Gastroenterol Hepatol 2006;21:887-893.
230. Heathcote EJ. Overlap of autoimmune hepatitis and primary biliary cirrhosis: an evaluation of a modified scoring system. Am J Gastroenterol 2002;97:1090-1092.
231. Czaja AJ, Carpenter HA, Santrach PJ, Moore SB. Genetic predispositions for immunological features in chronic liver diseases other than autoimmune hepatitis. J Hepatol 1996;24:52-59.
232. Loria P, Lonardo A, Leonardi F, Fontana C, Carulli L, Verrone AM, et al. Non-organ-specific autoantibodies in nonalcoholic fatty liver disease: prevalence and correlates. Dig Dis Sci 2003;48:2173-2181.
233. Adams LA, Lindor KD, Angulo P. The prevalence of autoantibodies and autoimmune hepatitis in patients with nonalcoholic fatty liver disease. Am J Gastroenterol 2004;99:1316-1320.
234. Mackie FD, Peakman M, Ma Y, Sallie R, Smith H, Davis ET, et al. Primary and secondary liver/kidney microsomal response following infection with hepatitis C virus. Gastroenterology 1994;106: 1672-1675.
235. Cassani F, Muratori L, Manotti P, Lenzi M, Fusconi M, Ballardini G, et al. Serum autoantibodies and the diagnosis of type-1 autoimmune hepatitis in Italy: a reappraisal at the light of hepatitis C virus infection. Gut 1992;33:1260-1263.
236. Abuaf N, Lunel F, Giral P, Borotto E, Laperche S, Poupon R, et al. Non-organ specific autoantibodies associated with chronic C virus hepatitis. J Hepatol 1993;18:359-364.
237. Czaja AJ. Autoimmune hepatitis and viral infection. Gastroenterol Clin North Am 1994;23:547-566.
238. Pawlotsky JM, Roudot-Thoraval F, Simmonds P, Mellor J, Ben Yahia MB, Andre C, et al. Extrahepatic immunologic manifestations in chronic hepatitis C and hepatitis C virus serotypes. Ann Intern Med 1995;122:169-173.
239. Clifford BD, Donahue D, Smith S, Cable E, Luttig B, Manns MP, et al. High prevalence of serological markers of autoimmunity in patients with chronic hepatitis C. Hepatology 1995;231:613-619.
240. Czaja AJ. Extrahepatic immunologic features of chronic viral hepatitis. Dig Dis 1997;15:125-144.
241. Czaja AJ, Carpenter HA. Histological findings in chronic hepatitis C with autoimmune features. Hepatology 1997;26:459-466.
242. Maddrey WC, Boitnott JK. Drug-induced chronic liver disease. Gastroenterology 1977;72:1348-1353.
243. Seeff LB. Drug-induced chronic liver disease, with emphasis on chronic active hepatitis. Semin Liver Dis 1981;1:104-115.
244. Gough A, Chapman S, Wagstaff K, Emery P, Elias E. Minocycline induced autoimmune hepatitis and systemic lupus erythematosus-like syndrome. BMJ 1996;312:169-172.
245. Crosson J, Stillman MT. Minocycline-related lupus erythematosus with associated liver disease. J Am Acad Dermatol 1997;36:867-868.
246. Herzog D, Hajoui O, Russo P, Alvarez F. Study of immune reactivity of minocycline-induced chronic active hepatitis. Dig Dis Sci 1997;42: 1100-1103.
247. Helfgott SM, Sandberg-Cook J, Zakim D, Nestler J. Diclofenac-associated hepatotoxicity. JAMA 1990;264:2660-2662.
248. Scully LJ, Clarke D, Barr RJ. Diclofenac induced hepatitis. 3 cases with features of autoimmune chronic active hepatitis. Dig Dis Sci 1993;38:744-751.

249. Germano V, Picchianti Diamanti A, Baccano G, Natale E, Onetto Muda A, Priori R, et al. Autoimmune hepatitis associated with infliximab in a patient with psoriatic arthritis. Ann Rheum Dis 2005;64: 1519-1520.
250. Fedotin MS, Lefer LG. Liver disease caused by propylthiouracil. Arch Intern Med 1975;135:319-321.
251. van Heyningen C. Drug-induced acute autoimmune hepatitis during combination therapy with atorvastatin and ezetimibe. Ann Clin Biochem 2005;42:402-404.
252. Sharp JR, Ishak KG, Zimmerman HJ. Chronic active hepatitis and severe hepatic necrosis associated with nitrofurantoin. Ann Intern Med 1980;92:14-19.
253. Maddrey WC, Boitnott JK. Severe hepatitis from methyldopa. Gastroenterology 1975;68:351-360.
254. Black M, Mitchell JR, Zimmerman HJ, Ishak KG, Epler GR. Isoniazid-associated hepatitis in 114 patients. Gastroenterology 1975;69:289-302.
255. Nadir A, Agrawal S, King PD, Marshall JB. Acute hepatitis associated with the use of a Chinese herbal product, ma-huang. Am J Gastroenterol 1996;91:1436-1438.
256. Kamiyama T, Nouchi T, Kojima S, Murata N, Ikeda T, Sato C. Autoimmune hepatitis triggered by administration of an herbal medicine. Am J Gastroenterol 1997;92:703-704.
257. Borum ML. Fulminant exacerbation of autoimmune hepatitis after the use of ma huang. Am J Gastroenterol 2001;96:1654-1655.
258. Cohen SM, O'Connor AM, Hart J, Merel NH, Te HS. Autoimmune hepatitis associated with the use of black cohosh: a case study. Menopause 2004;11:575-577.
259. Veerappan GR, Mulhall BP, Holtzmuller KC. Vaccination-induced autoimmune hepatitis. Dig Dis Sci 2005;50:212-213.
260. Berry PA, Smith-Laing G. Hepatitis A vaccine associated with autoimmune hepatitis. World J Gastroenterol 2007;13:2238-2239.
261. Csepregi A, Treiber G, Rocken C, Malfertheiner P. Acute exacerbation of autoimmune hepatitis induced by Twinrix. World J Gastroenterol 2005;11:4114-4116.
262. Nakamura K, Yoneda M, Yokohama S, Tamori K, Sato Y, Aso K, et al. Efficacy of ursodeoxycholic acid in Japanese patients with type 1 autoimmune hepatitis. J Gastroenterol Hepatol 1998;13:490-495.
263. Siegel AB, McBride RB, El-Serag HB, Hershman DL, Brown RS Jr, Renz JF, et al. Racial disparities in utilization of liver transplantation for hepatocellular carcinoma in the United States, 1998-2002. Am J Gastroenterol 2008;103:120-127.
264. Flores YN, Yee HF Jr, Leng M, Escarce JJ, Bastani R, Salmeron J, et al. Risk factors for chronic liver disease in Blacks, Mexican Americans, and Whites in the United States: results from NHANES IV, 1999–2004. Am J Gastroenterol 2008;103:2231-2238.
265. Davis GL, Czaja AJ, Baggenstoss AH, Taswell HF. Prognostic and therapeutic implications of extreme serum aminotransferase elevation in chronic active hepatitis. Mayo Clin Proc 1982;57:303-309.
266. Czaja AJ, Rakela J, Ludwig J. Features reflective of early prognosis in corticosteroid-treated severe autoimmune chronic active hepatitis. Gastroenterology 1988;95:448-453.
267. Czaja AJ. Corticosteroids or not in severe acute or fulminant autoimmune hepatitis: therapeutic brinksmanship and the point beyond salvation. Liver Transpl 2007;13:953-955.
268. Lankisch TO, Strassburg CP, Debray D, Manns MP, Jacquemin E. Detection of autoimmune regulator gene mutations in children with type 2 autoimmune hepatitis and extrahepatic immune-mediated diseases. J Pediatr 2005;146:839-842.
269. Czaja A. Features and consequences of untreated autoimmune hepatitis. Liver Int 2009;29:816-823.
270. Czaja AJ, Carpenter HA, Santrach PJ, Moore SB. Genetic predispositions for the immunological features of chronic active hepatitis. Hepatology 1993;18:816-822.
271. Kirk AP, Jain S, Pocock S, Thomas HC, Sherlock S. Late results of the Royal Free Hospital prospective controlled trial of prednisolone therapy in hepatitis B surface antigen negative chronic active hepatitis. Gut 1980;21:78-83.
272. Schalm SW, Summerskill WH, Go VL. Prednisone for chronic active liver disease: pharmacokinetics, including conversion to prednisolone. Gastroenterology 1977;72:910-913.
273. Summerskill WHJ, Korman MG, Ammon HV, Baggenstoss AH. Prednisone for chronic active liver disease: dose titration, standard dose and combination with azathioprine compound. Gut 1975;16: 876-883.
274. Floreani A, Niro G, Rosa Rizzotto E, Antoniazzi S, Ferrara F, Carderi I, et al. Type I autoimmune hepatitis: clinical course and outcome in an Italian multicentre study. Aliment Pharmacol Ther 2006;24: 1051-1057.
275. Seo S, Toutounjian R, Conrad A, Blatt L, Tong MJ. Favorable outcomes of autoimmune hepatitis in a community clinic setting. J Gastroenterol Hepatol 2008;23:1410-1414.
276. Koretz RL, Lewin KJ, Higgins J, Fagen ND, Gitnick GL. Chronic active hepatitis. Who meets treatment criteria? Dig Dis Sci 1980;25: 695-699.
277. Czaja AJ. Safety issues in the management of autoimmune hepatitis. Expert Opin Drug Safety 2008;7:319-333.
278. Uribe M, Go VL, Kluge D. Prednisone for chronic active hepatitis: pharmacokinetics and serum binding in patients with chronic active hepatitis and steroid major side effects. J Clin Gastroenterol 1984;6: 331-335.
279. Maggiore G, Bernard O, Hadchouel M, Hadchouel P, Odievre M, Alagille D. Treatment of autoimmune chronic active hepatitis in childhood. J Pediatr 1984;104:839-844.
280. Maggiore G, Veber F, Bernard O, Hadchouel M, Homberg JC, Alvarez F, et al. Autoimmune hepatitis associated with anti-actin antibodies in children and adolescents. J Pediatr Gastroenterol Nutr 1993;17:376-381.
281. Roberts EA. Autoimmune hepatitis. Indian J Pediatr 1995;62: 525-531.
282. Czaja AJ. Treatment strategies in autoimmune hepatitis. Clin Liver Dis 2002;6:799-824.
283. Czaja AJ, Freese DK. Diagnosis and treatment of autoimmune hepatitis. Hepatology 2002;36:479-497.
284. Czaja AJ. Treatment of autoimmune hepatitis. Semin Liver Dis 2002; 22:365-378.
285. Montano Loza AJ, Czaja AJ. Current therapy for autoimmune hepatitis. Nat Clin Pract Gastroenterol Hepatol 2007;4:202-214.
286. Larsen FS. Treatment of patients with severe autoimmune hepatitis. Minerva Gastroenterol Dietol 2008;54:57-63.
287. Luxon BA. Diagnosis and treatment of autoimmune hepatitis. Gastroenterol Clin North Am 2008;37:461-478, vii-viii.
288. Bacon BR, Treuhaft WH, Goodman AM. Azathioprine-induced pancytopenia. Occurrence in two patients with connective-tissue diseases. Arch Intern Med 1981;141:223-226.
289. Maddocks JL, Lennard L, Amess J, Amos R, Thomas RM. Azathioprine and severe bone marrow depression. Lancet 1986;1:156.
290. Jeurissen ME, Boerbooms AM, van de Putte LB. Pancytopenia related to azathioprine in rheumatoid arthritis. Ann Rheum Dis 1988;47: 503-505.
291. Lennard L, Van Loon JA, Weinshilboum RM. Pharmacogenetics of acute azathioprine toxicity: relationship to thiopurine methyltransferase genetic polymorphism. Clin Pharmacol Ther 1989;46:149-154.
292. Ben Ari Z, Mehta A, Lennard L, Burroughs AK. Azathioprine-induced myelosuppression due to thiopurine methyltransferase deficiency in a patient with autoimmune hepatitis. J Hepatol 1995;23: 351-354.
293. Rosenkrantz JG, Githens JH, Cox SM, Kellum DL. Azathioprine (Imuran) and pregnancy. Am J Obstet Gynecol 1967;97:387-394.
294. Steven MM, Buckley JD, Mackay IR. Pregnancy in chronic active hepatitis. Q J Med 1979;48:519-531.
295. de Boer NK, Jarbandhan SV, de Graaf P, Mulder CJ, van Elburg RM, van Bodegraven AA. Azathioprine use during pregnancy: unexpected intrauterine exposure to metabolites. Am J Gastroenterol 2006;101: 1390-1392.

296. Penn I. Tumor incidence in human allograft recipients. Transplant Proc 1979;11:1047-1051.
297. Wang KK, Czaja AJ, Beaver SJ, Go VL. Extrahepatic malignancy following long-term immunosuppressive therapy of severe hepatitis B surface antigen-negative chronic active hepatitis. HEPATOLOGY 1989;10: 39-43.
298. Heneghan MA, McFarlane IG. Current and novel immunosuppressive therapy for autoimmune hepatitis. HEPATOLOGY 2002;35:7-13.
299. Lebovics E, Schaffner F, Klion FM, Simon C. Autoimmune chronic active hepatitis in postmenopausal women. Dig Dis Sci 1985;30: 824-828.
300. Wang KK, Czaja AJ. Prognosis of corticosteroid-treated hepatitis B surface antigen-negative chronic active hepatitis in postmenopausal women: a retrospective analysis. Gastroenterology 1989;97: 1288-1293.
301. Reuther LO, Sonne J, Larsen NE, Larsen B, Christensen S, Rasmussen SN, et al. Pharmacological monitoring of azathioprine therapy. Scand J Gastroenterol 2003;38:972-977.
302. Collier J. Bone disorders in chronic liver disease. HEPATOLOGY 2007; 46:1271-1278.
303. Stellon AJ, Davies A, Compston J, Williams R. Bone loss in autoimmune chronic active hepatitis on maintenance corticosteroid therapy. Gastroenterology 1985;89:1078-1083.
304. Worns MA, Teufel A, Kanzler S, Shrestha A, Victor A, Otto G, et al. Incidence of HAV and HBV infections and vaccination rates in patients with autoimmune liver diseases. Am J Gastroenterol 2008; 103:138-146.
305. Banerjee S, Rahhal R, Bishop WP. Azathioprine monotherapy for maintenance of remission in pediatric patients with autoimmune hepatitis. J Pediatr Gastroenterol Nutr 2006;43:353-356.
306. Debray D, Maggiore G, Giradet JP, Mallet E, Bernard O. Efficacy of cyclosporin A in children with type 2 autoimmune hepatitis. J Pediatr 1999;135:111-114.
307. Alvarez F, Ciocca M, Cañero-Velasco C, Ramonet M, de Davila MT, Cuarterolo M, et al. Short-term cyclosporine induces a remission of autoimmune hepatitis in children. J Hepatol 1999;30:222-227.
308. Malekzadeh R, Nasseri-Moghaddam S, Kaviani MJ, Taheri H, Kamalian N, Sotoudeh M. Cyclosporin A is a promising alternative to corticosteroids in autoimmune hepatitis. Dig Dis Sci 2001;46: 1321-1327.
309. Cuarterolo M, Ciocca M, Velasco CC, Ramonet M, Gonzalez T, Lopez S, et al. Follow-up of children with autoimmune hepatitis treated with cyclosporine. J Pediatr Gastroenterol Nutr 2006;43: 635-639.
310. Wright SH, Czaja AJ, Katz RS, Soloway RD. Systemic mycosis complicating high dose corticosteroid treatment of chronic active liver disease. Am J Gastroenterol 1980;74:428-432.
311. Czaja AJ, Davis GL, Ludwig J, Tashwell HF. Complete resolution of inflammatory activity following corticosteroid treatment of HBsAg-negative chronic active hepatitis. HEPATOLOGY 1984;4:622-627.
312. DePinho RA, Goldberg CS, Lefkowitch JH. Azathioprine and the liver. Evidence favoring idiosyncratic, mixed cholestatic-hepatocellular injury in humans. Gastroenterology 1984;86:162-165.
313. Tragnone A, Bazzocchi G, Aversa G, Pecorelli MG, Elmi G, Venerato S, et al. Acute pancreatitis after azathioprine treatment for ulcerative colitis. Ital J Gastroenterol 1996;28:102-104.
314. Eland IA, van Puijenbroek EP, Sturkenboom MJ, Wilson JH, Stricker BH. Drug-associated acute pancreatitis: twenty-one years of spontaneous reporting in The Netherlands. Am J Gastroenterol 1999;94: 2417-2422.
315. Bajaj JS, Saeian K, Varma RR, Franco J, Knox JF, Podoll J, et al. Increased rates of early adverse reaction to azathioprine in patients with Crohn's disease compared to autoimmune hepatitis: a tertiary referral center experience. Am J Gastroenterol 2005;100:1121-1125.
316. Ziegler TR, Fernandez-Estivariz C, Gu LH, Fried MW, Leader LM. Severe villus atrophy and chronic malabsorption induced by azathioprine. Gastroenterology 2003;124:1950-1957.
317. Read AE, Wiesner RH, LaBrecque DR, Tifft JG, Mullen KD, Sheer RL, et al. Hepatic veno-occlusive disease associated with renal transplantation and azathioprine therapy. Ann Intern Med 1986;104: 651-655.
318. Katzka DA, Saul SH, Jorkasky D, Sigal H, Reynolds JC, Soloway RD. Azathioprine and hepatic venocclusive disease in renal transplant patients. Gastroenterology 1986;90:446-454.
319. Vernier-Massouille G, Cosnes J, Lemann M, Marteau P, Reinisch W, Laharie D, et al. Nodular regenerative hyperplasia in patients with inflammatory bowel disease treated with azathioprine. Gut 2007;56: 1404-1409.
320. Czaja AJ, Carpenter HA. Thiopurine methyltransferase deficiency and azathioprine intolerance in autoimmune hepatitis. Dig Dis Sci 2006; 51:968-975.
321. Langley PG, Underhill J, Tredger JM, Norris S, McFarlane IG. Thiopurine methyltransferase phenotype and genotype in relation to azathioprine therapy in autoimmune hepatitis. J Hepatol 2002;37: 441-447.
322. Heneghan MA, Allan ML, Bornstein JD, Muir AJ, Tendler DA. Utility of thiopurine methyltransferase genotyping and phenotyping, and measurement of azathioprine metabolites in the management of patients with autoimmune hepatitis. J Hepatol 2006;45:584-591.
323. Uribe M, Chavez-Tapia NC, Mendez-Sanchez N. Pregnancy and autoimmune hepatitis. Ann Hepatol 2006;5:187-189.
324. Heneghan MA, Norris SM, O'Grady JG, Harrison PM, McFarlane IG. Management and outcome of pregnancy in autoimmune hepatitis. Gut 2001;48:97-102.
325. Candia L, Marquez J, Espinoza LR. Autoimmune hepatitis and pregnancy: a rheumatologist's dilemma. Semin Arthritis Rheum 2005;35: 49-56.
326. Aguilar HI, Burgart LJ, Geller A, Rakela J. Azathioprine-induced lymphoma manifesting as fulminant hepatic failure. Mayo Clin Proc 1997;72:643-645.
327. Johnson PJ, McFarlane IG, Williams R. Azathioprine for long-term maintenance of remission in autoimmune hepatitis. N Engl J Med 1995;333:958-963.
328. Lewis GP, Jusko WJ, Graves L, Burke CW. Prednisone side-effects and serum-protein levels. A collaborative study. Lancet 1971;2: 778-780.
329. Czaja AJ. Low-dose corticosteroid therapy after multiple relapses of severe HBsAg-negative chronic active hepatitis. HEPATOLOGY 1990;11: 1044-1049.
330. Varma RR, Michelsohn NH, Borkowf HI, Lewis JD. Pregnancy in cirrhotic and noncirrhotic portal hypertension. Obstet Gynecol 1977; 50:217-222.
331. Lee MG, Hanchard B, Donaldson EK, Charles C, Hall JS. Pregnancy in chronic active hepatitis with cirrhosis. J Trop Med Hyg 1987;90: 245-248.
332. Schramm C, Herkel J, Beuers U, Kanzler S, Galle PR, Lohse AW. Pregnancy in autoimmune hepatitis: outcome and risk factors. Am J Gastroenterol 2006;101:556-560.
333. Werner M, Bjornsson E, Prytz H, Lindgren S, Almer S, Broome U, et al. Autoimmune hepatitis among fertile women: strategies during pregnancy and breastfeeding? Scand J Gastroenterol 2007;42:986-991.
334. Whitacre CC, Reingold SC, O'Looney PA. A gender gap in autoimmunity. Science 1999;283:1277-1278.
335. Buchel E, Van Steenbergen W, Nevens F, Fevery J. Improvement of autoimmune hepatitis during pregnancy followed by flare-up after delivery. Am J Gastroenterol 2002;97:3160-3165.
336. Gisbert JP, Gonzalez-Guijarro L, Cara C, Pajares JM, Moreno-Otero R. Thiopurine methyltransferase activity in patients with autoimmune hepatitis [in Spanish]. Med Clin (Barc) 2003;121:481-484.
337. Otterness D, Szumlanski C, Lennard L, Klemetsdal B, Aarbakke J, Park-Hah JO, et al. Human thiopurine methyltransferase pharmacogenetics: gene sequence polymorphisms. Clin Pharmacol Ther 1997;62: 60-73.

338. Yates CR, Krynetski EY, Loennechen T, Fessing MY, Tai HL, Pui CH, et al. Molecular diagnosis of thiopurine S-methyltransferase deficiency: genetic basis for azathioprine and mercaptopurine intolerance. Ann Intern Med 1997;126:608-614.
339. Black AJ, McLeod HL, Capell HA, Powrie RH, Matowe LK, Pritchard SC, et al. Thiopurine methyltransferase genotype predicts therapy-limiting severe toxicity from azathioprine. Ann Intern Med 1998;129: 716-718.
340. Gisbert JP, Gomollon F, Cara C, Luna M, Gonzalez-Lama Y, Pajares JM, et al. Thiopurine methyltransferase activity in Spain: a study of 14,545 patients. Dig Dis Sci 2007;52:1262-1269.
341. Kaskas BA, Louis E, Hindorf U, Schaeffeler E, Deflandre J, Graepler F, et al. Safe treatment of thiopurine S-methyltransferase deficient Crohn's disease patients with azathioprine. Gut 2003;52:140-142.
342. Cuffari C, Dassopoulos T, Turnbough L, Thompson RE, Bayless TM. Thiopurine methyltransferase activity influences clinical response to azathioprine in inflammatory bowel disease. Clin Gastroenterol Hepatol 2004;2:410-417.
343. McLeod HL, Relling MV, Liu Q, Pui CH, Evans WE. Polymorphic thiopurine methyltransferase in erythrocytes is indicative of activity in leukemic blasts from children with acute lymphoblastic leukemia. Blood 1995;85:1897-1902.
344. Kanzler S, Gerken G, Lohr H, Galle PR, Meyer zum Buschenfelde KH, Lohse AW. Duration of immunosuppressive therapy in autoimmune hepatitis. J Hepatol 2001;34:354-355.
345. Montano-Loza AJ, Carpenter HA, Czaja AJ. Improving the end point of corticosteroid therapy in type 1 autoimmune hepatitis to reduce the frequency of relapse. Am J Gastroenterol 2007;102: 1005-1012.
346. Czaja AJ, Beaver SJ, Shiels MT. Sustained remission after corticosteroid therapy of severe hepatitis B surface antigen-negative chronic active hepatitis. Gastroenterology 1987;92:215-219.
347. Czaja AJ, Menon KV, Carpenter HA. Sustained remission after corticosteroid therapy for type 1 autoimmune hepatitis: a retrospective analysis. HEPATOLOGY 2002;35:890-897.
348. Czaja AJ, Ammon HV, Summerskill WH. Clinical features and prognosis of severe chronic active liver disease (CALD) after corticosteroid-induced remission. Gastroenterology 1980;78:518-523.
349. Czaja AJ, Wolf AM, Baggenstoss AH. Laboratory assessment of severe chronic active liver disease during and after corticosteroid therapy: correlation of serum transaminase and gamma globulin levels with histologic features. Gastroenterology 1981;80:687-692.
350. Verma S, Gunuwan B, Mendler M, Govindrajan S, Redeker A. Factors predicting relapse and poor outcome in type I autoimmune hepatitis: role of cirrhosis development, patterns of transaminases during remission and plasma cell activity in the liver biopsy. Am J Gastroenterol 2004;99:1510-1516.
351. Miyake Y, Iwasaki Y, Terada R, Takagi S, Okamaoto R, Ikeda H, et al. Persistent normalization of serum alanine aminotransferase levels improves the prognosis of type 1 autoimmune hepatitis. J Hepatol 2005;43:951-957.
352. Czaja AJ, Carpenter HA. Histological features associated with relapse after corticosteroid withdrawal in type 1 autoimmune hepatitis. Liver Int 2003;23:116-123.
353. Czaja AJ, Ludwig J, Baggenstoss AH, Wolf A. Corticosteroid-treated chronic active hepatitis in remission: uncertain prognosis of chronic persistent hepatitis. N Engl J Med 1981;304:5-9.
354. Schalm SW, Ammon HV, Summerskill WH. Failure of customary treatment in chronic active liver disease: causes and management. Ann Clin Res 1976;8:221-227.
355. Montano-Loza AJ, Carpenter HA, Czaja AJ. Features associated with treatment failure in type 1 autoimmune hepatitis and predictive value of the model of end-stage liver disease. HEPATOLOGY 2007;46: 1138-1145.
356. Tan P, Marotta P, Ghent C, Adams P. Early treatment response predicts the need for liver transplantation in autoimmune hepatitis. Liver Int 2005;25:728-733.
357. Czaja AJ, Carpenter HA. Empiric therapy of autoimmune hepatitis with mycophenolate mofetil: comparison with conventional treatment for refractory disease. J Clin Gastroenterol 2005;39:819-825.
358. Yachha SK, Srivastava A, Chetri K, Saraswat VA, Krishnani N. Autoimmune liver disease in children. J Gastroenterol Hepatol 2001;16: 674-677.
359. Squires RH Jr. Autoimmune hepatitis in children. Curr Gastroenterol Rep 2004;6:225-230.
360. Alvarez F. Treatment of autoimmune hepatitis: current and future therapies. Curr Treat Options Gastroenterol 2004;7:413-420.
361. Saadah OI, Smith AL, Hardikar W. Long-term outcome of autoimmune hepatitis in children. J Gastroenterol Hepatol 2001;16: 1297-1302.
362. Hegarty JE, Nouri Aria KT, Portmann B, Eddleston AL, Williams R. Relapse following treatment withdrawal in patients with autoimmune chronic active hepatitis. HEPATOLOGY 1983;3:685-689.
363. Montano-Loza AJ, Carpenter HA, Czaja AJ. Consequences of treatment withdrawal in type 1 autoimmune hepatitis. Liver Int 2007;27: 507-515.
364. Stellon AJ, Keating JJ, Johnson PJ, McFarlane IG, Williams R. Maintenance of remission in autoimmune chronic active hepatitis with azathioprine after corticosteroid withdrawal. HEPATOLOGY 1988;8: 781-784.
365. Luth S, Herkel J, Kanzler S, Frenzel C, Galle PR, Dienes HP, et al. Serologic markers compared with liver biopsy for monitoring disease activity in autoimmune hepatitis. J Clin Gastroenterol 2008;42: 926-930.
366. Danielson A, Prytz H. Oral budesonide for treatment of autoimmune chronic hepatitis. Aliment Pharmacol Ther 1994;8:585-590.
367. Wiegand J, Schuler A, Kanzler S, Lohse A, Beuers U, Kreisel W, et al. Budesonide in previously untreated autoimmune hepatitis. Liver Int 2005;25:927-934.
368. Manns MP, Woynarowski M, Kreisel W, Oren R, Rust C, Hultcrantz R, et al. Budesonide 3 mg bid in combination with azathioprine as maintenance treatment of autoimmune hepatitis--final results of a large multicenter international trial [Abstract]. HEPATOLOGY 2008;48: 376A-377A.
369. Manns MP, Bahr MJ, Woynarowski M, Kreisel W, Oren R, Gunther R, et al. Budesonide 3 mg tid is superior to prednisone in combination with azathioprine in the treatment of autoimmune hepatitis. J Hepatol 2008;48:S369-S370.
370. Kerkar N, Annunziato RA, Foley L, Schmeidler J, Rumbo C, Emre S, et al. Prospective analysis of nonadherence in autoimmune hepatitis: a common problem. J Pediatr Gastroenterol Nutr 2006;43:629-634.
371. Mistilis SP, Vickers CR, Darroch MH, McCarthy SW. Cyclosporin, a new treatment for autoimmune chronic active hepatitis. Med J Aust 1985;143:463-465.
372. Hyams JS, Ballow M, Leichtner AM. Cyclosporine treatment of autoimmune chronic active hepatitis. Gastroenterology 1987;93:890-893.
373. Person JL, McHutchison JG, Fong T-L, Redeker AG. A case of cyclosporine-sensitive, steroid resistant, autoimmune chronic active hepatitis. J Clin Gastroenterol 1993;17:317-320.
374. Sherman KE, Narkewicz M, Pinto PC. Cyclosporine in the management of corticosteroid-resistant type 1 autoimmune chronic active hepatitis. J Hepatol 1994;21:1040-1047.
375. Jackson LD, Song E. Cyclosporin in the treatment of corticosteroid resistant autoimmune chronic active hepatitis. Gut 1995;36:459-461.
376. Fernandez NF, Redeker AG, Vierling JM, Villamil FG, Fong T-L. Cyclosporine therapy in patients with steroid resistant autoimmune hepatitis. Am J Gastroenterol 1999;94:241-248.
377. Van Thiel DH, Wright H, Carroll P, Abu-Elmagd K, Rodriguez-Rilo H, McMichael J, et al. Tacrolimus: a potential new treatment for autoimmune chronic active hepatitis: results of an open-label preliminary trial. Am J Gastroenterol 1995;90:771-776.
378. Aqel BA, Machicao V, Rosser B, Satyanarayana R, Harnois DM, Dickson RC. Efficacy of tacrolimus in the treatment of steroid refractory autoimmune hepatitis. J Clin Gastroenterol 2004;38:805-809.

379. Larsen FS, Vainer B, Eefsen M, Bjerring PN, Adel Hansen B. Low-dose tacrolimus ameliorates liver inflammation and fibrosis in steroid refractory autoimmune hepatitis. World J Gastroenterol 2007;13: 3232-3236.
380. Czaja AJ, Carpenter HA, Lindor KD. Ursodeoxycholic acid as adjunctive therapy for problematic type 1 autoimmune hepatitis: a randomized placebo-controlled treatment trial. HEPATOLOGY 1999;30:1381-1386.
381. Czaja AJ, Lindor KD. Failure of budesonide in a pilot study of treatment-dependent autoimmune hepatitis. Gastroenterology 2000;119: 1312-1316.
382. Pratt DS, Flavin DP, Kaplan MM. The successful treatment of autoimmune hepatitis with 6-mercaptopurine after failure with azathioprine. Gastroenterology 1996;110:271-274.
383. Burak KW, Urbanski SJ, Swain MG. Successful treatment of refractory type 1 autoimmune hepatitis with methotrexate. J Hepatol 1998; 29:990-993.
384. Kanzler S, Gerken G, Dienes HP, Meyer zum Buschenfelde KH, Lohse AW. Cyclophosphamide as alternative immunosuppressive therapy for autoimmune hepatitis--report of three cases. Z Gastroenterol 1997;35:571-578.
385. Richardson PD, James PD, Ryder SD. Mycophenolate mofetil for maintenance of remission in autoimmune hepatitis in patients resistant to or intolerant of azathioprine. J Hepatol 2000;33:371-375.
386. Devlin SM, Swain MG, Urbanski SJ, Burak KW. Mycophenolate mofetil for the treatment of autoimmune hepatitis in patients refractory to standard therapy. Can J Gastroenterol 2004;18:321-326.
387. Chatur N, Ramji A, Bain VG, Ma MM, Marotta PJ, Ghent CN, et al. Transplant immunosuppressive agents in non-transplant chronic autoimmune hepatitis: the Canadian association for the study of liver (CASL) experience with mycophenolate mofetil and tacrolimus. Liver Int 2005;25:723-727.
388. Oo YH, Neuberger J. Use of mycophenolate in the treatment of autoimmune hepatitis. Liver Int 2005;25:687-691.
389. Inductivo-Yu I, Adams A, Gish RG, Wakil A, Bzowej NH, Frederick RT, et al. Mycophenolate mofetil in autoimmune hepatitis patients not responsive or intolerant to standard immunosuppressive therapy. Clin Gastroenterol Hepatol 2007;5:799-802.
390. Hlivko JT, Shiffman ML, Stravitz RT, Luketic VA, Sanyal AJ, Fuchs M, et al. A single center review of the use of mycophenolate mofetil in the treatment of autoimmune hepatitis. Clin Gastroenterol Hepatol 2008;6:1036-1040.
391. Hennes EM, Oo YH, Schramm C, Denzer U, Buggisch P, Wiegard C, et al. Mycophenolate mofetil as second line therapy in autoimmune hepatitis? Am J Gastroenterol 2008;103:3063-3070.
392. Aw MM, Dhawan A, Samyn M, Bargiota A, Mieli-Vergani G. Mycophenolate mofetil as rescue treatment for autoimmune liver disease in children: a 5-year follow-up. J Hepatol 2009;51:156-160.
393. Heneghan MA, Al-Chalabi T, McFarlane IG. Cost-effectiveness of pharmacotherapy for autoimmune hepatitis. Expert Opin Pharmacother 2006;7:145-156.
394. Wang KK, Czaja AJ. Hepatocellular carcinoma in corticosteroid-treated severe autoimmune chronic active hepatitis. HEPATOLOGY 1988; 8:1679-1683.
395. Park SZ, Nagorney DM, Czaja AJ. Hepatocellular carcinoma in autoimmune hepatitis. Dig Dis Sci 2000;45:1944-1948.
396. Montano-Loza AJ, Carpenter HA, Czaja AJ. Predictive factors for hepatocellular carcinoma in type 1 autoimmune hepatitis. Am J Gastroenterol 2008;103:1944-1951.
397. Yeoman AD, Al-Chalabi T, Karani JB, Quaglia A, Devlin J, Mieli-Vergani G, et al. Evaluation of risk factors in the development of hepatocellular carcinoma in autoimmune hepatitis: Implications for follow-up and screening. HEPATOLOGY 2008;48:863-870.
398. Zhang BH, Yang BH, Tang ZY. Randomized controlled trial of screening for hepatocellular carcinoma. J Cancer Res Clin Oncol 2004;130:417-422.
399. Bruix J, Sherman M. Management of hepatocellular carcinoma. HEPATOLOGY 2005;42:1208-1236.
400. European Liver Transplant Registry. www.eltr.org
401. Scientific Registry of Transplant Recipients. www.ustransplant.org
402. Ahmed M, Mutimer D, Hathaway M, Hubscher S, McMaster P, Elias E. Liver transplantation for autoimmune hepatitis: a 12-year experience. Transplant Proc 1997;29:496.
403. Prados E, Cuervas-Mons V, De La Mata M, Fraga E, Rimola A, Prieto M, et al. Outcome of autoimmune hepatitis after liver transplantation. Transplantation 1998;66:1645-1650.
404. Vogel A, Heinrich E, Bahr MJ, Rifai K, Flemming P, Melter M, et al. Long-term outcome of liver transplantation for autoimmune hepatitis. Clin Transplant 2004;18:62-69.
405. Milkiewicz P, Hubscher SG, Skiba G, Hathaway M, Elias E. Recurrence of autoimmune hepatitis after liver transplantation. Transplantation 1999;68:253-256.
406. Devlin J, Donaldson P, Portmann B, Heaton N, Tan KC, Williams R. Recurrence of autoimmune hepatitis following liver transplantation. Liver Transpl Surg 1995;1:162-165.
407. Birnbaum AH, Benkov KJ, Pittman NS, McFarlane-Ferreira Y, Rosh JR, LeLeiko NS. Recurrence of autoimmune hepatitis in children after liver transplantation. J Pediatr Gastroenterol Nutr 1997;25:20-25.
408. Götz G, Neuhaus R, Bechstein WO, Lobeck H, Berg T, Hopf U, et al. Recurrence of autoimmune hepatitis after liver transplantation. Transplant Proc 1999;31:430-431.
409. Czaja AJ. Autoimmune hepatitis after liver transplantation and other lessons of self-intolerance. Liver Transpl 2002;8:505-513.
410. Demetris AJ, Adeyi O, Bellamy CO, Clouston A, Charlotte F, Czaja A, et al. Liver biopsy interpretation for causes of late liver allograft dysfunction. HEPATOLOGY 2006;44:489-501.
411. Ratziu V, Samuel D, Sebagh M, Farges O, Saliba F, Ichai P, et al. Long-term follow-up after liver transplantation for autoimmune hepatitis: evidence of recurrence of primary disease. J Hepatol 1999;30: 131-141.
412. Manns MP, Bahr MJ. Recurrent autoimmune hepatitis after liver transplantation – when non-self becomes self. HEPATOLOGY 2000;32:868-870.
413. Kotlyar DS, Campbell MS, Reddy KR. Recurrence of diseases following orthotopic liver transplantation. Am J Gastroenterol 2006;101: 1370-1378.
414. Duclos-Vallee JC, Sebagh M, Rifai K, Johanet C, Ballot E, Guettier C, et al. A 10 year follow up study of patients transplanted for autoimmune hepatitis: histological recurrence precedes clinical and biochemical recurrence. Gut 2003;52:893-897.
415. Faust TW. Recurrent primary biliary cirrhosis, primary sclerosing cholangitis, and autoimmune hepatitis after transplantation. Liver Transpl 2001;7:S99-S108.
416. Neuberger J, Portmann B, Calne R, Williams R. Recurrence of autoimmune chronic active hepatitis following orthotopic liver grafting. Transplantation 1984;37:363-365.
417. Wright HL, Bou-Abboud CF, Hassanenstein T, Block GD, Demetris AJ, Starzi TE, et al. Disease recurrence and rejection following liver transplantation for autoimmune chronic active liver disease. Transplantation 1992;53:136-139.
418. Neuberger J. Recurrence of primary biliary cirrhosis, primary sclerosing cholangitis, and autoimmune hepatitis. Liver Transpl Surg 1995;1: 109-115.
419. Gonzalez-Koch A, Czaja AJ, Carpenter HA, Roberts SK, Charlton MR, Porayko MK, et al. Recurrent autoimmune hepatitis after orthotopic liver transplantation. Liver Transpl 2001;7:302-310.
420. Hubscher SG. Recurrent autoimmune hepatitis after liver transplantation: diagnostic criteria, risk factors, and outcome. Liver Transpl 2001;7:285-291.
421. Reich DJ, Fiel I, Guarrera JV, Emre S, Guy SR, Schwartz ME, et al. Liver transplantation for autoimmune hepatitis. HEPATOLOGY 2000;32: 693-700.
422. Hurtova M, Duclos-Vallee JC, Johanet C, Emile JF, Roque-Afonso AM, Feray C, et al. Successful tacrolimus therapy for a severe recurrence of type 1 autoimmune hepatitis in a liver graft recipient. Liver Transpl 2001;7:556-558.

423. Kerkar N, Dugan C, Rumbo C, Morotti RA, Gondolesi G, Shneider BL, et al. Rapamycin successfully treats post-transplant autoimmune hepatitis. Am J Transplant 2005;5:1085-1089.
424. Kerkar N, Hadzic N, Davies ET, Portmann B, Donaldson PT, Rela M, et al. De-novo autoimmune hepatitis after liver transplantation. Lancet 1998;351:409-413.
425. Jones DE, James OF, Portmann B, Burt AD, Williams R, Hudson M. Development of autoimmune hepatitis following liver transplantation for primary biliary cirrhosis. HEPATOLOGY 1999;30:53-57.
426. Heneghan MA, Portmann BC, Norris SM, Williams R, Muiesan P, Rela M, et al. Graft dysfunction mimicking autoimmune hepatitis following liver transplantation in adults. HEPATOLOGY 2001;34:464-470.
427. Gupta P, Hart J, Millis JM, Cronin D, Brady L. De novo hepatitis with autoimmune antibodies and atypical histology: a rare cause of late graft dysfunction after pediatric liver transplantation. Transplantation 2001;71:664-668.
428. Hernandez HM, Kovarik P, Whitington PF, Alonso EM. Autoimmune hepatitis as a late complication of liver transplantation. J Pediatr Gastroenterol Nutr 2001;32:131-136.
429. Spada M, Bertani A, Sonzogni A, Petz W, Riva S, Torre G, et al. A cause of late graft dysfunction after liver transplantation in children: de-novo autoimmune hepatitis. Transplant Proc 2001;33:1747-1748.
430. Tamaro G, Sonzogni A, Torre G. Monitoring "de novo" autoimmune hepatitis (LKM positive) by serum type-IV collagen after liver transplant: a paediatric case. Clin Chim Acta 2001;310:25-29.
431. Tan CK, Sian Ho JM. Concurrent de novo autoimmune hepatitis and recurrence of primary biliary cirrhosis post-liver transplantation. Liver Transpl 2001;7:461-465.
432. Tsuji H, Hiramatsu K, Minato H, Kaneko S, Nakanuma Y. Auxiliary partial orthotopic liver transplantation with de novo autoimmune hepatitis in the allograft and leftover primary biliary cirrhosis in the native liver. Semin Liver Dis 2005;25:371-377.
433. Inui A, Sogo T, Komatsu H, Miyakawa H, Fujisawa T. Antibodies against cytokeratin 8/18 in a patient with de novo autoimmune hepatitis after living-donor liver transplantation. Liver Transpl 2005;11:504-507.
434. Keaveny AP, Gordon FD, Khettry U. Post-liver transplantation de novo hepatitis with overlap features. Pathol Int 2005;55:660-664.
435. Venick RS, McDiarmid SV, Farmer DG, Gornbein J, Martin MG, Vargas JH, et al. Rejection and steroid dependence: unique risk factors in the development of pediatric posttransplant de novo autoimmune hepatitis. Am J Transplant 2007;7:955-963.
436. Demetris AJ, Sebagh M. Plasma cell hepatitis in liver allografts: Variant of rejection or autoimmune hepatitis? Liver Transpl 2008;14:750-755.
437. Salcedo M, Vaquero J, Banares R, Rodriguez-Mahou M, Alvarez E, Vicario JL, et al. Response to steroids in de novo autoimmune hepatitis after liver transplantation. HEPATOLOGY 2002;35:349-356.
438. Neuberger J. Transplantation for autoimmune hepatitis. Semin Liver Dis 2002;22:379-386.
439. Ayata G, Gordon FD, Lewis WD, Pomfret E, Pomposelli JJ, Jenkins RL, et al. Liver transplantation for autoimmune hepatitis: a long-term pathologic study. HEPATOLOGY 2000;32:185-192.
440. Andries S, Casamayou L, Sempoux C, Burlet M, Reding R, Bernard Otte J, et al. Posttransplant immune hepatitis in pediatric liver transplant recipients: incidence and maintenance therapy with azathioprine. Transplantation 2001;72:267-272.
441. Petz W, Sonzogni A, Bertani A, Spada M, Lucianetti A, Colledan M, et al. A cause of late graft dysfunction after pediatric liver transplantation: de novo autoimmune hepatitis. Transplant Proc 2002;34:1958-1959.