DIAGNOSIS AND MANAGEMENT OF AUTOIMMUNE HEPATITIS IN ADULTS AND CHILDREN: 2019 PRACTICE GUIDANCE AND GUIDELINES FROM THE AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

Cara L. Mack,[1] David Adams,[2] David N. Assis,[3] Nanda Kerkar,[4] Michael P. Manns,[5] Marlyn J. Mayo,[6] John M. Vierling,[7] Mouaz Alsawas,[8] Mohammad H. Murad,[8] Albert J. Czaja[8]

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1 University of Colorado School of Medicine, Children's Hospital Colorado

2 NIHR Biomedical Research Centre, Queen Elizabeth Hospital and University of Birmingham

3 Yale School of Medicine

4 University of Rochester

5 Hannover Medical School

6 University of Texas Southwestern Medical Center

7 Baylor College of Medicine

8 Mayo Clinic, Rochester, MN

PURPOSE AND SCOPE

The objectives of this document are to provide guidance in the diagnosis and management of autoimmune hepatitis (AIH) based on current evidence and expert opinion, and to present guidelines to clinically relevant questions based on systematic reviews of the literature and the quality of evidence (1). This practice guideline/guidance constitutes an update of the guidelines on AIH published in 2010 by the American Association for the Study of Liver Diseases (AASLD) (2). It updates the epidemiology, diagnosis, management, and outcomes of AIH in adults and children.

The document is divided into "Guideline recommendations" and "Guidance statements". Guideline recommendations were based on evidence derived from systematic reviews of the medical literature and supported, if appropriate, by meta-analyses. The systematic reviews and meta-analyses were conducted independently by the Mayo Clinic Evidence-Based Practice Center. Findings were analyzed and interpreted by a multi-disciplinary panel of experts, including both content and methodology experts, who rated the quality of evidence and determined the strength of each recommendation. The quality of clinical evidence was determined by its source (e.g. randomized controlled trial or observational study), and the strength of the recommendation was determined by assessing the quality of evidence, balance of benefits and harms, patient values and preferences, and utilization of resources and costs. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system was used to categorize each recommendation as strong or conditional (Table 1) (3, 4). Details of the methodology, systematic reviews, and meta-analyses are published separately. The Guideline recommendations focus on pertinent management issues for which sufficient evidence was available to render a recommendation. They address glucocorticoid and azathioprine

management as initial therapy and conventional therapy, second-line medications after failure of conventional therapy and maintenance management after liver transplantation [see Supplementary Table 1 for PICO questions (patient/ intervention/ comparison/ outcomes) related to systematic reviews].

"Guidance statements" were developed by consensus of an expert panel based on formal review and analysis of the published literature on the topic. The quality (level) of evidence and the strength of each guidance statement were not formally rated for the guidance statements. The "Guidance statements" were used to address topics for which a sufficient number of randomized controlled trials were not available to justify a systematic review and meta-analysis. The "Guidance statements" and "Guideline recommendations" were also reviewed by members of the AIH Association, a 501(c)(3) non-profit organization, in order to incorporate patient and public perspectives. The "Guidance statements" and "Guideline recommendations are intended to provide health care practitioners with updated information and rigorously assessed, evidence-based recommendations. They are intended to aid, not supersede, clinical judgment. For ease of reading this AIH guidance/ guidelines document, a glossary of definitions is provided in Table 2.

INTRODUCTION

Autoimmune hepatitis is an immune-mediated inflammatory liver disease of uncertain cause which affects all ages, both genders, and all ethnicities. Patients may be asymptomatic, chronically ill, or present with acute liver failure, and the diagnosis must be considered in all patients with acute or chronic liver inflammation, including patients with graft dysfunction after liver transplantation. Autoimmune hepatitis does not have a signature diagnostic feature, and the diagnosis requires the presence of a constellation of typical features which can vary between patients with the same disease and can occur in other liver diseases. Progression to advanced

hepatic fibrosis, cirrhosis, death from liver failure or liver transplantation are possible outcomes. Treatment with immunosuppressive agents has been life-saving, but management regimens may be long-term, associated with serious side effects, and variably effective.

BACKGROUND

Epidemiology

AIH occurs at all ages and within all ethnic groups, and its manifestations appear to vary by race and ethnicity. Alaskan natives have a high frequency of icteric AIH at presentation; Hispanics more commonly present with cirrhosis; and African-Americans have accelerated progression of disease and a higher rate of recurrence after liver transplantation (LT) compared to other races (5, 6). Female predominance occurs in adults (71-95% women) (7-12) and children (60-76% girls) (13-16). Early epidemiological reports suggested that the onset of AIH had age peaks at 10-30 years and 40-60 years, but the findings may have been influenced by referral bias (17-19). Older peak ages at onset (>60 years) have been reported in Denmark (11), and New Zealand (10).

The estimated incidence of AIH varies worldwide depending on the region and the age of onset. Incidence rates in adults range from 0.67 (southern Israel) to 2 cases per 100,000 person-years (Canterbury region of New Zealand) (10, 17, 20). Pediatric incidences are lower, ranging from 0.23 (Canada) (16) to 0.4 per 100,000 person-years (United States) (15). Over the past few decades there has been a near 50% increase in incidence in Spain, Denmark, Sweden, and the Netherlands (11, 12, 17, 21-23). The prevalence of AIH in adults ranges from 4 (Singapore) to 42.9 (Alaska natives) per 100,000 persons (17, 24, 25). The prevalence in children ranges from 2.4 (non-native Canadian children) (26) and 3 per 100, 000 persons (United States) (15) to 9.9 per 100,000 persons (native Canadian children) (17, 26).

Genetic Predispositions

In common with other autoimmune diseases, the primary genetic associations in AIH involve major histocompatibility complex loci. HLA-associations cluster within the conserved 8.1 ancestral haplotype which defines the alleles carried by most Caucasians (27) and results from linkage disequilibrium within HLA class I, II and III loci: *HLA-A1,* Cw7, B8, *TNFAB*a2b3*, *TNFN*S*, *C2*C*, *Bf*s*, *C4A*Q0*, *C4B*1*, *DRB1*03:01*, *DRB1*04:01*, *DRB1*13:01*, *DRB3*01:01*, *DQA1*05:01*, *DQB1*02:01* (28-32). *HLA-DRB1*03:01* haplotypes associated with AIH are the result of additional, genetic re-combinations.

AIH also has non-HLA genetic associations, but the odds ratios for risk of AIH are far lower than those for HLA alleles. Susceptibility for AIH has been associated with genetic polymorphisms encoding cytotoxic T lymphocyte antigen-4 (CTLA-4) (33), tumor necrosis factor-alpha (TNF-α) (34, 35), Fas (CD95 or apoptosis antigen-1 [APO-1]) (36, 37), vitamin D receptor (VDR) (38, 39), signal transducer and activator of transcription 4 (STAT4) (40), transforming growth factor-beta 1 (TGF-β1) (41), macrophage migration inhibitory factor (MIF) (42), SH2B adapter protein 3 (SH2B3) (43), caspase recruitment domain family member 10 (CARD10) (43), and the interleukin (IL)-23 receptor (44). Dysfunctional products of genetic variants or deficient levels of gene product may disrupt homeostatic mechanisms that affect the proliferation and survival of autoreactive T and B cells, regulate cytokine production, and modulate inflammatory and immune responses.

AIH is a complex genetic disease that requires interplay among genetic, epigenetic, immunologic and environmental factors. A rare exception is AIH associated with an autosomal recessive mutation in the *autoimmune regulator* (*AIRE*) gene on chromosome 21q22.3 which has been associated with autoimmune polyglandular syndrome type 1 (APS-1) (45). Environmental exposures play greater roles than genetics in shaping the immune repertoire, and specific

environmental factors, such as viral infections or xenobiotic exposures, can act as environmental triggers for loss of self-tolerance to autoantigens in persons genetically susceptible to AIH (46, 47).

Pathogenesis

Autoreactive CD4 and CD8 T cells break self-tolerance to hepatic autoantigens as the result of environmental triggers and inability of autoantigen-specific natural T regulatory (nTregs) and inducible T regulatory (iTregs) cells to prevent autoreactivity (48-50) (Figure 1). Concurrently, in the absence of effective B regulatory (Breg) inhibition, autoreactive B cells produce autoantibodies (51). Peptide autoantigens are presented by class II and class I HLA alleles to autoreactive T cell receptors on CD4 T helper (Th) cells and CD8 cytotoxic T lymphocytes (CTLs), respectively. Binding of different autoantigens to B cell receptors initiates secretion of specific autoantibodies.

The composition of the local cytokine milieu dictates CD4 Th cells to differentiate into Th1, Th2, Th9, Th17, iTregs, and T follicular helper (Tfh) cell subsets in the presence of co-stimulatory signaling (50). CD4 Th1 cells secrete cytokines that promote proliferation of autoantigen-specific CD8 CTLs and activation of macrophages. CD4 Th2 cytokines augment immunoglobulin production by B cells, while cytokines produced by Tfh cells induce their conversion to IgG-secreting plasma cells. CD4 Th17 cells intensify inflammation and tissue injury.

Autoantigen-specific iTregs can downregulate the proliferation and functions of all CD4 Th subtypes, and inadequate numbers and/or dysfunction of CD4 iTregs may play a key role in AIH (52, 53). Cytokine mediated transformation of CD4 iTregs into pathogenic CD4 Th17 cells also promotes perpetuation of AIH. Low doses of IL-2 preferentially stimulate proliferation and

function of CD4 iTregs, while high doses promote production of other pathogenic CD4 Th subsets.

Mucosal invariant T (MAIT) cells that react with bacterially processed vitamin B antigens presented by MHC class I-related molecules congregate in the peri-biliary region in AIH (54). MAIT cells can express characteristics of CD4 Th1 and Th17 cells, and they may transform CD4 iTregs into pro-inflammatory CD4 Th17 cells. Inflammatory infiltrates composed of CD4 Th subsets, CD8 CTLs, MAIT cells, B cells, plasma cells and innate immune cells, including NK and NKT cells and activated macrophages, can accumulate within the portal tracts.

Adhesion molecules and chemokines mediate trans-endothelial migration of immune cells into tissues (50, 55). Extension of inflammation into periportal hepatocytes (interface hepatitis) and lobular hepatitis causes apoptosis of hepatocytes and fibrogenesis in untreated patients with AIH. Uptake and processing of immune complexes of autoantigen and immunoglobulin by antigen-presenting cells greatly increases activation of autoantigen-specific CD8 CTLs, and autoantibodies may enhance CD8 CTL cytotoxicity of hepatocytes.

DIAGNOSIS

Diagnostic Requisites and Subtypes

The diagnosis of AIH is based on histological abnormalities (interface hepatitis), characteristic clinical and laboratory findings (elevated serum aspartate [AST] and alanine [ALT] aminotransferase levels and increased serum immunoglobulin G [IgG] concentration) and the presence of one or more characteristic autoantibodies (2, 56). Autoimmune hepatitis lacks a signature diagnostic marker, and the diagnosis requires characteristic features and the exclusion

of other diseases that may resemble it (e.g. viral hepatitis, drug-induced liver injury, Wilson disease, hereditary hemochromatosis) (56).

There are two types of AIH based on the specific autoantibodies that are present. Type 1 is characterized by antinuclear antibodies (ANA) and/or smooth muscle antibodies (SMA)/anti-actin antibodies, and type 2 is characterized by antibodies to liver kidney microsome type 1 (anti-LKM1), usually in the absence of ANA and SMA (57). The characteristic clinical features of these two types are presented in Table 3. In addition, up to 20% of AIH cases are negative for ANA, SMA and LKM1 autoantibodies, despite the presence of other characteristic features of AIH (seronegative AIH). If seronegative AIH is suspected, other autoantibodies may be sought, as indicated in Table 4 and Figure 2. Classification of AIH into types assists in management and aids in predicting outcomes in children, but it may be less informative in adults (58-60).

Autoantibodies

ANA, SMA, and anti-LKM1 constitute the conventional serological repertoire for the diagnosis of AIH (Table 4) (2, 60). ANA are detected in 80% of white North American adults with AIH at presentation; SMA are present in 63%; and anti-LKM1 are present in 3% (61). Forty-nine percent of patients with AIH have ANA, SMA, or anti-LKM1 as an isolated serological finding at presentation, and 51% have multiple autoantibodies (61). ANA can also occur as an isolated serological finding in PSC (29%), chronic hepatitis C (26%) chronic hepatitis B (32%), non-alcoholic fatty liver disease (NAFLD) (34%), and chronic alcoholic liver disease (21%), and SMA can occur as an isolated serological finding in PSC (6%), chronic hepatitis C (6%), and chronic alcoholic liver disease (4%). ANA and SMA are concurrent in <10% of liver diseases outside of AIH, and the diagnostic accuracy for AIH improves from ~58% to 74% if two autoantibodies are detected at presentation (61).

Anti-LKM1 are commonly detected in the absence of ANA and SMA, and this observation has justified their assessment after first testing for ANA and SMA (57) (Figure 2). Furthermore, anti-LKM1 have a low sensitivity for AIH in North American adults (1%) (61), and their assessment after first demonstrating the absence of ANA and SMA is appropriate in these patients. Anti-LKM1 are detected in 13-38% of British and Canadian children with AIH (13, 16, 62), and determinations of ANA, SMA and anti-LKM1 are usually made together at presentation. Autoantibody titers in adults and children roughly reflect disease severity and treatment response (63, 64), but they are not established biomarkers of disease activity or treatment outcome (63).

Anti-SLA are present in 7-22% of patients with type 1 AIH, and they have high specificity (99%) for the diagnosis (65-71) (Table 4). Anti-SLA have been the sole markers of AIH in 14-20% of patients (65, 67, 68), and they have been associated with severe disease and relapse after drug withdrawal (68, 70, 72-74). Atypical p-ANCA are frequently present in patients with type 1 AIH (50-92%) (75-77), but they lack diagnostic specificity, occurring in primary sclerosing cholangitis (PSC), AIH-PSC overlap syndrome, ulcerative colitis and minocycline-related liver injury (76, 78). Occasionally atypical p-ANCA may be the only autoantibodies detected (56, 79, 80).

Antibodies against filamentous (F) actin (anti-actin) are a subset of SMA, and they are present in 86-100% of patients with AIH and SMA (81-83) (Table 4). Antibody to alpha-actinin (anti-α-actinin) is an investigational marker that is present in 42% of patients with AIH and 66% of patients with anti-actin (84). Dual reactivity to anti-actin and anti-α-actinin has been associated with severe acute AIH, incomplete treatment response, and relapse (84-86).

Antibodies to liver cytosol type 1 (anti-LC1) are present in 32% of patients with anti-LKM1 (87), and they occur mainly in children with severe liver disease (87, 88) (Table 4).

Antibodies to liver kidney microsome type 3 (anti-LKM-3) are present in 17% of patients with type 2 AIH (89) and may be useful in evaluating otherwise seronegative patients (90-93). Anti-LC1 and anti-LKM3 have not been rigorously assessed in the United States (94).

Antibody determinations should be selective and consistent with the clinical phenotype being assessed. Additional serological markers may be sought depending on results of the earlier tests and in accordance with the evolving diagnostic possibilities (Figure 2).

Histological Findings

The diagnosis of AIH cannot be made without liver biopsy and compatible histological findings. Interface hepatitis is the histological hallmark of AIH, accompanied by plasma cell infiltration in 66% and lobular hepatitis in 47% (95). Centrilobular necrosis is also found in 29% (96-100), and it occurs with similar frequency in patients with and without cirrhosis (99). Emperipolesis is the penetration of one intact cell into another intact cell with both cells retaining viability (as opposed to phagocytosis) (101, 102). Emperipolesis is present in 65% of patients with AIH, and hepatocyte rosettes are present in 33% (103) (Figure 3). None of the individual histological findings is specific for AIH, but the findings of interface hepatitis with portal lymphocytic or lymphoplasmacytic cells extending into the lobule, emperipolesis, and rosettes are considered typical of AIH (103).

Cirrhosis is present in 28-33% of adults at presentation, especially in the elderly (9, 104-107), as well as in 38% of children (13, 108). Cirrhosis develops in 40% of adults with multi-lobular necrosis or bridging necrosis (105, 109, 110). The histological examination at presentation is essential to exclude alternative or concurrent diagnoses, grade the severity of inflammatory activity, and indicate the stage of fibrosis (111-114). IgG4-positive plasma cells may be present in some patients with AIH (115-117), but the clinical impact of this finding remains unclear. Histological findings of NAFLD/non-alcoholic steatohepatitis (NASH) are present in 17-30% of

patients with AIH (118, 119), and liver tissue examination may identify patients with AIH and NASH that are at increased risk of liver-related mortality (RR, 7.65) and adverse outcome (RR, 2.55) (118).

The histological features of AIH with acute liver failure predominate in the centrilobular zone, and consist of 4 principal features (100). Central perivenulitis is present in 65%; plasma cell-enriched inflammatory infiltrate in 63%; massive hepatic necrosis in 42%; and lymphoid follicles in 32%. Sixty-six percent of patients with acute liver failure will have two (21%), three (26%), or all four (19%) of these features (100).

Diagnostic Scoring Systems

The diagnostic scoring system of the International Autoimmune Hepatitis Group (IAIHG) was created by an international panel in 1993 (120), revised in 1999 (56), and simplified in 2008 (121) (Supplemental Table 2). The original revised scoring system has greater sensitivity for AIH compared to the simplified scoring system (100% vs 95%), whereas the simplified scoring system has superior specificity (90% vs 73%) and accuracy (92% vs 82%), using clinical judgment as the gold standard (122). The revised diagnostic scoring system is preferable for patients with complex or unusual features, whereas the simplified scoring system is most accurate for typical patients (122).

Reassessment of patients with the revised scoring system should be considered whenever the simplified system yields a low score. In children, a meta-analysis of 4 studies pertaining to the accuracy of the simplified criteria revealed a sensitivity of 77% and a specificity of 95% (123). In that study, false negative scores (~17%) were associated with seronegative AIH.

The revised original diagnostic scoring system can be applied to children and accepts lower autoantibody titers than in adults as having diagnostic significance (56). Substitution of

the serum gamma glutamyl transferase (GGT) level for the serum alkaline phosphatase level in the ratio with the serum ALT or AST level may improve the specificity of the revised original scoring system for children by indicating the likelihood of biliary disease (124).

Limitations to the revised original and simplified scoring systems include: 1. Lack of validation by prospective studies; 2. Lack of accuracy in the setting of concurrent PSC, primary biliary cholangitis (PBC), NAFLD/ NASH, liver transplantation (LT), or fulminant liver failure (125, 126); 3. Failure to include other serological markers, such as anti-SLA (56, 121); 4. Dependence on autoantibody determinations by indirect immunofluorescence (titers) rather than by enzyme-linked immunoassay (units) (127). Diagnostic scoring systems can aid in establishing a diagnosis of AIH in challenging cases, but they are most useful in defining cohorts of patients with AIH for clinical studies (56).

GUIDANCE STATEMENTS

- **The diagnosis of AIH requires compatible *histological findings* and is further supported by the following features: A. *elevated serum aminotransaminase levels*; B. elevated serum IgG level and/or positive *serological marker(s)*; C. *exclusion* of viral, hereditary, metabolic, cholestatic, and drug-induced diseases that may resemble AIH.**
- **Initial serological testing should include determinations of ANA and SMA in adults and ANA, SMA, and anti-LKM1 in children; consider additional autoantibody tests if warranted to secure the diagnosis.**
- **Diagnostically challenging cases should be reviewed by or referred to an experienced liver center prior to initiating therapy.**

CLINICAL MANIFESTATIONS

Presentations

Symptomatic

Most patients with AIH present after the development of chronic non-specific symptoms (fatigue, malaise, arthralgias, or amenorrhea). Easy fatigability is the main complaint in 85% of patients, and jaundice may be present (128). Symptoms of pruritus or hyperpigmentation are inconsistent with the diagnosis (56), and weight loss suggests a serious complication (malignancy). Physical signs are usually absent, apart from signs of advanced chronic liver disease (spider nevi, caput medusa, splenomegaly, ascites, palmar erythema) or manifestations of extrahepatic autoimmune disease (vitiligo, inflammatory bowel disease [IBD]) (129).

Asymptomatic

AIH is asymptomatic in 25-34% of patients (60, 104, 130). Asymptomatic patients infrequently achieve spontaneous laboratory improvement (12%) (131), may have histological findings similar to those of symptomatic patients (130), frequently develop symptoms within 2-120 months (mean interval, 32 months) (26-70%) (104, 130), and experience a 10-year survival that is less than that of treated patients with more severe disease (67% versus 98%) (131). The absence of symptoms should not discourage treatment (130-132).

Acute severe hepatitis and acute liver failure

AIH presents with an acute onset (duration, <30 days) in 25-75% of patients (133-136). Acute liver failure (ALF) associated with hepatic encephalopathy occurs in 3-6% of North American and European patients (100, 137) (see definitions in Table 2). Spontaneous exacerbation or a superimposed viral, toxic, or drug-induced liver injury on previously undiscovered AIH (acute on chronic liver disease) must be excluded (138, 139). ANA are absent or weakly positive in 29-39% of patients with acute severe AIH, and the serum IgG level is

normal in 25-39% (140, 141). Histological assessment is a key diagnostic test (141). Lobular hepatitis, lymphoplasmacytic infiltrate, and interface hepatitis support the diagnosis of acute AIH, and similar features in the presence of cirrhosis suggest exacerbated chronic disease (138). Central perivenulitis, lymphoplasmacytic infiltrate, lymphoid follicles, and massive hepatic necrosis can be found in AIH with acute liver failure (100). Unenhanced computed tomography (CT) demonstrates heterogeneous hypoattenuated regions within the liver in 65% of patients with acute severe AIH and may be disease-specific (142).

Autoantibody-negative hepatitis

ANA, SMA, and anti-LKM1 are absent in 19-34% of North American and German patients originally diagnosed as cryptogenic hepatitis and then re-classified as AIH by the revised original diagnostic scoring system (143, 144). Lower frequencies of autoantibody-negative AIH have been reported in other ethnicities (145) and by other diagnostic criteria, including clinical judgment and glucocorticoid-responsiveness (146, 147). ANA and SMA may be expressed later in the course of the disease (63), or the demonstration of SLA and atypical pANCA may direct the diagnosis to AIH (148) (Figure 2).

GUIDANCE STATEMENT

- **The diagnosis of AIH must be considered in all patients presenting with acute or chronic liver disease, including patients with asymptomatic liver test abnormalities, acute liver failure, and autoantibody-negative hepatitis.**

Concurrent immune diseases

Concurrent autoimmune diseases are present in 14-44% of patients with AIH (129, 149-152), and they have been recognized with similar frequencies in patients with type 1 and type 2 disease (149). Autoimmune thyroid disease has been the most common concurrent autoimmune disease in type 1 AIH (10-18%) (129, 150-152), whereas type 1 diabetes (153), autoimmune

thyroid disease (153), and autoimmune skin diseases (vitiligo, leucocytoclastic vasculitis, urticaria, alopecia areata) have been most common in type 2 AIH (152).

Patients with concurrent immune disease are commonly asymptomatic or have mild symptoms (129), but in rare instances, the severity of the concurrent disease may obscure the underlying liver disease (129). In 10-15% of children with APS-1, AIH may accompany at least two of the three components of the syndrome (muco-cutaneous candidiasis, hypoparathyroidism, and adrenocortical insufficiency) (154, 155).

Extrahepatic autoimmune disease occurs most frequently in women (152) and the type varies by age group (156). Patients aged ≥60 years have autoimmune thyroid and rheumatic diseases more commonly than adults ≤30 years (42% versus 13%), whereas young adults more often have inflammatory bowel disease (IBD) and autoimmune hemolytic anemia (13% versus 0%) (156). Furthermore, concurrent autoimmune disease is more common in patients with HLA DRB1*04:01 (156-158) or a family history of autoimmune disease in first-degree relatives (152, 159).

The frequency of celiac disease in patients with AIH is higher than in the general population (2.8-3.5%) (160, 161). Among Italian children with AIH, celiac disease was present in 16% (162). Both laboratory and serological features associated with celiac disease can be confused with AIH, and concurrent celiac disease may contribute to the degree of liver dysfunction in AIH (160, 161, 163-167). Pediatric patients with AIH and celiac disease who avoided gluten had higher frequencies of sustained remission after withdrawal of glucocorticoids than AIH children without celiac disease (33% versus 8%) (166).

GUIDANCE STATEMENTS

- **AIH patients should be screened for celiac and thyroid diseases at diagnosis.**

- **AIH patients should be assessed for rheumatoid arthritis, IBD, autoimmune hemolytic anemia, diabetes, and other extrahepatic autoimmune diseases based on symptomatology and medical provider concern.**

Overlap Syndromes or Cholestatic Variants

Overlap syndromes between AIH and PBC or PSC are clinical descriptions and not validated pathological entities (126, 168-173). Their major clinical value is to identify individuals who may not respond to conventional treatment for AIH (173-176).

AIH-PBC overlap syndrome

The "Paris criteria" identify patients with overlapping features of AIH and PBC (177). Two of the following three criteria for PBC should be met: 1. Serum alkaline phosphatase level (ALP) ≥2-fold the upper limit of normal range (ULN) or serum GGT level ≥5-fold ULN; 2. Presence of antimitochondrial antibodies (AMA); 3. Florid bile duct lesions on histological examination (126, 178, 179). Criteria for AIH in setting of PBC (in addition to the presence of interface hepatitis) are: 1. Serum ALT level ≥5-fold ULN; 2. Serum IgG level ≥2-fold ULN or presence of SMA (126, 177, 180). A single-center comparison of the "Paris criteria" and the AIH scoring systems found that the "Paris criteria" were more reliable (sensitivity, 92%; specificity, 97%) (181). Importantly, the "Paris Criteria" may not capture all patients with the AIH-PBC overlap syndrome who have less pronounced cholestatic laboratory features (173, 175, 182).

The International Autoimmune Hepatitis Group (IAIHG) has emphasized that the criteria for the diagnosis of AIH-PBC has not been independently validated and that it is difficult to interpret the reported high sensitivity and specificity of the "Paris criteria" (126). They have also emphasized that the diagnostic scoring systems for AIH were not developed or validated for the diagnosis of the overlap syndromes and that they should not be used for this purpose (126).

Antibodies to pyruvate dehydrogenase-E2 (AMA) are present in 8-12% of patients with AIH in the absence of histological features of bile duct injury or loss (65, 183). These patients respond well to glucocorticoid therapy, and they do not evolve into PBC (183). Liver tissue examination is required to exclude the AIH-PBC overlap syndrome, and the presence of AMA in patients with AIH is insufficient to make this diagnosis.

AIH-PSC overlap syndrome

Criteria for the diagnosis of AIH-PSC overlap syndrome [also known as autoimmune sclerosing cholangitis (ASC) in children (108)] include the presence of typical features of AIH, absence of AMA, and evidence of large duct PSC by endoscopic or magnetic resonance cholangiography, or evidence of small duct PSC based on "onion skinning" periductal fibrosis on histology (173). Chronic ulcerative colitis (UC) is present in 16% of adults with AIH, and 42% of patients with AIH and concurrent UC have cholangiographic changes of PSC (184). Ulcerative colitis is present in 20% of children with AIH, and it affects up to 45% with AIH-PSC overlap syndrome (108). Patients with cholestatic laboratory abnormalities, absence of AMA, histological features compatible with PSC or PBC, and normal cholangiograms may have small duct PSC (185) or AMA-negative PBC, respectively (186). The diagnosis of AIH-PSC overlap syndrome should be considered in all patients with AIH and chronic UC, unexplained cholestatic laboratory findings, or nonresponse to conventional glucocorticoid therapy (173).

GUIDANCE STATEMENTS

- **Patients with AIH, cholestatic laboratory/histological findings consistent with PBC, and a positive AMA should be considered to have AIH-PBC overlap syndrome.**
- **Patients with AIH, cholestatic laboratory findings, histological features of bile duct injury or loss, and concurrent chronic ulcerative colitis should be evaluated for large**

duct PSC by cholangiography to determine whether they have the AIH-PSC overlap syndrome.

- **The "Paris criteria" can aid in diagnosing the AIH-PBC overlap syndrome, but the criteria may exclude patients with AIH-PBC who have less severe cholestatic features.**
- **Neither the revised nor simplified IAIHG diagnostic scoring systems for AIH should be used for assessing overlap syndromes.**

Drug-Induced Autoimmune Hepatitis-like Injury

Drug-induced liver injury can mimic AIH (187-191), and an unpredictable idiosyncratic or hypersensitivity drug reaction has been implicated in 2-17% of patients with classical features of AIH (187, 189, 191). Minocycline (187, 192-198), nitrofurantoin (187, 199-205), and infliximab (206-221) have been most commonly incriminated, and multiple other agents have been implicated (Table 5). Immune-related adverse events (irAEs), including hepatitis, have been reported with the use of immune activating agents, such as the checkpoint inhibitors (222-224). The liver injuries associated with the checkpoint inhibitors have usually improved with glucocorticoid therapy, but they have lacked the laboratory and histological features characteristic of AIH (225-229). Furthermore, some cases have been resistant to glucocorticoid therapy and associated with bile duct injury (230). The liver injuries associated with the checkpoint inhibitors should not be confused with AIH.

The clinical phenotype of drug-induced AIH-like injury is summarized in Table 6 (56, 188, 190). The latency interval from drug exposure to disease onset ranges from 1-8 weeks to 3-12 months (231-233), but nitrofurantoin and minocycline can have latency periods that exceed 12 months (234). The clinical history should detail all previous exposures to drugs and supplements.

The histological findings of interface hepatitis with portal and periportal infiltrates of lymphocytes, lobular hepatitis, plasma cells and eosinophils are similar to those of classical AIH, except for the absence of advanced fibrosis or cirrhosis in most instances (187, 190, 231, 232, 235, 236). Centrilobular zone 3 necrosis may be present (187, 233), and bridging fibrosis (Ishak score ≥4) is rare (237).

The diagnosis is supported by an acute onset, features of hypersensitivity, published literature on the implicated drug, latency period from drug exposure to liver injury, and absence of advanced fibrosis or cirrhosis at presentation (188). Liver tissue examination is warranted if the diagnosis is uncertain, laboratory findings indicate severe injury, or the institution of glucocorticoid therapy is being considered.

Treatment requires withdrawal of the offending agent with close monitoring until complete and sustained resolution of clinical and laboratory findings (187, 231, 232) (Table 6). Resolution typically occurs within one month (rarely 3 months) (187, 231, 238, 239). In accordance with "Hy's Law", serum aminotransferase levels >3-fold ULN and total serum bilirubin level >2-fold UNL increases the risk of death or need for LT in 9-12% of patients (240-242). Satisfaction of criteria for "Hy's Law" supports the institution of glucocorticoid therapy (187). Other reasons to consider glucocorticoid management are failure of the laboratory tests to improve after discontinuation of the medication or worsening of symptoms or laboratory tests at any time during the observation period.

Sustained biochemical resolution after glucocorticoid withdrawal strengthens the diagnosis of a self-limited drug-induced liver injury, whereas recrudescence of laboratory abnormalities are consistent with AIH (187, 188). Recrudescent disease should be managed as AIH with immunosuppressive therapy (243, 244). An algorithm based on the serum ALT level >

17.3 ULN, total serum bilirubin level > 6.6 ULN, and AST:ALT > 1.5 has a sensitivity of 80% and specificity of 82% for drug-induced ALF; this algorithm is a promising enhancement of Hy's Law (242).

The outcome of drug-induced AIH-like injury has been excellent (187, 231, 232) (Table 6). The infrequent exceptions have been reported mainly as case reports or abstracts (245), and idiosyncratic drug reactions do have a mortality of 5% and need for LT in 4.5% (234, 246). The LiverTox website (https://livertox.nlm.nih.gov/aboutus.html) of the U.S. Drug-induced Liver Injury Network is a valuable resource for evaluating suspected drug-induced liver injury. It is a joint effort of the Liver Disease Research Branch of the National Institutes of Diabetes and Digestive and Kidney Diseases (NIDDK) and the Division of Specialized Information Services of the National Library of Medicine (MLN), National Institutes of Health.

GUIDANCE STATEMENTS

- **Drug-induced autoimmune hepatitis-like liver injury must always be considered in the differential diagnosis of AIH.**
- **The offending agent must be withdrawn and monitoring maintained to ensure laboratory resolution.**
- **Glucocorticoid therapy for drug-induced autoimmune hepatitis-like injury should be instituted when symptoms or disease activity are severe (e.g. fulfill Hy's Law) or if symptoms and laboratory tests fail to improve or worsen after discontinuation of the offending drug.**
- **Laboratory flare after glucocorticoid withdrawal suggests underlying AIH and the need for immunosuppressive therapy.**

NONINVASIVE FIBROSIS ASSESSMENT

Noninvasive Assessment of Hepatic Fibrosis by Serum Biomarker Panels

Among 14 serum-based biomarker panels for hepatic fibrosis, the FibroTest® (247-249), the serum AST/platelet ratio index (APRI) (250), the Fibrosis-4 index (FIB-4) (251, 252), and the enhanced liver fibrosis (ELF) test (253, 254) have emerged as the better candidates in AIH (255-258). However, their role in AIH and their relative merit in assessing the progression or reversal of hepatic fibrosis, immediate and long-term prognosis, risk of hepatocellular carcinoma (HCC), and treatment outcome remain unknown (259).

Noninvasive Assessment of Hepatic Fibrosis by Liver Stiffness

Vibration-controlled transient elastography (VCTE or Fibroscan®)

VCTE or Fibroscan® correlates strongly with the histological stage of fibrosis in AIH (260-262), but its accuracy in quantifying fibrosis is impaired when undertaken within the first 3 months of treatment (260). Since liver stiffness estimated by VCTE is affected by both inflammation and fibrosis (260, 263, 264), the VCTE results at presentation correlate with histological grade of inflammation rather than stage of fibrosis (260). After at least 6 months of successful immunosuppressive therapy to reduce hepatic inflammation, VCTE can accurately diagnose cirrhosis and distinguish advanced stages of fibrosis (F3, F4) from less severe stages (F0-F2) (260). The cut-off values that best predicted fibrosis stages (defined as the highest sum of sensitivity plus specificity) were 5.8 kilopascal (kPa) for F≥2, 10.5 kPa for F≥3, and 16 kPa for F≥4 (260). Improvements in liver stiffness correlate with biochemical remission, regression of fibrosis, and favorable prognosis when assessed after 6 months of treatment (265).

Magnetic resonance elastography (MRE)

The findings of MRE correlate strongly with fibrosis stage, and MRE appears to outperform VCTE for staging hepatic fibrosis in some studies performed in other liver diseases (266-269). Furthermore, MRE assessment of splenic stiffness can have prognostic value for predicting portal hypertension and esophageal varices (270). In AIH, the accuracy (97%), sensitivity (90%), specificity (100%), positive predictive value (100%), and negative predictive value (90%) of MRE for advanced hepatic fibrosis are excellent (269).

MRE has outperformed conventional magnetic resonance imaging (MRI), the fibrosis scoring systems (FIB-4, APRI), and the conventional laboratory tests (AST, ALT, INR, platelet count) for the diagnosis of cirrhosis in AIH (269). In one study, liver inflammation affected the assessment of fibrosis stage by MRE when the grade of fibrosis was ≤F2 (271). In another study, liver stiffness in untreated patients with AIH was higher than in treated patients (3.83 kPa versus 3.7 kPa, *P*=NS) (269). This trend was seen at each fibrosis stage from F0-F3 (F0, 3.1 kPa vs 2.61 kPa; F1, 2.94 kPa vs 2.74 pKa; F2, 3.2 pKa vs 2.63 kPa; F3, 4.1 kPa vs 3.99 kPa) and reversed in F4 (6.5 pKa vs 5.9 pKa) (269). Differences in liver stiffness detected by MRE in untreated and treated patients with AIH have not been statistically significant, but the findings suggest that liver stiffness assessed by MRE can be influenced by therapy, possibly by reducing liver inflammation or hepatic fibrosis. MRE and VCTE have not been compared head-to-head in AIH.

Acoustic radiation force impulse imaging (ARFI)

ARFI assesses liver stiffness by measuring changes in wave propagation speed, and the displacement of short duration bursts of radiated sound waves are interpreted as changes in liver stiffness (256, 272, 273). The accuracy of ARFI for cirrhosis exceeds 90% (sensitivity, 93%;

specificity, 85%) (274), and results by meta-analysis of 13 studies have been comparable to VCTE in predicting fibrosis stage ≥2 and cirrhosis (275). Splenic stiffness by ARFI has also correlated with the grade of esophageal varices, and ARFI may evolve as a method to assess manifestations of portal hypertension (276, 277). ARFI can over-estimate hepatic fibrosis in patients with massive hepatic necrosis, cholestasis, severe inflammation, and hepatic congestion (278).

GUIDANCE STATEMENTS

- **Serum-based biomarker panels for hepatic fibrosis are unestablished in AIH and should not be used.**
- **VCTE can identify advanced fibrosis or cirrhosis in patients with AIH with reasonable accuracy, but it should be deferred for at least 6 months after successful treatment of AIH in order to avoid the confounding effects of hepatic inflammation.**

PRE-TREATMENT EVALUATION

The aims of the pre-treatment evaluation of patients with AIH are to limit treatment-related complications and ensure an optimal therapeutic response.

Pre-treatment assessment of thiopurine methyltransferase (TPMT) activity

Pre-treatment testing of TPMT activity identifies those rare patients with zero or near-zero TPMT activity who are at risk for severe myelosuppression when treated with azathioprine (AZA) or 6-mercaptopurine (6-MP) (279, 280). Absent or near-absent TPMT activity occurs in only 0.3-0.5% of the normal population (281-284), but the possibility of preventing severe bone marrow toxicity may warrant its use without an analysis of cost effectiveness (285-288). Genotypic and phenotypic screening for blood TPMT activity does not reduce the frequency of other common AZA or 6-MP side effects such as nausea, rash, and arthralgias (289-291), and

normal TPMT activity does not preclude the occurrence of dose-dependent toxicities (including cytopenia) in AIH (291, 292).

GUIDANCE STATEMENT

- **Consider screening patients with AIH for absent or near-absent TPMT activity prior to initiating treatment with azathioprine.**

Vaccinations

Vaccination status should be reviewed and updated, ideally prior to the institution of immunosuppressive therapy (293-295). Live, attenuated vaccines are not recommended in persons on high doses of immunosuppression, whereas recombinant and inactivated vaccines are considered safe. Response rates to vaccines are lower in immunosuppressed patients, but not so low as to preclude their use.

Patients unprotected against infections with the hepatitis A virus (HAV) and hepatitis B virus (HBV) should undergo vaccination prior to immunosuppressive treatment if possible (294). Susceptibility to HAV infection (51%) and HBV infection (86%) has been demonstrated in most patients with autoimmune liver diseases, and the incidence of infection has been 1.3 (HAV infection) and 1.4 (HBV infection) per 1,000 person-years (294). Protective antibodies have developed in all patients vaccinated for HAV and in 76% of patients vaccinated for HBV with vaccination failures attributed mainly to concomitant immunosuppressive therapy (294).

GUIDANCE STATEMENTS

- **Vaccines should be administered to all susceptible patients with AIH according to the age-specific guidelines of the Centers for Disease Control and Prevention (https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/immunocompetence.html)**
- **Patients unprotected against HAV and HBV infection should undergo vaccination, preferably before immunosuppressive therapy.**

Detection and Prevention of Reactivation of Hepatitis B Virus Infection

Patients on immunosuppressive agents are at risk for reactivation of hepatitis B virus (HBV) infection, and guidelines have been developed recommending routine pre-treatment screening of patients for hepatitis B surface antigen (HBsAg) and antibodies to hepatitis B core antigen (anti-HBc) (296-299). Based on the serological profile (HBsAg-positive versus HBsAg-negative/anti-HBc-positive) and the type, dose, and duration of immunosuppressive therapy, a risk of HBV reactivation during treatment can be estimated as high (≥10%), moderate (1-10%), and low (<1%) (298). Depending on the risk category, a preemptive treatment or monitoring strategy with the intent of on-demand therapy can be developed (298, 299). Prophylactic anti-viral therapy, preferably with entecavir or tenofovir, during immunosuppressive treatment and for at least 6 months after treatment (or at least 12 months after treatment with anti-CD20 agents) has been recommended for individuals at high-moderate risk of HBV reactivation. Watchful monitoring with intent of on-demand therapy has been recommended for patients at low risk (298, 299).

The risk of HBV reactivation in patients with AIH who are treated with conventional regimens of prednisone or prednisolone in combination with azathioprine is unknown. Furthermore, the reported risk levels in glucocorticoid-treated patients relate mainly to individuals with HBsAg who are at risk of developing viremia detected by HBV DNA (300). These patients warrant antiviral prophylaxis, but they constitute a small percentage of patients with AIH who would be considered for glucocorticoid therapy (296-298, 300).

HBsAg-negative patients with anti-HBc constitute another risk category for reactivation, but reverse seroconversion (appearance of HBsAg and HBV DNA in a previously HBsAg-negative patient) has occurred mainly in patients treated with B-cell depleting agents, TNF

inhibitors, and chemotherapeutic agents (300). Traditional immunosuppressive agents (azathioprine, 6-MP) have been associated with a low risk (<<1%) of reverse seroconversion as has glucocorticoid therapy for ≥4 weeks for autoimmune disorders (296, 298). Risk increases with the dose and duration of glucocorticoids, and moderate (10-20 mg daily)-high (>20 mg daily) dose glucocorticoids for ≥4 weeks has been associated with a risk of reverse seroconversion of 1-10% (298).

Patients with AIH typically undergo serological testing for HBV (HBsAg, anti-HBc, and anti-HBs) during the diagnostic phase of their evaluation, and individuals requiring close monitoring for HBV reactivation during glucocorticoid therapy can be identified prior to treatment. The goal of management is to achieve clinical and biochemical remission on low dose glucocorticoid regimens in combination with azathioprine, and close serological monitoring for reverse seroconversion is justified in these low risk patients. Assessments of serum HBV DNA and HBsAg at 1-3 month intervals has been suggested by the AASLD (299). High dose therapy or the institution of B-cell depleting agents, cytokine antagonists, calcineurin inhibitors, or other immune inhibitory agents may increase the risk of reverse seroconversion, and it is best avoided in these patients. Otherwise, the institution of preemptive anti-viral therapy in these patients should be considered.

GUIDANCE STATEMENTS

- **Patients with AIH who are HBsAg-negative/anti-HBc-positive during the diagnostic phase of their evaluation should undergo periodic serological testing (HBsAg, HBV DNA) during conventional therapy with prednisone or prednisolone in conjunction with azathioprine to detect HBV reactivation and the need for on-demand antiviral therapy.**

- **Patients with serological evidence of previous HBV infection who are treated with high dose glucocorticoids or other immune modulators, especially B cell depleting agents, are at moderate risk for HBV reactivation and should be considered for preemptive anti-viral therapy.**

Bone maintenance

Bone density assessments by dual energy x-ray absorptiometry (DEXA) of lumbar vertebrae and hips should be performed at baseline in patients with risk factors for osteoporosis and every 2-3 years in adult patients with ongoing risk factors for osteoporosis (301-303). The most common risk factors are past or prolonged use of glucocorticoids, postmenopausal status, history of low trauma fracture, and age (>65 years for females and >70 years for males) (303). Elemental calcium (1000-1200 mg daily) and vitamin D (at least 400-800 IU daily) has been recommended for patients on glucocorticoid therapy (301, 304).

Vitamin D insufficiency (serum 25-hydroxyvitamin D level, ≤29 ng/ml) occurs in 68-81% of patients with AIH (305, 306) and severe vitamin D deficiency (serum 25-hydroxyvitamin D level, <20 ng/ml) occurs in 20% (306). These findings justify assessment of the serum 25-hydroxyvitamin D level in all patients at diagnosis and vitamin D supplementation as indicated clinically (307). Similar dosing and monitoring strategies are used in children.

Clinical trials support the use of bisphosphonates when osteoporosis is present (301, 308, 309). Regular weight-bearing exercise can help control weight and eliminate immobility as a basis for bone loss (301).

Metabolic syndrome

The metabolic syndrome is defined by a cluster of risk factors for cardiovascular disease and type 2 diabetes mellitus that may be aggravated or induced by prolonged glucocorticoid

therapy, and its presence should be assessed prior to the institution of such therapy. The five principal components of the metabolic syndrome are hypertension, hypertriglyceridemia, low high-density lipoprotein cholesterol level, fasting hyperglycemia, and central obesity (waist-hip ratio or body mass index>30 kg/m^2) (310, 311). Three abnormal findings of the five possible manifestations justify the diagnosis. The presence of metabolic syndrome at presentation or during treatment might require modification of the glucocorticoid regimen, supplemental therapies, and life-style adjustments (exercise, weight reduction) (311).

GUIDANCE STATEMENTS

- **Bone mineral densitometry should be performed at baseline in all adult patients with AIH who have risk factors for osteoporosis, and it should be repeated every 2-3 years of continuous glucocorticoid treatment.**
- **Serum levels of 25-hydroxyvitamin D should be determined at diagnosis and annually thereafter.**
- **Supplementation with elemental calcium (1000-1200 mg daily) and vitamin D (at least 400-800 IU daily) should be provided while on glucocorticoid therapy and supplemented as clinically indicated in patients with vitamin D insufficiency.**
- **Bisphosphonate therapy is indicated for AIH patients with documented osteoporosis.**
- **Assessment for all features of metabolic syndrome should be performed prior to and during therapy, and its presence may require individualized treatment adjustments and life-style modifications.**

Pre-treatment counseling

Sufficient time should be spent prior to initiating treatment to ensure that patients understand not only the potential side effects of the medication, but also the positive benefits of

achieving therapeutic remission and the comparative risks associated with inadequately-treated disease (312). Non-compliance or problematic adherence are commonplace among patients with chronic diseases, particularly among adolescents (312-314).

Depression and anxiety are more common in patients with AIH than in the general population (314, 315), mainly because of concerns about disease progression (316-318). Depression is moderate in 19% and moderately severe in 10% of patients, and it correlates strongly with physical fatigue (315). Anxiety relates mainly to misconceptions about the nature and outcome of the disease and its treatment, and it can predispose to non-adherence (312, 314).

Low scores on health-related quality of life (HRQoL) assessments have been strongly associated with glucocorticoid use (319-322). Pre-treatment psychological disturbances, especially depression, may be intensified during glucocorticoid treatment (321). The combined effects of depression, anxiety, and glucocorticoid-related emotional lability may impact on treatment outcome (322, 323). Manifestations of depression and changes in the quality of life should be monitored throughout management of AIH as they may justify targeted counseling, individualized adjustments in the doses of glucocorticoids, or adjunctive anti-depressive or anti-anxiety interventions (324). These manifestations can be assessed by structured, validated questionnaires such as the 12-Item Short Form Survey (SF-12), the depression module of the Patient Health Questionnaire, and the Generalized Anxiety Disorders Screener (GAD-7) (316, 317).

GUIDANCE STATEMENTS

- **Potential barriers to long-term medication compliance should be identified proactively and addressed at the start of treatment and monitored thereafter.**

- **Manifestations of depression and changes in the quality of life should be monitored throughout management of AIH, and they can be assessed objectively by structured, validated questionnaires.**

PREGNANCY COUNSELING

The effects of AIH and its medications on fetal-maternal health should be discussed before pregnancy if possible. Data on risks and outcomes of pregnancy in AIH are derived from recent case series (2002-2012) encompassing 142 conceptions (325-328). Amenorrhea and decreased fertility occur when AIH is poorly controlled (329), whereas menstruation signals improved overall health. Exact fertility rates are not known, but in 53 British women with AIH (81 pregnancies), 41% had cirrhosis (325).

Fetal Complications

The live birth rate is 73% in mothers with AIH (325). The fetal loss and stillbirth rate of 27% is higher than the general population (7%-15%), but similar to women with chronic disease (24%-29%). Anti-phospholipid antibodies are strongly associated with AIH (326), and they may be a separate, but related, cause of pre-term delivery. Premature births occur in ~20% of pregnancies (325), but there are no specific birth defects associated with AIH.

Maternal complications

The overall maternal complication rate during the pregnancy or within 12 months of delivery is 38% (325, 327). Prematurity is primarily due to a flare in AIH. Flares occur mainly in patients who are not on therapy or who have not been in remission during the year prior to conception. Patients with AIH who are pregnant or planning pregnancy within the next year should be continued on treatment to reduce the risk of flare and hepatic decompensation. Flares are three times more common post-partum (328), and the low rate of flare during pregnancy may relate in part to the effects of pregnancy implantation factor (PIF) (330, 331).

In pregnant patients with cirrhosis, progressive increase in blood volume can lead to an increased risk of variceal bleeding. Pre-emptive identification and eradication of varices with variceal ligation is necessary as β-blockers and terlipressin have potential adverse effects in pregnancy (Table 7). The safety of endoscopy during pregnancy has been addressed in other guidelines (332).

Medication Safety in Pregnancy

Corticosteroids

Whereas data from 1997-2002 suggested an increased risk of cleft lip and palate during the first trimester of pregnancy in glucocorticoid-treated women, data from 2003-2009 reported by the US National Birth Defects Prevention case control study showed no association, presumably because of lower doses given in the latter era (333) (Table 7). The placental enzyme, 11-beta-hydroxysteroid dehydrogenase 2, converts prednisolone (the active drug) into prednisone (the inactive pro-drug), and it may protect the fetus from high levels of glucocorticoids.

Azathioprine (AZA)

AZA-related adverse events have not been reported in the pregnancy or baby. Initial concerns about possible teratogenicity were derived from animal studies that used supra-therapeutic doses (334). A systematic review and meta-analysis of 3,000 pregnant patients with IBD (335) found no increase in the risk of low birth weight or birth defects in mothers taking AZA. However, the risk of preterm birth was increased (OR, 1.45) (Table 7). Small amounts of AZA are detectable in the milk of lactating mothers, and low levels of 6-thioguanine nucleotide (6-TGN) have been detected in newborns (336).

Mycophenolate mofetil (MMF)

Data from the National Transplantation Pregnancy Registry and post-marketing surveillance indicate that MMF use during pregnancy is associated with first trimester pregnancy loss and birth defects, most commonly ear, heart, and cleft defects (337) (Table 7). Thus, MMF should be avoided during pregnancy. The FDA recommends a negative pregnancy test within 1 week of starting MMF and use of two effective methods of birth control for 4 weeks prior and 6 weeks after use of MMF. Small amounts of MMF are detectable in the milk of lactating mothers (337).

GUIDANCE STATEMENTS

- **Family planning should include the goal of achieving biochemical remission of AIH for one year prior to conception.**
- **Women of reproductive potential should receive prenatal counseling on the significant adverse effect of active AIH on pregnancy and the risk of flares during and after pregnancy.**
- **Maintenance doses of glucocorticoids and/or AZA should be continued throughout pregnancy.**
- **MMF is contraindicated during pregnancy, and women should be counseled about the adverse effects of MMF on pregnancy prior to initiating MMF treatment.**
- **Women with cirrhosis who are pregnant or plan to become pregnant within the next year should be screened for varices by endoscopy either prior to conception or during the second trimester of gestation and treated with band ligation.**
- **Women with AIH should be monitored closely for the first 6 months postpartum for early detection of a flare.**

FIRST-LINE TREATMENTS

The objectives of first-line therapy are to improve symptoms, control hepatic inflammation, achieve biochemical remission, prevent disease progression, and promote the regression of fibrosis at the lowest risk of drug-induced complication. The ideal laboratory response is normalization of serum ALT, AST, and IgG levels (2, 338, 339). All patients with AIH are candidates for therapy except individuals with inactive disease by clinical, laboratory, and histological assessment.

Prednisone or Prednisolone With and Without Azathioprine

Prednisone alone, 40-60 mg daily in adults and 1-2 mg/kg daily in children (maximum dose 40-60 mg daily) or a lower dose of prednisone, 20-40 mg daily, in combination with AZA (AZA adult dosing: United States: 50-150 mg daily, Europe: 1-2 mg/kg daily; pediatric dosing: 1-2 mg/kg daily), is administered with an antacid during an induction phase (Figure 4). Some centers advocate using prednisone 1 mg/kg for adult patients and then reducing the dose once a response is documented. In Europe, prednisolone is preferred over prednisone, and equivalent or weight-based doses of prednisolone (1 mg/kg daily) are administered in conjunction with weight-based doses of AZA (1-2 mg/kg daily). In some centers, AZA is started at the same time as glucocorticoids, whereas most centers recommend waiting 2 weeks before starting AZA to confirm steroid responsiveness, evaluate TPMT status, and assess treatment response by excluding the rare possibility of AZA-induced hepatitis.

Once a biochemical remission has been achieved (see definition in Table 2), response guided therapy is advocated. The dose of prednisone or prednisolone is reduced gradually to 20 mg daily or a dose sufficient to achieve biochemical remission while monitoring laboratory tests every 2 weeks. Thereafter, a gradual taper is recommended (2.5-5 mg every 2-4 weeks) to achieve a lower dose of 5-10 mg daily that maintains laboratory remission. Prednisone or prednisolone may then be discontinued completely, leaving the patient on only AZA or alternative

glucocorticoid-sparing drugs. Alternate day predniso(lo)ne is advocated by some because of fewer side effects, but this regimen may also reduce immunosuppression (340, 341). In children, the goals of therapy are to eventually be glucocorticoid-free and to prevent the multiple long term complications of glucocorticoids.

Treatment of AIH with prednisone monotherapy is appropriate for patients in whom the duration of treatment is expected to be <6 months (e.g. suspected drug-induced AIH-like injury) or AZA is contraindicated (known AZA intolerance or complete TPMT deficiency). In the setting of AZA intolerance, MMF is an acceptable alternative therapy to maintain remission. Prolonged prednisone monotherapy, especially at doses >10 mg daily, is frequently associated with well-known drug toxicities and should be avoided (342) (Table 8).

The typical starting dose of AZA is 50-100 mg daily in adults and 1-2 mg/kg daily in children. Evolving leukopenia or thrombocytopenia warrants dose reduction or drug withdrawal. AZA should be discontinued if the cytopenia does not recover in 1-2 weeks. Most cases of cytopenia in AZA-treated patients with AIH are associated with cirrhosis (290, 291).

The AZA dose can be further adjusted to achieve a therapeutic range and avoid toxicity by monitoring thiopurine metabolite levels (343-346). In children with AIH, the 6-TGN (6-thioguanine nucleotide) level is titrated between 100-300 pmol/8x10 RBC to avoid bone-marrow toxicity, and the 6-methyl-mercaptopurine (6-MMP) level is kept <5700 pmol/8x10 RBC to prevent hepatotoxicity (343, 347). Non-adherence to treatment should be suspected in patients who fail to respond to induction therapy or in those who relapse. Text messaging (348) and electronic monitoring (349) may also be useful in reducing non-adherence in children. AZA should not be used in patients with active malignancy since it acts synergistically with ultraviolet light to enhance mutational damage (350).

In adults with AIH, routine measurement of 6-TGN levels in unselected patients has had limited value since 6-TGN levels have been similar between patients with normalized serum aminotransferase levels and those with partial improvement(345). 6-TGN determinations might prove useful in assessing treatment compliance in adults and in developing management strategies for adults with an incomplete response (e.g. increasing the dose of AZA or adding allopurinol to the regimen) (345).

Budesonide and AZA

The efficacy and safety of budesonide (which has a 90% first-pass effect on the liver) in combination with AZA was demonstrated in a randomized trial of newly diagnosed AIH which targeted laboratory remission after 6 months. Patients receiving budesonide (3 mg thrice daily, reduced to twice daily following remission) combined with weight-based AZA (1-2 mg/kg daily) achieved laboratory remission after 6 months more frequently (60% vs. 39%) and with fewer steroid-specific side effects (SSSE) (28% vs. 53%) compared to prednisone (40 mg daily tapered to 10 mg daily) combined with weight-based AZA (351). A potential long-term benefit of budesonide therapy is preservation of the bone mineral density (352, 353).

Patients with acute liver failure or cirrhosis were not included in this randomized trial of budesonide. Patients with cirrhosis should not receive budesonide since portosystemic shunting may reduce drug efficacy and promote SSSE by allowing budesonide to bypass the liver (354, 355). Portal vein thrombosis has also been reported in cirrhotic patients taking budesonide, albeit portal vein thrombosis is a known complication of cirrhosis independent of budesonide use (356) (Table 8). Patients who fail to normalize their laboratory tests on prednisone therapy are also less likely to respond to budesonide treatment (352), and therefore the drug should not be used as a rescue therapy for steroid-refractory AIH (353, 357). The role of budesonide as first-line treatment

in acute severe AIH or acute liver failure is unknown, and thus it is not recommended in these settings.

In a subgroup analysis, children receiving budesonide and AZA achieved laboratory remission after 6 months as frequently as those receiving prednisone and AZA. The occurrence of SSSE was lower but not statistically different between the groups, with the notable exception of lower weight gain in budesonide-treated children (358). Budesonide with AZA may be considered in children with AIH, particularly if the disease is mild or if there are concerns that prednisone may worsen concurrent obesity, depression or acne, thus potentially jeopardizing medication adherence.

Systematic Review and Meta-analysis of First-line Regimens

We performed a systematic review and meta-analysis to investigate whether first-line treatment with prednisone or prednisolone alone or in combination with AZA was superior to budesonide in combination with AZA in patients with newly diagnosed AIH. Outcomes were frequency of remission, interval to remission, frequency and type of medication-associated side effects, and the frequency of death or liver transplantation. Out of 1,712 records that were identified in a database search, 578 were fully assessed for eligibility, 5 were included in a qualitative meta-analysis (20, 351, 358-360) and 2 were included in a quantitative meta-analysis (20, 351).

The meta-analysis revealed that biochemical remission was more likely with the use of budesonide and AZA compared to prednisone and AZA (OR 2.19, 95% CI: 1.30-3.67) [High Grade of evidence] (Table 9), but the analysis was based on a single randomized-clinical trial (351). None of the studies reported on the time to remission or outcomes such as histological resolution, progression to cirrhosis, death, and transplantation. Furthermore, only one study reported a lower frequency of steroid-related side effects in patients treated with budesonide and

AZA [Low Grade of Evidence] (351). The individual determinants that constituted the strength assessment for the recommendation of either budesonide and AZA or prednisone and AZA as first-line therapy (systematic review 1 [SR1]) are shown in Table 10.

GUIDELINE RECOMMENDATIONS

1) **For children and adults who present with AIH who do not have cirrhosis or acute severe AIH, the AASLD suggests as initial first-line treatment budesonide and azathioprine or prednisone/prednisolone and azathioprine (conditional recommendation, low certainty).**
2) **For children and adults with AIH who have cirrhosis or who present with acute severe AIH, the AASLD suggests that budesonide not be used (conditional recommendation, very low certainty).**

Alternative First-line Regimens

MMF has been used in place of AZA as a front-line therapy in combination with prednisolone (361). A single center experience with MMF as front-line treatment in combination with prednisone reported a remission rate of ~75% after 24 months (362). A recent meta-analysis found few evaluable studies comparing MMF and prednisone with prednisone and AZA (363). MMF/prednisone was superior to prednisone/AZA in the normalization of serum ALT, AST and IgG levels and in the rate of non-response. First-line treatment with MMF seemed to be at least as effective as AZA when each was combined with prednisone, but data are insufficient to recommend its first-line use.

Calcineurin inhibitors have been used to a limited extent as first-line agents in AIH (16, 364-368). Cyclosporine (CsA) has induced biochemical remission in children with AIH (365) with good results during long term follow-up (369, 370). Trough levels of cyclosporine are

typically maintained higher initially (i.e.150-200 ng/ml) and then tapered to 50-70 ng/ml after a year, providing their disease is in remission (369). Tacrolimus (TAC) reduced serum AST and ALT levels by 70% and 80% after 3 months (364), but this early promise has not been developed further. At this time, there is insufficient data to recommend calcineurin inhibitors as front-line agents.

Special Consideration: Acute Severe AIH or Acute Liver Failure due to AIH

Patients presenting with acute severe AIH (371) or acute liver failure (ALF) (100, 136, 372) (see definitions in Table 2) constitute a management dilemma in which the potential advantages of glucocorticoid therapy must be balanced against the risks of the treatment, namely infection (373) and delay of liver transplant (LT) (374, 375). Glucocorticoid therapy (usually prednisone or prednisolone alone, 0.5-1 mg/kg daily in adults and up to 2 mg/kg in children) has been effective in 20-100% of patients with acute severe AIH and has not been associated with an increase in sepsis (136, 371, 373, 376-378). In patients with AIH and ALF, glucocorticoid therapy has not been associated with improved overall survival, and survival has been less in treated patients with MELD scores >40 (372). Reports of improvement in patients with ALF and mild encephalopathy have been sparse, and glucocorticoid therapy may be deleterious in patients with severe decompensation (371, 373).

The key to success in managing acute severe AIH is to abandon ineffective treatment quickly (within 1-2 weeks depending on clinical status and treatment response) and to proceed to LT (371, 374, 375, 377, 379). Failure to improve any laboratory test reflective of liver inflammation or function, especially hyperbilirubinemia, or any evidence of clinical deterioration or hepatic encephalopathy during treatment justifies immediate consideration of LT (371, 377, 379). Hepatic encephalopathy at presentation defines AIH with ALF, and LT is more likely to improve survival than protracted glucocorticoid treatment (371, 373, 377).

GUIDANCE STATEMENTS

- **Patients with acute severe AIH should receive a treatment trial with prednisone or prednisolone alone, whereas patients with AIH and ALF should be evaluated directly for LT.**
- **Patients with acute severe AIH who do not improve laboratory tests or clinically worsen within 1-2 weeks of glucocorticoid therapy should be evaluated for LT.**

Putative Predictors of Treatment Response

The rapidity of response to treatment is the most important index of outcome, and the liver aminotransferase levels should improve within two weeks (379). Elderly patients (≥60 years old) respond more quickly to treatment than young adults, and they are characterized by HLA DRB1*04:01 (380, 381). Biochemical remission that is achieved within 6 months is associated with a significantly lower frequency of progression to cirrhosis or need for LT, and individualized adjustments in therapy may be justified to improve the speed of response (380). Laboratory manifestations of cholestasis (increased serum alkaline phosphatase or GGT levels) have been associated with incomplete or delayed response and may indicate an alternative diagnosis (e.g. overlap syndrome) (173).

Other biomarkers predictive of response are evolving. In type 1 AIH, persistent production of SMA or anti-actin in the setting of biochemical remission have been associated with histological features of active liver inflammation (382). Elevated ferritin levels (>2.1-fold ULN) at the time of diagnosis have been associated with subsequent biochemical remission, and the predictive value of remission has increased when both elevated serum ferritin and low IgG values (<1.9-fold ULN) have been present at baseline (383). Vitamin D deficiency at presentation has been associated with histological severity, poor treatment response, progression to cirrhosis, and increased mortality or

need for liver transplantation (305-307), and increased serum levels of angiotensin-converting enzyme have correlated with fibrosis scores (384).

Treatment Withdrawal

Sustained normal serum levels of AST, ALT, and IgG for at least 2 years have been proposed as requisites before attempting treatment withdrawal (385, 386). Patients with cirrhosis may have chronic elevation of the serum IgG level, and they are not excluded from treatment withdrawal if other tests are normal during a prolonged (≥2 year) period of stability (387, 388). Restoration of the liver tissue to normal reduces the risk of subsequent relapse to 28% (387), and liver biopsy prior to drug withdrawal has been the preferred strategy (387-389). Liver biopsy, however, may not be mandatory before treatment withdrawal in all adults (385).

In adult patients with and without pre-withdrawal liver biopsy, the frequency of relapse (30% versus 21%, P=0.57) was similar after treatment for at least 2 years, during which serum AST and ALT levels had been normal or near-normal (390). Of 28 treated patients with AIH who were in biochemical remission for at least 2 years before withdrawal, 15 patients (54%) remained in biochemical remission after treatment withdrawal during a median follow-up of 28 months (range, 17-57 months) (386). These patients were characterized by a serum ALT level <50% ULN and a normal serum IgG level <1,200 mg/dL (386). Liver biopsy was performed in 13 patients prior to drug withdrawal, and of the 11 patients with normal liver tests and normal liver tissue, 46% subsequently relapsed. These findings suggest that sustained normal liver tests during treatment may have gradations within the normal range that predict outcome, possibly better than liver tissue examination. Pre-withdrawal liver biopsy is still strongly advised in children to ensure resolution of inflammation (108). In a retrospective study of 35 children with AIH, 16 (46%) had lack of inflammation on pre-withdrawal liver biopsy after 2 years of biochemical remission and

were weaned off of immunosuppression (385). Fourteen of these 16 patients (87%) had a sustained remission off immunosuppression, with a median follow-up of 3.4 years.

VCTE is emerging as a noninvasive method that may also aid in the withdrawal decision (260, 265). Patients achieving a complete biochemical remission decreased their liver stiffness by 7.5%/year (P=0.003), whereas patients not achieving biochemical remission showed a slight but non-significant increase in liver stiffness by 1.7%/year (265). Patients achieving biochemical remission had an average liver stiffness measurement of 6.4±3.2 pKa compared to the average liver stiffness measurement of 9.2±9.1 kPa in the patients who did not achieve biochemical remission (P=0.06) (265). A liver stiffness threshold below which biochemical remission was expected was not determined. The findings of VCTE have not been correlated with outcome after treatment withdrawal or compared with histological examination in predicting sustained remission after treatment, and its role in predicting relapse after drug withdrawal is unknown.

Laboratory surveillance for relapse must be continued indefinitely at regular intervals of increasing length depending on test stability (391). Long-term follow-up studies in adults and children of at least 3 years duration have indicated that the frequency of achieving a treatment-free remission is 19-40% (392-394).

Relapse

Relapse occurs in 50-87% of adults and 60-80% of children after drug withdrawal (244, 339, 388, 395, 396). In patients satisfying the remission criterion of biochemical normality for ≥2 years during treatment, the relapse frequency is 46% in adults (386) and 80% in children (108). Long-term biochemical remission has been possible in 20% of children with type 1 AIH, but rarely in children with type 2 AIH (62, 108).

Relapse is typically asymptomatic, manifested by mild increases in serum AST or ALT level, and rapidly responsive to re-treatment (395). Its main risks relate to delayed or failed detection resulting in increased hepatic fibrosis in 10% (243) and clinical deterioration in 3% (243). Fifty percent of all relapses occur within the first 3 months after drug withdrawal, and the frequency of relapse decreases after the first year to 3% per year over the next 3 years (391). Ninety percent of relapses occur within 28 months (mean interval, 5±0.6 months; median, 3 months; range, 1-28 months), but late relapses are possible (range, 49-265 months after drug withdrawal) (391).

The principal predisposing factors for relapse are the duration and completeness of inactive disease prior to treatment withdrawal (386, 390). Various other factors have been proposed, including psychological stress (323), concurrent autoimmune disease (244), treatment with multiple agents (244), increased serum ALT and IgG levels at drug withdrawal (106, 339, 386), portal plasma cells in the liver tissue pre-withdrawal (106, 389), delayed biochemical remission 6-TGN (397), and prednisolone monotherapy (398).

Patients who relapse almost invariably respond to re-treatment with the original regimen (244, 395). Ninety-four percent achieve laboratory resolution in 4±1 months, and 59% achieve histological resolution in 8±2 months (392, 395). Subsequent attempts at drug withdrawal are commonly followed by another relapse (395), and adult patients should be treated long-term after their first relapse. Cirrhosis develops more commonly in patients with repeated relapses after drug withdrawal than in patients who have relapsed once and been re-treated (38% versus 10%, P=0.02), and liver-related death or LT is also more common (20% versus 3%, P=0.02) (243).

Complete drug withdrawal has been possible in 12% of patients who have relapsed previously after 69±8 months of re-treatment, and it can be attempted in individuals with inactive

disease for at least 24 months (388). In children with relapse and subsequent biochemical remission on re-treatment, a second assessment to gauge histological remission and treatment withdrawal can be considered after an additional 2 years of normal laboratory tests.

Biochemical remission is induced with the standard glucocorticoid and AZA regimen and then the dose of AZA is adjusted up to 2 mg/kg daily as the dose of prednisone or prednisolone is reduced to the lowest dose possible or fully withdrawn (399, 400). Patients intolerant of AZA can be treated with MMF or, in adults, low-dose predniso(lo)ne (≤7.5 mg daily) only can be instituted (401, 402).

GUIDANCE STATEMENTS

- **Drug withdrawal and achievement of a long-term treatment-free remission of AIH are possible in a minority of patients and should be considered in patients who have normalized serum aminotransferase and IgG levels for at least 2 years.**
- **Liver tissue examination prior to drug withdrawal is valuable in excluding unsuspected inflammation and reducing the frequency of relapse, but it is not mandatory in adults.**
- **Patients must be closely monitored for relapse with regular laboratory assessments during the first 12 months after treatment withdrawal and annually thereafter to cover for life-long risk.**
- **Relapse requires prompt re-institution of the original treatment until biochemical remission and subsequent transition to a long-term maintenance regimen.**

SECOND-LINE TREATMENTS

Second line therapies have been used to manage treatment failure, incomplete response, and drug intolerance (403, 404) (see definitions in Table 2). Treatment failure occurs in 7-9% of

adults and is associated with increased risk of progression to cirrhosis and liver failure, with mortality rates as high as 30% (404). Second-line therapies for treatment failure include MMF (405-411), calcineurin inhibitors [CsA (412-417), TAC (418-421)], 6-mercaptopurine (422, 423), and biologics [rituximab (424), infliximab (425)].

Incomplete response manifests as an improvement in laboratory findings, but without complete normalization of serum AST, ALT or IgG levels. Incomplete response occurs in ~15% of adults and children. Patients unable to normalize liver tests and liver tissue within 36 months have a higher frequency of cirrhosis and need for LT (380, 404). Second-line therapies for incomplete response include MMF and calcineurin inhibitors.

Treatment intolerance indicates the inability to continue therapy due to side effects of the drug (342, 351). Treatment ending side effects occur in 13%. Some patients who cannot tolerate AZA will tolerate 6-MP to maintain remission (422, 423). Other therapies to consider are MMF and TAC.

Mycophenolate Mofetil

MMF has been given to AIH patients intolerant of AZA or have an incomplete response or treatment failure with glucocorticoid/AZA. In a meta-analysis involving 5 studies and 309 patients (426), the pooled overall response rate was 58% (82% for AZA intolerance and 32% for treatment failure). MMF based therapies were well tolerated, with a pooled adverse event rate of 14%, leading to discontinuation in 8%. Another meta-analysis (427) based on 15 out of 1,532 studies indicated that the combination of MMF and prednisone was the most widely used second line treatment. The MMF regimen reduced serum AST and ALT levels in 79% and achieved histological remission in 89%.

The effectiveness of MMF as second-line therapy has also been supported by a recent study indicating the induction of biochemical remission in 60% (428). As in previous studies,

MMF therapy was more frequently effective in patients intolerant of primary therapy than in those with treatment failure to primary therapy (62% versus 38%). Predictors of a favorable response included older age and lower levels of IgG and the international normalized ratio (INR).

Similar findings have been reported in pediatric patients with treatment failure (417). Normalization of serum ALT and AST levels by month 6 was achieved in 36% of children treated with MMF, 83% treated with CsA, and 50% treated with TAC patients. MMF was well tolerated, and adverse events occurred in 45% compared to 78% treated with CsA and 42% treated with TAC.

Calcineurin Inhibitors

Multiple studies on the use of TAC in the setting of treatment failure, incomplete response, and AZA intolerance have confirmed its moderate-to-high efficacy. TAC has been administered in combination with prednisone, budesonide, AZA, or MMF with serum trough levels ranging from 1-10 ng/ml. Two single center studies reported normalization of serum aminotransferases in response to TAC in 91-92% of adult cases (418, 429), and a third single center study showed normalization of either serum ALT or IgG level in 79% (421). A multi-centered study of patients with either AZA intolerance or incomplete response/ treatment failure documented normalization of serum aminotransferases in 73% (94% with AZA-intolerance and 57% with incomplete response or treatment failure) (419).

Two meta-analyses on the use of TAC in adults as second-line therapy revealed improvement or normalization of serum aminotransferases in 75-94% (427, 430). Similar response rates have been reported in single center studies in children (367, 420). Side effects necessitating decreased dose or cessation of TAC occurred in ~25%. The most frequently

reported side effects were neurologic symptoms (tremors, headaches), renal complications (hypertension, insufficiency), and hair loss. Cyclosporin A may be considered as the second-line therapy of choice for patients with concurrent diabetes when compared to TAC, as diabetes can develop as a side effect of TAC.

Systematic review and meta-analysis of second-line regimens

We performed a systematic review to answer the question of whether 6-MP, MMF or a calcineurin inhibitor demonstrated superior efficacy in the setting of treatment failure or incomplete response in adults and children. A comprehensive search of several databases identified 1,712 records. After screening and exclusion of articles for various methodological reasons, 4 articles were included in a qualitative analysis and 2 in a quantitative meta-analysis (408, 419, 420, 431). Based on the available studies, a direct comparison was performed between MMF and TAC. There was insufficient data to evaluate the use of 6-mercaptopurine as a second-line therapy. No significant differences in outcome (remission rate, frequency of transplant or death) were reported between MMF and TAC therapies (Table 11). The individual determinants that constituted the strength assessment for the recommendation of preferred second-line therapy (systematic review 2 [SR2]) are shown in Table 10.

GUIDELINE RECOMMENDATIONS

3) In children or adults with AIH who have treatment failure, incomplete response, or drug intolerance to first-line agents, the AASLD suggests the use of mycophenolate mofetil or tacrolimus to achieve and maintain biochemical remission (conditional recommendation, low certainty).

4) Based on a superior ease of use and side-effect profile, the AASLD suggests a trial of mycophenolate mofetil over tacrolimus as the initial second-line agent in patients with AIH (conditional recommendation, very low certainty).

EVOLVING SALVAGE THERAPIES

Antibodies to tumor necrosis factor-alpha (anti-TNF-α)

Monoclonal antibodies to TNF-α (infliximab) are known to cause liver injury, and may even cause drug-induced AIH-like injury (208, 432-434). Anti-TNF antibodies may also have a therapeutic role in AIH. In the largest single center retrospective analysis of infliximab therapy in AIH, 11 difficult-to-treat adult patients, including 7 with cirrhosis, received infusions of infliximab (5mg/kg) (425). Six patients normalized serum aminotransferase and IgG levels; 7 patients developed infectious complications; and 1 patient stopped treatment due to an allergic reaction and incomplete response.

Another single center retrospective analysis in 11 pediatric and adolescent patients with IBD and autoimmune liver disease included 2 patients with type 1 AIH and 9 with AIH-PSC overlap (435). Infliximab (5 mg/kg) was infused to treat the IBD, and 3 patients were later treated with adalimumab after infliximab intolerance or failure. The IBD improved in most patients, and liver enzymes improved in five. The heterogeneity of the population and its

principal goal of treating the IBD precluded conclusions about the role of anti-TNF-α agents in AIH. The weak evidence on efficacy and the increased risk of infection, especially in patients with cirrhosis, does not justify the use of anti-TNF-α agents as second-line treatments.

Antibodies to CD20 (anti-CD20)

Rituximab, a monoclonal antibody directed against the B cell surface receptor CD20, has been used to treat 2 children with AIH who were not responding to glucocorticoids/ AZA, and both normalized serum AST and ALT levels (436). Rituximab has also been infused in 6 adult patients with AIH, including 3 with AZA intolerance and 3 who were non-responders to glucocorticoids/ AZA and MMF (424). Serum aminotransferases and IgG levels improved significantly in all patients and biochemical remission was achieved in 67%. Evidence favoring the use of B cell depleting antibodies is limited and does not justify their use as second-line treatments. A prospective randomized clinical trial is ongoing that evaluates ianalumab (VAY736) in patients with AIH who are non-responders or intolerant to glucocorticoids/ AZA (NCT03217422).

Thioguanine (Tioguanine)

Thioguanine is directly metabolized to the 6-thioguanine nucleotides (6-TGN) that are the metabolically active metabolites of azathioprine (437, 438). The 6-thioguanine metabolites are responsible for the therapeutic immunosuppressive effect of azathioprine, but they can also cause myelosuppression, especially in the presence of TPMT deficiency. The methylated metabolites associated with the conversion of azathioprine to 6-TGN have been associated with azathioprine intolerance, and the production of these methylated metabolites may be reduced by treatment with thioguanine.

Thioguanine has normalized serum aminotransferases in 64% of patients with AIH unresponsive to azathioprine, and the frequency of side effects (11%) has been less than those reported with the second-line therapies of MMF or 6-MP (12-50%) (439). Of 38 patients treated for intolerable side effects of azathioprine, 29 (76%) were able to continue treatment with thioguanine and 24 (83%) achieved biochemical remission (440). Seven of 11 patients (64%) in one study (440) and all three patients in another study (441) with insufficient response to azathioprine improved after receiving thioguanine. The major concern about treatment with thioguanine has been liver toxicity, especially the development of nodular regenerative hyperplasia (442), but dosing schedules of thioguanine not exceeding 25 mg daily have minimized this risk in patients with IBD (443).

Thioguanine has been proposed as a second-line treatment for patients with AIH who are intolerant of azathioprine, and it may also be considered in patients with nonresponse to thiopurine therapy (azathioprine, 6-MP) (439-441). The inclusion of thioguanine as a second-line treatment for AIH awaits further demonstration of its safety and efficacy in a multi-center collaborative treatment trial.

GUIDANCE STATEMENTS

- **In children or adults with AIH who have non-response to first-line treatment, the accuracy of the original diagnosis and medication adherence should be re-evaluated.**
- **Anti-TNF and anti-CD20 are possible alternative therapies after first-line and second-line regimens have failed, but the data supporting their use are limited.**

TREATMENT OF OVERLAP SYNDROMES

Management of the overlap syndromes has been empiric and includes glucocorticoids, glucocorticoids in combination with azathioprine, ursodeoxycholic acid (UDCA), and

glucocorticoids in combination with UDCA (126, 173, 176, 444). The IAIHG advises that management be directed at the predominant manifestations of the overlap syndrome (126), and regimens directed at a single component of the overlap syndrome have been able to improve liver tests in patients with a predominant AIH or cholestatic phenotype. Patients with AIH-PBC that have not satisfied Paris criteria (175, 182) have improved with conventional immunosuppressive therapy for AIH, and patients with predominantly PBC and background features of AIH have improved with UDCA alone (445). Early reports of the AIH-PSC overlap syndrome described responses to conventional immunosuppressive therapy for AIH (446). Regimens directed at a single predominant component of the overlap syndrome are based on the premise that these syndromes are single diseases with mixed atypical clinical features rather than concurrent diseases (447).

Most reports have described combination regimens directed at both the AIH and cholestatic components. Prednisone or prednisolone (30 mg daily tapered over 4 weeks to 10 mg daily) in combination with UDCA (13-15 mg/kg daily) has been superior to glucocorticoids alone and UDCA alone in patients satisfying Paris criteria (177), and combination therapy has been advocated for patients satisfying Paris criteria for the AIH-PBC overlap syndrome (126, 177, 179). Combination therapy has improved laboratory tests, stabilized hepatic fibrosis, and preserved the 5-year transplant-free (100%) and 10 year overall survival (92%) in patients with AIH-PBC (181).

Prednisone or prednisolone (0.5 mg/kg daily tapered to 10-15 mg daily) with UDCA (13-15 mg/kg daily) has improved survival and reduced frequency of transplantation compared to classical PSC (448), and this regimen has been advocated by the European and American liver societies for the AIH-PSC overlap syndrome (179, 449). UDCA, 10 mg/kg twice daily (dose not exceeding 1.5-2 g daily), in conjunction with prednisone or prednisolone has been used in children

with AIH-ASC (62). Treatment outcomes have been variable in adults with AIH-PSC, and laboratory resolution has been less common than in AIH (22% versus 64%). Furthermore, treatment failure (33% versus 10%) and death from liver failure or need for LT (33% versus 8%) have been more common than in AIH (126, 450, 451).

GUIDANCE STATEMENT

- **Consider adding ursodeoxycholic acid to prednisone or prednisolone in combination with azathioprine in adults and children with AIH and overlap syndromes.**

LONG-TERM OUTCOMES

The overall 10- and 20-year survival of treated AIH in a non-transplant center is 91% and 70%, respectively, and the standardized mortality ratio (SMR) is 1.63 for all cause death (95% CI: 1.25-2.02) and 1.86 after inclusion of LT as "death" (95% CI: 1.49-2.26) (452). The 10-year liver-related mortalities in the United States range from 6.2-7.5% (105, 453, 454), and they are similar to those in the United Kingdom (9%) (452), and Denmark (10.2%) (11). Cirrhosis is present in 28-33% of patients at presentation, especially in patients aged ≥60 years (156), and it may develop in 10-40% of treated patients (9, 104-107). Cirrhosis has been associated with reduced survival (11, 23, 452), and LT has been necessary in 21% of steroid-refractory patients (455). Factors that may affect the treatment response and long-term outcome are age at onset, ethnicity, and malignancy.

Age-related impact

Elderly patients with AIH frequently have advanced hepatic fibrosis at presentation, commonly have concurrent thyroid or rheumatic diseases, and tend to respond better to glucocorticoid therapy than adult patients aged <30 years (156). AIH occurs with similar frequency in all adult age groups, and the propensity for better treatment response among the elderly may be associated with immunosenescence and their higher frequency of HLA DRB1*04

(47% versus 13%) (156, 456). The findings suggest that AIH is undiagnosed at early fibrotic stages in the elderly and that age-related genetic susceptibilities affect outcome.

Ethnicity

Clinical phenotype, treatment response, and outcome can vary in different ethnic groups within the same geographical region (17, 457). African-American patients have more advanced stages of hepatic fibrosis at presentation than white American patients (453). They are younger at presentation, commonly have cirrhosis (57-85% versus 38%), have higher frequencies of liver failure (38% versus 9%), require LT more commonly (52% versus 23%), and have greater mortality (24% versus 6%) (453, 458). Asian Americans with AIH have a higher mortality (29%) than Hispanic-Americans (5%) and white Americans (8%) with AIH, and hospitalizations for AIH have been more frequent for African-Americans and Hispanics than for whites (459). In Europe, black patients with AIH have similar differences from white patients with AIH (younger age at presentation, increased risk of liver transplantation, and greater risk of liver-related death). They differ by having similar responses to standard therapy and higher frequency of systemic lupus erythematosus (460).

HCC and extra-hepatic malignancies

HCC develops in 1-9% of patients with AIH and cirrhosis (annual incidence, 1.1-1.9%) (111, 112, 114, 461, 462). The standardized incidence ratio is 23.3 (95% CI: 7.5-54.3) (463), and the standardized mortality ratio is 42.3 (95% CI: 20.3-77.9) (464). Risk factors for HCC are cirrhosis ≥10 years, portal hypertension, continuous inflammation, and immunosuppressive therapy ≥3 years (113). Five percent of treated patients with AIH develop extrahepatic malignancies of diverse cell types (cervix, lymphatic tissue, breast, bladder, soft tissue, and skin) (465). Non-melanoma skin cancers are most common (466), and the standardized incidence ratio for extrahepatic malignancy is 2.7 (95% CI: 1.8-3.9) (464). These risks justify surveillance

strategies that include hepatic ultrasonography, with or without serum alpha-fetoprotein (AFP) level, every 6 months in patients with cirrhosis (467-469) and adherence to standard guidelines for detection of extrahepatic malignancy (288).

GUIDANCE STATEMENT

- **Cancer surveillance should include hepatic ultrasonography, with or without serum AFP level, every 6 months in patients with cirrhosis and adherence to standard guidelines for detection of extrahepatic malignancy.**

LIVER TRANSPLANTATION

AIH is the indication for LT in 2-3% of recipients in Europe (470, 471) and approximately 5% of recipients in the United States (472). The number of new listings for LT for AIH in the U.S. is 0.5 per million population per year, but this number reflects an ongoing decrease in AIH listings of 0.012 listings per million population per year (473). Patient and graft survivals in European adults from 2000-2009 have been 1 year, 88% and 84% and 5 year, 80% and 72% (471). In the United States, patient and graft survivals for children transplanted from 2002-2012 have been 1 year, 95% and 91%, and 5 year, 91% and 84% (474). The 5-year patient and graft survivals for AIH in American adults are 80-90% and 74%, respectively (475). Patient survivals have been similar in pediatric and adult patients up to 50 years of age (476). Infection has been the most frequent cause of death within 30-180 days after LT (477), especially during the early postoperative period for patients >50 years old (476).

Acute (81% versus 47%) and steroid-resistant (38% vs. 13%) rejection after LT have occurred more frequently in adult patients transplanted for AIH than in patients transplanted for alcoholic cirrhosis (478). Furthermore, the incidence of chronic rejection has been higher in patients transplanted for AIH (16%) than in patients transplanted for PBC (8.2%), PSC (5.2%),

or alcoholic cirrhosis (2%) (479). More recent experience (2000-2010) has demonstrated a frequency of late acute rejection of 9% in AIH (471, 480). The frequency of chronic rejection has varied from 14-17% in AIH (versus 2% in alcoholic cirrhosis) (479, 481). These findings continue to suggest an increased frequency of acute and chronic rejection in AIH compared to other liver diseases.

Continuation of glucocorticoid therapy after LT, rather than weaning patients to achieve a glucocorticoid-free immunosuppressive regimen, has been touted to protect against rejection and recurrence of AIH (478, 482-485). However, discontinuation of steroids after LT has been advocated to reduce risks of infection and steroid-related side effects (486-497). The topic of long-term use of corticosteroids after LT remains controversial, but the literature suggests that some patients can be safely weaned off of corticosteroids.

Systematic review and meta-analysis of glucocorticoid use after LT

We performed a systematic review and meta-analysis to investigate whether continuous glucocorticoid treatment after LT was associated with fewer episodes of acute cellular rejection, recurrent AIH, graft loss, re-transplantation, and better graft and patient survival compared to steroid withdrawal after LT. Out of 1,712 records that were identified in a database search, 578 were fully assessed for eligibility as full-text articles, 4 were judged suitable for qualitative synthesis and 2 were judged suitable for quantitative synthesis. The meta-analysis was unable to establish a significant difference between each management strategy (Table 12). The individual determinants that constitute the strength assessment for the recommendation of glucocorticoid withdrawal versus continued glucocorticoid treatment (systematic review 3 [SR3]) are shown in Table 10.

GUIDELINE RECOMMENDATION

5) Based on limited data to support long-term administration of glucocorticoids to prevent post-transplant rejection, graft loss, recurrent AIH, and reduced patient and graft survival in adults, the AASLD suggests that a gradual withdrawal of glucocorticoids be considered after LT (conditional recommendation, very low certainty).

Recurrent autoimmune hepatitis after liver transplantation

AIH recurs in 8-12% of patients within the first year after LT and 36-68% after 5 years (472, 492, 498-502). The frequency of recurrent AIH has been similar (20%) in recipients of grafts from living-related, living-unrelated, and deceased donors (503). The diagnostic criteria for recurrent AIH are the same as for the original disease, albeit some features may be less pronounced or absent because of concurrent immunosuppressive therapy or short duration of disease (499, 502). Recurrent AIH can sometimes be difficult to distinguish from alloimmune rejection. The laboratory profile and characteristic histological changes required for the diagnosis of recurrent AIH are detailed in Table 13. Histological features classically seen in rejection, including endothelialitis and bile duct damage, are usually absent in recurrent AIH. Standard glucocorticoid-based therapy is used to treat recurrent AIH, along with the possible addition of AZA or MMF.

De novo autoimmune hepatitis

De novo AIH denotes the development of AIH in a patient transplanted for a disease other than AIH (504) (Table 13). It was originally described in 4% of British children (median age, 10.3 years; range, 2-19.4 years) who developed clinical and histological features of AIH 6-45 months after LT for extrahepatic biliary atresia, Alagille syndrome, drug-induced acute liver

failure, and alpha 1-antitrypsin deficiency (504). It has been reported subsequently in North American, South American, Japanese, and Korean children from 0.1 to 9 years after LT representing 1-7% of pediatric recipients (504-510). *De novo* AIH has been described in adults after LT (511), especially in recipients transplanted for PBC (512-517) or chronic hepatitis C (518-520). The estimated frequency of *de novo* AIH in transplanted adults ranges from 1-3% with an overall incidence of 4 cases per 1000 patient-years (521).

The clinical features of *de novo* AIH are similar to those required for the diagnosis of AIH and recurrent AIH (2, 56, 385, 522). The term, "plasma cell hepatitis", was coined to describe the inflammatory infiltrates observed in adult liver transplant recipients with recurrence of hepatitis C virus infection (523). The plasmacytic nature of the inflammation was thought to resemble AIH or "de novo AIH" (523). $IgG4^+$ plasma cells have been identified in the infiltrates associated with severe portal, periportal, and perivenular necro-inflammatory activity and fibrosis in adult patients, which could indicate alloimmune and/or autoimmune responses (524).

The Banff working group on liver allograft pathology has proposed that "plasma cell-rich rejection" replace the terms, "plasma cell hepatitis" and "*de novo* autoimmune hepatitis", for graft dysfunction occurring >6 months after transplantation in association with severe lymphocytic cholangitis, plasma cell-rich central perivenulitis, and portal microvascular deposition of complement component 4d (C4d) (525, 526). This form of graft dysfunction has been described mainly in adult interferon-treated recipients with chronic hepatitis C (523, 527, 528), and distinguishes adults from children with *de novo* AIH (522). It may be prudent to separate *de novo* AIH from plasma cell hepatitis/rejection (522, 525, 526). Keys to the diagnosis and management of *de novo* AIH are provided in Table 13.

GUIDANCE STATEMENTS

- **Recurrent AIH or *de novo* AIH and plasma cell hepatitis/rejection must be suspected in liver transplant recipients with laboratory changes of allograft injury.**
- **Liver biopsy, serum IgG level, and autoantibodies should be obtained to distinguish immune-mediated disease from other causes of allograft dysfunction.**
- **Predniso(lo)ne with azathioprine should be added to the calcineurin inhibitor to achieve biochemical remission in recurrent AIH or de novo AIH.**

FUTURE DIRECTIONS AND UNMET NEEDS

The unmet clinical needs in AIH will drive studies that improve the outcomes of current management, enhance quality of life, prevent disease recurrence, improve management of atypical populations (especially overlap syndromes), and increase understanding of the epidemiology and pathophysiology of AIH through real world international databases (529).

Pharmacological and biological agents that can restore homeostatic mechanisms that modulate immune responses (530-533), reduce oxidative and nitrosative stresses (534), or inhibit hepatic fibrosis (535) will be evaluated to supplement or replace current treatments (Table 14). The ability to correct deficient immune cell mediators by the transfer of autologous expanded populations (Tregs, mesenchymal stromal cells, or myeloid-derived suppressor cells) will be another promising investigational front (536, 537).

Prognostic biomarkers that predict the risk of treatment failure, relapse, or progression to cirrhosis and therapeutic biomarkers that reflect biochemical and histological response are needed to individualize management strategies and establish endpoints of treatment (538). Antibodies to programmed cell death-1 protein (PD-1) (539), soluble circulating PD-1 levels (540), macrophage migration inhibitory factor (MIF) (541, 542), micro-ribonucleic acid-21 (miR-21) (543), and soluble CD163 (544) are evolving biomarkers that may guide future management. Similarly, metabolomic profiling may emerge as a means of distinguishing AIH

from other liver diseases (drug-induced liver injury, PBC) (545, 546) and assessing treatment outcome (547).

Population-based epidemiological studies that have demonstrated an increasing incidence of AIH in Spain, Denmark, and the Netherlands (17) must energize efforts to understand the environmental risk factors for AIH in different geographical regions by promoting highly targeted, population-based investigations. Key epitopes that might trigger the disease must be sought among environmental agents (infections, pharmaceuticals, diet, and pollutants) (548) and within the intestinal microbiome (549).

The intestinal microbiome is an under-evaluated source of microbial antigens and activated immune cells that is actively being evaluated in diverse immune-mediated diseases, including AIH (549). Intestinal dysbiosis, circulating gut-derived lipopolysaccharides, and weakening of the intestinal mucosal barrier have already been described in patients with AIH (550, 551), and changes in the intestinal microbiome have been associated with female bias in autoimmune disease (552-554). Future investigations that re-enforce and extend these observations in AIH may identify interventions that can reduce risk, severity, and relapse (549, 555).

The management and outcome of AIH and the overall well-being of patients with AIH will continue to improve as understanding of its pathogenic mechanisms evolve, molecular interventions that counter its homeostatic disruptions emerge, and adjunctive measures tailored by greater awareness and responsiveness to individual need are instituted.

WHAT'S NEW SINCE 2010 GUIDELINES?

- Histological features of non-alcoholic fatty liver disease (NAFLD) are present in 17-30% of adult patients with autoimmune hepatitis (AIH), and concurrent NAFLD may influence response to therapy.
- Diagnostic scoring systems should be used only to support clinical judgment in challenging cases of AIH and to define AIH cohorts for clinical studies.
- Immune checkpoint inhibitors have been associated with immune-mediated liver injury and is frequently steroid-responsive, but the liver injury lacks autoantibodies and typical histological features of AIH.
- Elastography may be used to assess the stages of hepatic fibrosis non-invasively.
- Testing for thiopurine methyltransferase activity prior to azathioprine treatment is encouraged in all patients.
- Budesonide and azathioprine or predniso(lo)ne and azathioprine are recommended as first line AIH treatments in children and adults who do not have cirrhosis, acute severe hepatitis, or acute liver failure (ALF).
- Azathioprine can be continued throughout pregnancy, whereas the use of mycophenolate mofetil is contraindicated in pregnancy.
- Liver tissue examination prior to drug withdrawal in individuals with ≥2 years of biochemical remission is preferred, but not mandatory in adults and preferred in children.
- Mycophenolate mofetil or tacrolimus can be used as second line treatments in children and adults with AIH who have failed to respond to first line therapy.
- Patients with acute severe AIH should receive predniso(lo)ne followed by liver transplant (LT) if no improvement within 2 weeks, whereas patients with AIH and ALF should be evaluated directly for LT.
- Glucocorticoids can be discontinued after LT, and patients monitored for recurrence of AIH.

Table 1

GRADE Assessment of Clinical Studies

Study Design	Rating Quality	Strength Determinants	Strength and Implications of Recommendation
Randomized controlled trial Observational	High Moderate Low Very low	Quality of evidence Balance of benefits and harms Patient values and preferences Resources and costs Feasibility Acessibility Equity	Strong • Most people would want course • Most people should take course • Can be adapted as policy in most cases Conditional • Many people would select course • Requires decision aids and shared decision making • Debatable policy choice

Quality Down-grades: selection bias, inconsistency, imprecision, indirectness, publication bias
Quality Up-grades: large effect, very large effect, dose response gradient, confounders produce no effect

Table 2

Definitions of Autoimmune Hepatitis and Its Treatment Outcomes

Condition	Definition
AIH	Characteristic histologic abnormalities (lymphoplasmacytic interface hepatitis), elevated AST, ALT and total IgG and the presence of one or more characteristic autoantibodies.
Inactive Cirrhosis	Absence of inflammatory infiltrates in both portal tracts and fibrous bands in cirrhosis
Acute Severe AIH	Jaundice, INR > 1.5 < 2, no encephalopathy; no previously recognized liver disease (371)
Acute Liver Failure	INR ≥ 2; hepatic encephalopathy within 26 weeks of onset of illness; no previously recognized liver disease (100, 136)
Biochemical Remission	Normalization of serum AST, ALT and IgG* levels
Histological Remission	Absence of inflammation in liver tissue after treatment
Treatment Failure	Worsening laboratory or histological findings despite compliance with standard therapy
Incomplete Response	Improvement of laboratory and histological findings that are insufficient to satisfy criteria for remission
Relapse	Exacerbation of disease activity after induction of remission and drug withdrawal (or non-adherence)
Treatment Intolerance	Inability to continue maintenance therapy due to drug-related side effects

AIH, autoimmune hepatitis; ALT; serum alanine aminotransferase level; AST, serum aspartate aminotransferase level; IgG, serum immunoglobulin G level; INR, international normalized ratio. *Patients with cirrhosis in biochemical remission may have persistent elevation of IgG.

Table 3

Characteristic Features of Type 1 and Type 2 Autoimmune Hepatitis

Features	Type 1 AIH	Type 2 AIH
Frequency	USA adults, 96% (61, 556)	USA children, 9-12% (14-16) UK children, 38% (13)
Age at presentation	Peri-pubertal and adults	Usually under 14 years (153)
Mode of presentation	Chronic symptoms common Ascites or GI bleeding rare Asymptomatic in 25-34% Acute in 25-75% Acute severe in 2-6%	Acute onset (~40%) Acute liver failure possible (557, 558) Relapse frequent (108)
Laboratory features	Hypergammaglobulinemia	IgA levels may be reduced (153)
Autoantibodies	ANA SMA, anti-actin SLA	Anti-LKM1 [Anti-LC1, Anti-LKM3]
Concurrent immune diseases	Autoimmune thyroiditis Rheumatic diseases Inflammatory bowel disease	Autoimmune thyroiditis Diabetes mellitus Vitiligo
Autoimmune overlap with PSC (ASC in children)	Common in children Atypical p-ANCA positive	Rare Atypical p-ANCA negative
Overlap with PBC	Seen in adults (not children)	Not reported
Cirrhosis at presentation	Adults, 28-33% (especially elderly) Children, ≤33%	Rare
Remission after drug withdrawal	Possible	Rare, usually need long-term immunosuppression

AIH, autoimmune hepatitis; ANA, antinuclear antibodies; p-ANCA: perinuclear staining anti-neutrophil cytoplasmic antibody; anti-LC1; antibodies to liver cytosol type 1; anti-LKM1, antibodies to liver kidney microsome type 1; anti-LKM3, antibodies to liver kidney microsome type 3; ASC, autoimmune sclerosing cholangitis; GI, gastrointestinal; IgA, serum immunoglobulin A level; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; SLA, antibodies to soluble liver antigen; SMA, smooth muscle antibodies; UK, United Kingdom; USA, United States of America. Numbers in parentheses are references.

Table 4

Autoantibodies in the Diagnosis of Autoimmune Hepatitis

Antibody	Target Antigen	Diagnostic Value
ANA	Chromatin, ribonucleoproteins (559)	Type 1 AIH (56)
SMA	Filamentous actin (F-actin), vimentin, desmin (81, 560)	Type 1 AIH (56)
LKM1	Cytochrome P450 2D6 (CYP2D6) (561)	Type 2 AIH (153)
SLA	Sep [O-phosphoserine] tRNA:Sec [selenocysteine] tRNA synthase (562-566)	Type 1 AIH (69) Severe AIH (70, 72) Predicts relapse after treatment (73) Associated with poor outcome (70)
p-ANCA (atypical)	B-tubulin isotype 5 (77) Nuclear lamina proteins (567)	Type 1 AIH (75, 76, 568) PSC (568, 569) ASC (108)
Actin	Filamentous (F) actin (81)	Type 1 AIH (81, 83)
α-actinin	Filamentous actin cross-linking proteins (570)	Investigational (84) Type 1 AIH (85) Prognostic biomarker (85, 86)
LKM3	UDP glucuronosyltransferase family 1 (90, 93)	Type 2 AIH (90) Hepatitis D (90)
LC-1	Formiminotransferase cyclodeaminase (571, 572)	Type 2 AIH (571, 573)
LM	Cytochrome P450 1A2 (574, 575)	Dihydralazine-induced hepatitis (576) APECED hepatitis (577)
AMA	E2-subunits of pyruvate dehydrogenase complex (578)	PBC (578) PBC-AIH overlap syndrome (177) Type 1 AIH (183, 579, 580)

AIH, autoimmune hepatitis; ANA, antinuclear antibody; APECED, autoimmune polyendocrinopathy-candidias-ectodermal dystrophy; ASC, autoimmune sclerosing cholangitis; LC1, liver cytosol type 1; LKM, liver kidney/microsome; LM, liver microsome antibody; LT, liver transplantation; pANCA, perinuclear anti-neutrophil cytoplasmic antibody; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; SLA, soluble liver antigen; SMA, smooth muscle antibody. Numbers in parentheses are references.

Table 5

Drugs Associated with Liver Injuries Resembling Autoimmune Hepatitis

Definite Association	Probable Association	Possible Association
Minocycline (187, 192-198)	Propylthiouracil (581, 582)	Ipilimumab (anti-CTLA-4) (583)
Nitrofurantoin (187, 199-205)	Isoniazid (584)	Tremelimumab (anti-CTLA-4) (583)
Infliximab (206-221)	Diclofenac (585, 586)	Nivolumab (anti-PD-1) (583)
Alpha-methyldopa (587-589)	Etanercept (216, 433, 434)	Pembroluzimab (anti-PD-1) (230, 590)
Adalimumab (216, 434, 591-593)	Atorvastatin (594-597)	Atezolizumab (anti-PD-L1) (583)
Halothane (598, 599)	Rosuvastatin (600)	Black cohosh (herbal medicine) (601, 602)
Oxyphenisatin* (603)	Clometacine (604, 605)	Dai-saiko-to (herbal medicine) (606)
Dihydralazine* (575, 576, 607)		Germander (herbal medicine) (608)
Tienilic acid* (609)		Hydroxycut (nutritional supplement) (610)
		Trichloroethylene (toxin) (611)
		Papaverine (612)
		Indomethacin (613)
		Imatinab (614)

*Removed from marketplace.Anti-CTLA-4, antibody to cytototoxic T lymphocyte antigen-4; anti-PD-1, antibody to programmed death protein-1; anti-PD-L1, antibody to programmed death protein-ligand-1. Numbers in parentheses are references.

Table 6

Features of Drug-induced AIH-like Injury and AIH

Clinical features	Drug induced AIH-like Injury	AIH
Gender	Mainly women (187)	Female predominance, but males also affected (2, 385, 468)
Acute onset	Majority (>60%) (231)	<20% (2, 136)
Hypersensitivity (fever, rash, eosinophilia)	Up to 30% (231, 232, 615)	Unusual (2, 385, 468)
Temporal relationship with drug	Positive (231-234)	Negative (2, 56, 188)
HLA DRB1*03:01 or DRB1*04:01 association	None (236)	Common (29)
Concurrent autoimmune diseases	Unusual (187)	Present in 14-44% (129, 149-152)
Cirrhosis at presentation	Rare (187)	28-33% (9, 104-107)
Management	Stop offending drug ± glucocorticoids (187, 231, 232)	Glucocorticoids alone or with azathioprine (2, 385, 468)
Relapse after drug withdrawal	Rare (187)	60-87% (243, 244)
Progression to cirrhosis	Rare (187)	7-40% (105)
Survival without transplantation	90-100% (187, 232)	10-year survival, 89-91% (105, 452)

AIH, autoimmune hepatitis. Numbers in parentheses are references.

Table 7

Safety of Medications Commonly Used in the Pregnant Patient with Autoimmune Hepatitis

Medication	Safety Reports in Pregnancy
Terlipressin	Uterine ischemia
Octreotide	No harmful effects noted
Beta Blockers	Fetal bradycardia, fetal growth retardation
Lactulose	No harmful effects noted
Rifaximin	No harmful effects noted, but limited data
Corticosteroids	Inconsistent association with cleft abnormalities
Azathioprine	Premature birth
Mycophenolate Mofetil	Birth defects, spontaneous abortion
Tacrolimus	Premature birth, transient neonatal renal dysfunction

Table 8

Side Effects Associated with Prolonged First-Line Treatment Drugs in Autoimmune Hepatitis

Drug	Side Effects	Management options
Predniso(lo)ne	• Cosmetic: Facial rounding, hirsutism, alopecia, dorsal hump, striae • Systemic: Weight gain, glucose intolerance/diabetes, hypertension, fatty liver, osteoporosis, vertebral compression, cataracts, glaucoma, opportunistic infections • Quality of Life: Emotional instability, psychosis, depression, anxiety	• Actively taper to the lowest steroid dose needed for remission and attempt withdrawal after remission • Eye examinations for cataract and glaucoma • Life-style interventions for metabolic syndrome • Bone density monitoring • Vitamin D and calcium administration • Pro-active screening and management for quality of life and mental health symptoms
Budesonide	• Reduced intensity of the side effects from prednisone is possible despite first-pass metabolism • Unable to reach the liver with portal hypertensive shunts • Portal vein thrombosis in cirrhosis	• Taper budesonide to the lowest effective dose and attempt withdrawal after remission • Do not prescribe in cirrhosis and acute severe AIH
Azathioprine	• Hematologic: mild cytopenia, severe leukopenia or bone marrow failure (rare) • Gastrointestinal: nausea, emesis, pancreatitis • Neoplastic: non-melanoma skin cancer • Cholestatic liver damage (rare)	• Check TMPT metabolizer status prior to prescribing • Monitor cell counts at least every 6 months • Reduce dose if mild cytopenia occurs • Discontinue in severe cytopenia • Discontinue in GI intolerance • Avoid direct sunlight and have yearly dermatologic screening for skin cancer • Not recommended in decompensated cirrhosis or acute severe AIH

AIH, autoimmune hepatitis; TPMT, thiopurine methyltransferase

Table 9

Evidence Profile and Results of Systematic Review and Meta-analysis of First-line Therapies for Autoimmune Hepatitis

BUDESONIDE + AZATHIOPRINE VS PREDNISO(OL)NE + AZATHIOPRINE		
OUTCOME	**RESULTS**	**GRADE OF EVIDENCE QUALITY**
Biochemical remission	Two studies (one RCT[1] and one non-RCT[2]) [1] Manns MP, et al. Gastroenterology 2010;139:1198 [2] Delgado JS, et al. J Dig Dis 2013;14:611	**HIGH**
Rapidity of response	No studies reported rapidity of response	
Side effects (bone disease, cytopenia, weight gain, portal vein thrombosis)	One study[1] reported more steroid-specific side effects in prednisone group compared to budesonide group [1]Manns MP, et al Gastroenterology 2010;139:1198	**LOW**
Death	No studies reported death	
Liver transplantation	No studies reported liver transplantation	
Meta-analysis: I-squared test of heterogeneity	I^2=0.0%, *P*=0.495	
Meta-analysis: Odds Ratio (OR) (95% Confidence Interval[CI]) for biochemical remission	OR, 2.19; 95% CI, 1.30-3.67	
Meta-analysis: Conclusions	Few qualified studies Homogeneous test results between studies Current evidence insufficient to assess patient selection and long-term outcome Budesonide and azathioprine favored for biochemical remission Conditional recommendation with low certainty for use of budesonide and azathioprine in children and adults without cirrhosis, acute severe hepatitis, or acute liver failure	

RCT, randomized clinical trial

Table 10

Determinants of Recommendation Strength by GRADE Assessment of Clinical Studies

Strength Determinant	**SR1: "First-line Treatment" (Budesonide/AZA vs. Predniso(lo)ne/AZA**	**SR2: "Second-line Treatment" (MMF vs. TAC)**	**SR3: "Steroid withdrawal post-LT" (Pred vs. No Pred)**
1. Benefits vs. Harms	Budesonide >Pred	MMF>TAC	No Pred> Pred
2. Certainty	Limited	Limited	Limited
3. Cost	High cost/co-pay for budesonide	+MMF	No Pred
4. Patient values	Budesonide	+MMF (ease of use) +TAC (pregnancy)	No Pred
5. Feasibility	Co-pay may make it harder to get budesonide	Equal	Equal
6. Accessibility	Co-pay may make it harder to get budesonide	Equal	Equal
7. Equity	Equal	Equal	Equal

AZA, azathioprine; MMF, mycophenolate mofetil; No Pred, no predniso(lo)ne; Pred, predniso(ol)ne; SR, systematic review; TAC, tacrolimus.

Table 11

Evidence Profile and Results of Systematic Review and Meta-analysis of Second-line Therapies for Autoimmune Hepatitis

MYCOPHENOLATE MOFETIL VS TACROLIMUS		
OUTCOME	**RESULTS**	**GRADE OF EVIDENCE QUALITY**
Biochemical remission	Two retrospective studies[1,2] reported no significant difference in frequency of biochemical remission [1] Efe C, et al. Clin Gastroenterol Hepatol 2017;15:1950 [2] Chatur N, et al. Liver Int 2005;25:723	**LOW**
Drug intolerance	One study[1] reported drug intolerance and showed no significant difference between mycophenolate mofetil and tacrolimus in frequency of side effects [1] Efe C, et al. Clin Gastroenterol Hepatol 2017;15:1950	**VERY LOW**
Death or liver transplantation	One study[1] reported death or LT (together) and showed no significant difference in frequencies between mycophenolate mofetil and tacrolimus [1] Efe C, et al. Clin Gastroenterol Hepatol 2017;15:1950	**VERY LOW**
Meta-analysis: I-squared test of heterogeneity	I^2=59.6%, *P*=0.116	
Meta-analysis: Odds Ratio (OR) (95% Confidence Interval[CI]) for biochemical remission	OR, 1.95; 95% CI, 0.18-20.81	
Meta-analysis: Conclusions	Few qualified studies Heterogeneous test results between studies Low quality evidence to assess differences in frequency of biochemical remission Very low quality evidence to assess differences in frequency of side effects, mortality, or need for LT Conditional recommendation with very low certainty that mycophenolate mofetil be used over tacrolimus based on ease of use and side effect profile	

LT, liver transplantation

Table 12

Evidence Profile and Results of Systematic Review and Meta-analysis for Continuation versus Discontinuation of Steroids after Liver Transplantation for Autoimmune Hepatitis

CONTINUATION VS DISCONTINUATION OF STEROIDS AFTER LIVER TRANSPLANTATION		
OUTCOME	**RESULTS**	**GRADE OF EVIDENCE QUALITY**
Recurrent autoimmune hepatitis	Two retrospective studies[1,2] and one RCT[3] reported no significant difference in recurrence of autoimmune hepatitis after LT [1] Campsen J, et al. Liver Transplantation 2008;14:1281 [2] Heffron TG, et al. Transplant Proc 2002;34:3311 [3]Junge G, et al. Transplant Proc 2005;17:1695	**LOW**
Acute cellular rejection	No studies reported frequencies of acute cellular rejection	
Graft loss	No studies reported frequencies of graft loss	
Death	One RCT[3] reported no significant difference between the two groups [3]Junge G, et al. Transplant Proc 2005;17:1695	**VERY LOW**
Re-transplantation	No studies reported re-transplantation	
Meta-analysis: I-squared test of heterogeneity	I^2=38.6%, *P*=0.202	
Meta-analysis: Odds Ratio (OR) (95% Confidence Interval[CI]) for biochemical remission	OR, 0.62; 95% CI, 0.19-1.96	
Meta-analysis: Conclusions	Few qualified studies Heterogeneous test results between studies Low quality evidence to assess differences in frequency of recurrent autoimmune hepatitis after LT Very low quality evidence to assess differences in mortality after LT Conditional recommendation of very low certainty that steroids be discontinued after liver transplantation	

LT, liver transplantation; RCT, randomized clinical trial

Table 13

Diagnostic Features, Treatment, and Outcome of Recurrent and De Novo Autoimmune Hepatitis

Categories	Recurrent AIH	De Novo AIH
Clinical findings	Graft dysfunction at 2 mo-12 yrs (472, 492, 498) Asymptomatic to graft failure (616, 617) May be detected only by liver biopsy (501, 618)	Indication for LT other than AIH (504, 522) Exclude plasma cell-rich rejection/plasma cell hepatitis (522, 523, 525-527)
Laboratory findings	Increased serum AST, ALT, IgG levels (502)	Increased serum AST, ALT, IgG levels (504, 522)
Serological markers	Same antibodies as pre-LT AIH (619-621) ANA, SMA common (619) Anti-LKM1 rare (620)	ANA, SMA, anti-LKM1 (504, 522)
Histologic findings	Lobular hepatitis, focal necrosis, pseudo-rosettes (early) (622-625) Interface hepatitis, lymphoplasmacytic infiltration (late) (625) Lobular collapse, confluent/bridging necrosis (severe) (623-625)	Interface hepatitis (522) Lymphoplasmacytic infiltrates (522)
Treatment	Predniso(lo)ne, 30 mg daily, and AZA, 1-2 mg/kg daily (500, 502) Predniso(lo)ne dose reduction to 5-10 mg daily in 4-8 weeks (626) Predniso(lo)ne and AZA maintenance (502, 626) Continue calcineurin inhibitor (626, 627)	Children (502, 504, 626) • Predniso(lo)ne (1-2 mg/kg, <60 mg daily) and AZA (1-2 mg/kg daily) • Otherwise same as recurrent AIH Adults (502, 626, 628) • Same as recurrent AIH
Rescue regimens (empiric)	MMF for AZA (629) Switch calcineurin inhibitor (499, 627) Rapamycin (630)	MMF for AZA (420) Rapamycin (631)
Outcomes	5 yr patient survival, 86-100% (501, 616) Graft failure, 8-50% (616, 632-634) Re-transplantation, 33-60% (616, 617, 633) Recurrent AIH in re-transplanted liver, 33-100% (616, 617, 633)	Better in children than adults (504, 510, 522, 523, 527) Biochemical remission, 86% (504) Re-transplantation, 8% (509) Patient survival, 95% (628)

AIH, autoimmune hepatitis; ANA, antinuclear antibodies; anti-GSTT1, antibodies to glutathione-S-transferase T1; anti-LKM1, antibodies to liver kidney microsome type 1; AZA, azathioprine; LT, liver transplantation; IgG, immunoglobulin G; MMF, mycophenolate mofetil; SMA, smooth muscle antibodies. Numbers in parentheses are references.

Table 14

Current and Potential Therapies for Autoimmune Hepatitis Based on Evolving Knowledge of Immunopathogenic Mechanisms

Goal	Treatment	Mechanism of Action	Status of Development
Decrease the Numbers and/or Functions of Autoimmune Effector Cells and Pathogenic Autoantibodies	Immunosuppressive drugs: CNI, mTOR, antiproliferative agents	Inhibit proliferation of autoantigen-activated CD4 and CD8 T cells by reducing the amount and/or signaling of mitogenic IL-2 or block completion of T cell division.	SOC in multiple AI diseases. Combination therapies using sub-toxic doses of 2 or more agents attractive. Ongoing research into prevention and management of toxicities.
	Anti-CD20	B cell depletion	Off-label use as alternative therapy in AIH
	Anti-BAFF	B cell depletion followed by mobilization of memory B cells from lymphoid tissue. Potent inhibition of BAFF signaling in activated T cells	SOC in SLE. Ongoing clinical trial in AIH.
	Anti-BAFF, followed by anti-CD20	Depletion of memory B cells mobilized from lymphoid tissues by anti-BAFF	Clinical trials planned in AI diseases.
	Anti-CD40	Block CD40-CD40L (CD154) costimulation of T cells and B cells.	POC. Clinical trial initiated in liver transplantation.
	Efgartigimod	First in class antibody fragment to block FcRn to increase IgG clearance and prevent IgG recycling.	POC to reduce pathogenic autoantibodies and Ig-Autoantigen immune complexes.
	Inhibition of sphingosine-1-phosphate receptors	Prevent egress of activated T cells from lymph nodes into blood.	SOC in MS, new agents in development for other AI diseases.

	Myeloid-Derived Suppressor Cells	Inhibit autoreactive T cell activation and proliferation.	POC in preclinical models. Clinical trials planned in RA.
Decrease and/or Inhibit Proinflammatory Cytokines	Anti-TNFα or TNFα-Receptor	Reduce TNFα-mediated tissue injury and proinflammatory signaling pathways.	SOC in multiple AI diseases. Studied as an alternative therapy in AIH.
	Anti-IL-6 or anti-IL-6R	Reduce pathogenic effects of proinflammatory IL-6 signaling in innate and adaptive immune responses.	SOC in RA, clinical trials ongoing in other AI diseases.
	Anti-IL-12 (p40 subunit)	Reduce pathogenic effects of proinflammatory IL-12 signaling in innate and adaptive immune responses.	SOC in psoriasis and Crohn's disease. Also blocks IL-23 signaling
	Anti-IL-17a or Anti-17R	Reduce pathogenic effects of IL-17.	SOC for psoriasis and psoriatic arthritis. Clinical trials planned in other AI diseases.
	Anti-IL-21	Reduce multiple pathogenic effects of IL-21 in innate and adaptive immune responses.	Ongoing clinical trials in RA, T1DM and Crohn's disease.
	Anti-IL-23 (p19 or p40 subunits)	Reduce pathogenic effects of proinflammatory IL-23 stimulation of Th17 cells.	SOC in psoriasis and Crohn's disease
	Anti-Blys	Reduce pathogenic B cell selection, differentiation, and homeostasis	SOC in SLE
Inhibit Signaling of Proinflammatory Cytokines	mTOR inhibition	Decrease proliferation of activated CD4 and CD8 T cells by inhibiting signaling of IL-2.	SOC in solid organ transplantation and AI diseases. Alternative therapy in AIH.

	Tofacitinib (JAK3 Inhibitor of IL-2 signaling)	Decrease proliferation of activated CD4 and CD8 T cells by inhibiting signaling of IL-2.	SOC in RA. Clinical trials planned.
	Baricitinib (JAK1/2 Inhibitor of IL-6 and IFNγ signaling)	Reduce pathogenic effects of proinflammatory IL-6 signaling through IL-6R in innate and adaptive immune responses and pathogenic effects of IFNγ signaling in NK, NKT, CD4 and CD8 T cells.	SOC in RA. Ongoing clinical trial in PBC.
	Pacritinib (JAK2 Inhibitor of IL-12/IL-23 signaling)	Reduce proinflammatory IL-12 and Il-23 signaling that polarizes increases CD4 Th1 polarization, secretion of IFNγ and TNFα, cytotoxic activity of NK and CD8 CTLs and differentiation of pathogenic Th17 cells.	POC established. Ongoing clinical trials.
	Filotinib (JAK1 Inhibitor of IFNα/IFNβ signaling)	Reduce immunopathogenic gene expression induced by type 1 IFNs.	POC established. Ongoing clinical trials.
	Upadacitinib (Selective JAK1 Inhibitor of IFNα/IFNβ signaling)	Reduce immunopathogenic gene expression	SOC for refractory RA
Augment Effects of Immunosuppressant Cytokines	rHuIL-10	Reduce immunopathogenic effects of activated CD4 Th1 cells.	SOC to prevent pancreatitis post-ERCP Trial in UC terminated for concern of Guillain-Barre syndrome
Inhibit Transendothelial Migration of	Inhibition of chemokine receptors or integrins	Prevent tissue inflammation and injury by blocking transendothelial entry of	SOC inhibition of α4/β7 integrin in UC. Clinical trial in PSC ineffective.

Effector Cells from Blood into Tissues		effector cells from blood into target tissues. Prevent chemokine-induced terminal differentiation of effector cells.	Potential for clinical trials of other FDA-approved chemokine/integrin inhibitors.
Establish Immunoregulatory Control	Low dose IL-2 infusion to increase autoantigen-specific iTregs.	Expansion of pre-existing autoantigen-specific iTregs in vivo requires exposure to low concentrations of IL-2.	POC established. Clinical trials ongoing.
	Infusion of autoantigen-specific iTregs generated ex vivo.	Ex vivo generation of autologous autoantigen-specific iTregs followed by infusion to immunologically control autoantigen-specific CD4 Th cell subset responses.	POC of iTreg generation ex vivo established. Future clinical trials planned in AIH. Viability, function and distribution of iTregs after infusion unknown.
	Inhibition of Bromodomain and Extra-terminal (BET) family of proteins.	Inhibition of disease-specific epigenetic transcriptional enhancers, super enhancers and eRNA production to decrease autoimmune reactions.	POC established. Clinical trials ongoing.
	Mesenchymal Stem Cells	Inhibition of innate immune cells, effector T cells. Induction of antigen-specific iTregs. Reduction of TNFα secretion.	POC established. Clinical trials ongoing.
Establish Physiologic Immunoregulatory State of Pregnancy	PIF	Creation of immunosuppressive and immunomodulatory environment of pregnancy.	Phase 1b trial of synthetic PIF in AIH completed. Ongoing clinical trial.

SOC, standard of care regulatory approval; POC, proof of concept; IL, interleukin; iTregs, inducible T regulatory cells; Th, T helper cell; CNI, calcineurin inhibitor; mTOR, mechanistic target of rapamycin; BAFF, B cell activating factor; Blys, B lymphocyte stimulator;RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; T1DM, type 1 diabetes mellitus; MS, multiple sclerosis; JAK, Janus kinase; PBC,

primary biliary cholangitis; rHuIL-10, recombinant, human IL-10, UC, ulcerative colitis; PIF, pre-implantation factor

FIGURE LEGENDS

Figure 1. Current concepts of the immunopathogenesis of autoimmune hepatitis. Current knowledge supports a multi-step working model of the immunopathogenesis of AIH, in which a break in self-tolerance to hepatocyte autoantigens initiates immunological responses causing progressive hepatic necroinflammation and fibrogenesis (50). In the first step, thymic autoantigen-specific natural T regulatory cells (nTregs) are incapable of preventing immune responses to hepatic autoantigens during hepatic or systemic immune responses to environmental triggers, such as viral infections or xenobiotics. In the second step, professional antigen-presenting cells (APCs) present auto-antigenic peptides to autoreactive α/β T cell receptors (TCRs) on naïve $CD4^+$ T helper (Th) cells and $CD8^+$ T cells and APCs activate mucosal-associated invariant T (MAIT) cells by presenting bacterially processed vitamin B antigens to MAIT cell TCRs (54). Co-stimulation is a crucial third step, which induces expression of T cell genes required for proliferation, differentiation and maturation of autoantigen-specific $CD4^+$ Th subsets (e.g., Th1, Th2, Th3, Th9, Th17, inducible Tregs [iTregs], Tr1, T follicular helper [Tfh] cells) and both $CD8^+$ cytotoxic T lymphocytes (CTLs) and $CD8^+$ T regulatory cells (CD8 Tregs). In the fourth step, secretion of specific cytokines by subsets of $CD4^+$ Th cells produce a variety of immunological sequelae, including $CD4^+$ Th2 cytokine stimulation of B cell autoantibody production, $CD4^+$ Tfh cell activation of B cells into antibody-secreting plasma cells, Treg stimulation of B regulatory cell (Breg) development through IL-35 mechanisms and cytokine-activated macrophages and $CD4^+$ Th17 cell mediated pathogenic cytotoxicity. The fifth step is the cumulative failure of $CD4^+$ and $CD8^+$ Tregs and Bregs to control autoantigen-specific effector mechanisms causing hepatic injury (53). Moreover, exposure of $CD4^+$ iTregs to specific cytokines can transform them from regulatory cells into pathogenic $CD4^+$ Th17 cells (52). The sixth step is the generation of complex portal inflammatory infiltrates of effector cells that cause

cytotoxicity of periportal and lobular hepatocytes. Necroinflammatory destruction of hepatocytes results in activation of periportal stellate cells, which amplify local immune responses through contact dependent and independent mechanisms and cause progressive portal fibrosis, culminating in cirrhosis in the absence of effective immunosuppressive therapy.

Figure 2. Diagnostic algorithm for the evaluation of suspected AIH after exclusion of viral, drug-induced, hereditary and metabolic diseases. Antinuclear antibodies (ANA) and smooth muscle antibodies (SMA) should be assessed in adults (green panel), and antibodies to liver kidney microsome type 1 (LKM-1) assessed later if ANA and SMA are absent. ANA, SMA and LKM1 should be assessed in all pediatric (Peds) patients at presentation (green panel). The findings of the liver biopsy (dark blue panels) could support the diagnosis of AIH (dark red panel) or suggest alternative diagnoses that might include an overlap syndrome, primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), AIH with non-alcoholic fatty liver disease (NAFLD), or non-alcoholic steatohepatitis (NASH) (brown panels). The absence of ANA, SMA, and LKM1 justifies additional serological tests (green panel) that can include antibodies to soluble liver antigen (SLA), atypical perinuclear anti-neutrophil cytoplasmic antibody (pANCA), tissue transglutaminase (tTG), and antimitochondrial antibodies (AMA). Seropositivity for one of these autoantibodies could support the diagnosis of AIH (dark red panels) or suggest other diagnoses including celiac disease (dark brown panels).

Figure 3. Histological features characteristic of AIH. A. Lymphoplasmacytic inflammatory infiltration of the portal tract and interface hepatitis involving more than 50% of the portal tract circumference (arrows; H&E; magnification, x200). B. Plasma cell predominance in a portal inflammatory infiltrate (H&E; magnification, x600). C. Perivenulitis of a central vein (H&E; magnification, x400). D. A hepatocyte undergoing emperipolesis (arrows; H&E; magnification,

x600). E. Rosettes of regenerating hepatocytes (arrows; H&E; magnification, x600). Photomicrographs are courtesy of Sadhna Dhingra, M.D., Department of Pathology, Baylor College of Medicine, Houston, Texas.

Figure 4. First-line treatment of AIH in adults and children, recognizing adjustments based on the presence of cirrhosis or an acute severe presentation.

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REFERENCES

1. Merriman RB, Tran TT. AASLD practice guidelines: The past, the present, and the future. Hepatology 2016;63:31-34.
2. Manns MP, Czaja AJ, Gorham JD, Krawitt EL, Mieli-Vergani G, Vergani D, Vierling JM. Diagnosis and management of autoimmune hepatitis. Hepatology 2010;51:2193-2213.
3. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schunemann HJ, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924-926.
4. Goldet G, Howick J. Understanding GRADE: an introduction. J Evid Based Med 2013;6:50-54.
5. Gatselis NK, Zachou K, Koukoulis GK, Dalekos GN. Autoimmune hepatitis, one disease with many faces: etiopathogenetic, clinico-laboratory and histological characteristics. World J Gastroenterol 2015;21:60-83.
6. Palle SK, Naik KB, McCracken CE, Kolachala VL, Romero R, Gupta NA. Racial disparities in presentation and outcomes of paediatric autoimmune hepatitis. Liver Int 2019;39:976-984.
7. Czaja AJ, Carpenter HA, Santrach PJ, Moore SB, 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.
8. 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.
9. Werner M, Prytz H, Ohlsson B, Almer S, Bjornsson E, Bergquist A, Wallerstedt S, et al. Epidemiology and the initial presentation of autoimmune hepatitis in Sweden: a nationwide study. Scand J Gastroenterol 2008;43:1232-1240.
10. Ngu JH, Bechly K, Chapman BA, Burt MJ, Barclay ML, Gearry RB, Stedman CA. Population-based epidemiology study of autoimmune hepatitis: a disease of older women? J Gastroenterol Hepatol 2010;25:1681-1686.
11. Gronbaek L, Vilstrup H, Jepsen P. Autoimmune hepatitis in Denmark: incidence, prevalence, prognosis, and causes of death. A nationwide registry-based cohort study. J Hepatol 2014;60:612-617.
12. van Gerven NM, Verwer BJ, Witte BI, van Erpecum KJ, van Buuren HR, Maijers I, Visscher AP, et al. Epidemiology and clinical characteristics of autoimmune hepatitis in the Netherlands. Scand J Gastroenterol 2014;49:1245-1254.
13. Gregorio GV, Portmann B, Reid F, Donaldson PT, Doherty DG, McCartney M, Mowat AP, et al. Autoimmune hepatitis in childhood: a 20-year experience. Hepatology 1997;25:541-547.
14. Radhakrishnan KR, Alkhouri N, Worley S, Arrigain S, Hupertz V, Kay M, Yerian L, et al. Autoimmune hepatitis in children--impact of cirrhosis at presentation on natural history and long-term outcome. Dig Liver Dis 2010;42:724-728.
15. Deneau M, Jensen MK, Holmen J, Williams MS, Book LS, Guthery SL. Primary sclerosing cholangitis, autoimmune hepatitis, and overlap in Utah children: Epidemiology and natural history. Hepatology 2013;58:1392-1400.
16. Jimenez-Rivera C, Ling SC, Ahmed N, Yap J, Aglipay M, Barrowman N, Graitson S, et al. Incidence and characteristics of autoimmune hepatitis. Pediatrics 2015;136:e1237-1248.
17. Czaja AJ. Global disparities and their implications in the occurrence and outcome of autoimmune hepatitis. Dig Dis Sci 2017;62:2277-2292.
18. McFarlane IG. The relationship between autoimmune markers and different clinical syndromes in autoimmune hepatitis. Gut 1998;42:599-602.
19. McFarlane IG. Autoimmune hepatitis: Clinical manifestations and diagnostic criteria. Can. J. Gastroenterol. 2001;15:107-113.

20. Delgado JS, Vodonos A, Malnick S, Kriger O, Wilkof-Segev R, Delgado B, Novack V, et al. Autoimmune hepatitis in southern Israel: a 15-year multicenter study. J Dig Dis 2013;14:611-618.
21. Primo J, Merino C, Fernandez J, Moles JR, Llorca P, Hinojosa J. [Incidence and prevalence of autoimmune hepatitis in the area of the Hospital de Sagunto (Spain)]. Gastroenterol Hepatol 2004;27:239-243.
22. Primo J, Maroto N, Martinez M, Anton MD, Zaragoza A, Giner R, Devesa F, et al. Incidence of adult form of autoimmune hepatitis in Valencia (Spain). Acta Gastroenterol. Belg. 2009;72:402-406.
23. Danielsson Borssen A, Marschall HU, Bergquist A, Rorsman F, Weiland O, Kechagias S, Nyhlin N, et al. Epidemiology and causes of death in a Swedish cohort of patients with autoimmune hepatitis. Scand J Gastroenterol 2017;52:1022-1028.
24. 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.
25. Lee YM, Teo EK, Ng TM, Khor C, Fock KM. Autoimmune hepatitis in Singapore: a rare syndrome affecting middle-aged women. J Gastroenterol Hepatol 2001;16:1384-1389.
26. Chung HV, Riley M, Ho JK, Leung B, Jevon GP, Arbour LT, Barker C, et al. Retrospective review of pediatric and adult autoimmune hepatitis in two quaternary care centres in British Columbia: increased prevalence seen in British Columbia's First Nations community. Can J Gastroenterol 2007;21:565-568.
27. Price P, Witt C, Allcock R, Sayer D, Garlepp M, Kok CC, French M, et al. The genetic basis for the association of the 8.1 ancestral haplotype (A1, B8, DR3) with multiple immunopathological diseases. Immunol Rev 1999;167:257-274.
28. Fainboim L, Marcos Y, Pando M, Capucchio M, Reyes GB, Galoppo C, Badia I, et al. Chronic active autoimmune hepatitis in children. Strong association with a particular HLA-DR6 (DRB1*1301) haplotype. Hum Immunol 1994;41:146-150.
29. Strettell MD, Donaldson PT, Thomson LJ, Santrach PJ, Moore SB, Czaja AJ, Williams R. Allelic basis for HLA-encoded susceptibility to type 1 autoimmune hepatitis. Gastroenterology 1997;112:2028-2035.
30. Goldberg AC, Bittencourt PL, Mougin B, Cancado EL, Porta G, Carrilho F, Kalil J. Analysis of HLA haplotypes in autoimmune hepatitis type 1: identifying the major susceptibility locus. Hum Immunol 2001;62:165-169.
31. 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.
32. van Gerven NM, de Boer YS, Zwiers A, Verwer BJ, Drenth JP, van Hoek B, van Erpecum KJ, et al. HLA-DRB1*03:01 and HLA-DRB1*04:01 modify the presentation and outcome in autoimmune hepatitis type-1. Genes Immun 2015;16:247-252.
33. Agarwal K, Czaja AJ, Jones DE, Donaldson PT. Cytotoxic T lymphocyte antigen-4 (CTLA-4) gene polymorphisms and susceptibility to type 1 autoimmune hepatitis. Hepatology 2000;31:49-53.
34. Cookson S, Constantini PK, Clare M, Underhill JA, Bernal W, Czaja AJ, Donaldson PT. Frequency and nature of cytokine gene polymorphisms in type 1 autoimmune hepatitis. Hepatology 1999;30:851-856.
35. Qin B, Li J, Liang Y, Yang Z, Zhong R. The association between cytotoxic T lymphocyte associated antigen-4, Fas, tumour necrosis factor-alpha gene polymorphisms and autoimmune hepatitis: a meta-analysis. Dig Liver Dis 2014;46:541-548.
36. Hiraide A, Imazeki F, Yokosuka O, Kanda T, Kojima H, Fukai K, Suzuki Y, et al. Fas polymorphisms influence susceptibility to autoimmune hepatitis. Am. J. Gastroenterol. 2005;100:1322-1329.
37. 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.

38. 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.
39. Fan L, Tu X, Zhu Y, Zhou L, Pfeiffer T, Feltens R, Stoecker W, et al. Genetic association of vitamin D receptor polymorphisms with autoimmune hepatitis and primary biliary cirrhosis in the Chinese. J. Gastroenterol. Hepatol. 2005;20:249-255.
40. Migita K, Nakamura M, Abiru S, Jiuchi Y, Nagaoka S, Komori A, Hashimoto S, et al. Association of STAT4 polymorphisms with susceptibility to type-1 autoimmune hepatitis in the Japanese population. PLoS One 2013;8:e71382.
41. Paladino N, Flores AC, Fainboim H, Schroder T, Cuarterolo M, Lezama C, Ballerga EG, et al. The most severe forms of type I autoimmune hepatitis are associated with genetically determined levels of TGF-beta1. Clin Immunol 2010;134:305-312.
42. Bucala R. MIF, MIF alleles, and prospects for therapeutic intervention in autoimmunity. J Clin Immunol 2013;33 Suppl 1:S72-78.
43. de Boer YS, van Gerven NM, Zwiers A, Verwer BJ, van Hoek B, van Erpecum KJ, Beuers U, et al. Genome-wide association study identifies variants associated with autoimmune hepatitis type 1. Gastroenterology 2014;147:443-452.
44. Liu M, Zhu W, Wang J, Zhang J, Guo X, Wang J, Song J, et al. Interleukin-23 receptor genetic polymorphisms and ulcerative colitis susceptibility: A meta-analysis. Clin Res Hepatol Gastroenterol 2015;39:516-525.
45. Nagamine K, Peterson P, Scott HS, Kudoh J, Minoshima S, Heino M, Krohn KJ, et al. Positional cloning of the APECED gene. Nat Genet 1997;17:393-398.
46. Christen U, Hintermann E. Pathogen infection as a possible cause for autoimmune hepatitis. Int Rev Immunol 2014;33:296-313.
47. Floreani A, Leung PS, Gershwin ME. Environmental basis of autoimmunity. Clin Rev Allergy Immunol 2016;50:287-300.
48. Oo YH, Hubscher SG, Adams DH. Autoimmune hepatitis: new paradigms in the pathogenesis, diagnosis, and management. Hepatol Int 2010;4:475-493.
49. Trivedi PJ, Adams DH. Mucosal immunity in liver autoimmunity: a comprehensive review. J Autoimmun 2013;46:97-111.
50. Floreani A, Restrepo-Jimenez P, Secchi MF, De Martin S, Leung PSC, Krawitt E, Bowlus CL, et al. Etiopathogenesis of autoimmune hepatitis. J Autoimmun 2018;95:133-143.
51. Sakkas LI, Daoussis D, Mavropoulos A, Liossis SN, Bogdanos DP. Regulatory B cells: New players in inflammatory and autoimmune rheumatic diseases. Semin Arthritis Rheum 2019;48:1133-1141.
52. Kitz A, Singer E, Hafler D. Regulatory T cells: From discovery to autoimmunity. Cold Spring Harb Perspect Med 2018;8.
53. Saligrama N, Zhao F, Sikora MJ, Serratelli WS, Fernandes RA, Louis DM, Yao W, et al. Opposing T cell responses in experimental autoimmune encephalomyelitis. Nature 2019;572:481-487.
54. Chiba A, Murayama G, Miyake S. Mucosal-associated invariant T cells in autoimmune diseases. Front Immunol 2018;9:1333.
55. Oo YH, Adams DH. The role of chemokines in the recruitment of lymphocytes to the liver. J Autoimmun 2010;34:45-54.
56. Alvarez F, Berg PA, Bianchi FB, Bianchi L, Burroughs AK, Cancado EL, Chapman RW, et al. International Autoimmune Hepatitis Group Report: review of criteria for diagnosis of autoimmune hepatitis. J Hepatol 1999;31:929-938.
57. Czaja AJ, Manns MP. The validity and importance of subtypes in autoimmune hepatitis: a point of view. Am J Gastroenterol 1995;90:1206-1211.
58. Muratori P, Granito A, Quarneti C, Ferri S, Menichella R, Cassani F, Pappas G, et al. Autoimmune hepatitis in Italy: the Bologna experience. J Hepatol 2009;50:1210-1218.

59. Muratori P, Lalanne C, Fabbri A, Cassani F, Lenzi M, Muratori L. Type 1 and type 2 autoimmune hepatitis in adults share the same clinical phenotype. Aliment Pharmacol Ther 2015;41:1281-1287.
60. Czaja AJ. Diagnosis and management of autoimmune hepatitis: current status and future directions. Gut Liver 2016;10:177-203.
61. Czaja AJ. Performance parameters of the conventional serological markers for autoimmune hepatitis. Dig Dis Sci 2011;56:545-554.
62. Gregorio GV, Portmann B, Karani J, Harrison P, Donaldson PT, Vergani D, Mieli-Vergani G. Autoimmune hepatitis/sclerosing cholangitis overlap syndrome in childhood: a 16-year prospective study. Hepatology 2001;33:544-553.
63. Czaja AJ. Behavior and significance of autoantibodies in type 1 autoimmune hepatitis. J. Hepatol. 1999;30:394-401.
64. 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.
65. Czaja AJ, Carpenter HA, Manns MP. Antibodies to soluble liver antigen, P450IID6, and mitochondrial complexes in chronic hepatitis. Gastroenterology 1993;105:1522-1528.
66. Kanzler S, Weidemann C, Gerken G, Lohr HF, Galle PR, Meyer zum Buschenfelde KH, Lohse AW. Clinical significance of autoantibodies to soluble liver antigen in autoimmune hepatitis. J Hepatol 1999;31:635-640.
67. Ballot E, Homberg JC, Johanet C. Antibodies to soluble liver antigen: an additional marker in type 1 auto-immune hepatitis. J Hepatol 2000;33:208-215.
68. Baeres M, Herkel J, Czaja AJ, Wies I, Kanzler S, Cancado EL, Porta G, et al. Establishment of standardised SLA/LP immunoassays: specificity for autoimmune hepatitis, worldwide occurrence, and clinical characteristics. Gut 2002;51:259-264.
69. Eyraud V, Chazouilleres O, Ballot E, Corpechot C, Poupon R, Johanet C. Significance of antibodies to soluble liver antigen/liver pancreas: a large French study. Liver Int 2009;29:857-864.
70. Montano-Loza AJ, Shums Z, Norman GL, Czaja AJ. Prognostic implications of antibodies to Ro/SSA and soluble liver antigen in type 1 autoimmune hepatitis. Liver Int. 2012;32:85-92.
71. Efe C, Ozaslan E, Wahlin S, Purnak T, Muratori L, Quarneti C, Yuksel O, et al. Antibodies to soluble liver antigen in patients with various liver diseases: a multicentre study. Liver Int 2013;33:190-196.
72. Ma Y, Okamoto M, Thomas MG, Bogdanos DP, Lopes AR, Portmann B, Underhill J, et al. Antibodies to conformational epitopes of soluble liver antigen define a severe form of autoimmune liver disease. Hepatology 2002;35:658-664.
73. 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.
74. Czaja AJ. Autoantibodies as prognostic markers in autoimmune liver disease. Dig Dis Sci 2010;55:2144-2161.
75. Targan SR, Landers C, Vidrich A, Czaja AJ. High-titer antineutrophil cytoplasmic antibodies in type-1 autoimmune hepatitis. Gastroenterology 1995;108:1159-1166.
76. Bansi D, Chapman R, Fleming K. Antineutrophil cytoplasmic antibodies in chronic liver diseases: prevalence, titre, specificity and IgG subclass. J Hepatol 1996;24:581-586.
77. Terjung B, Sohne J, Lechtenberg B, Gottwein J, Muennich M, Herzog V, Mahler M, et al. p-ANCAs in autoimmune liver disorders recognise human beta-tubulin isotype 5 and cross-react with microbial protein FtsZ. Gut 2010;59:808-816.
78. Elkayam O, Levartovsky D, Brautbar C, Yaron M, Burke M, Vardinon N, Caspi D. Clinical and immunological study of 7 patients with minocycline-induced autoimmune phenomena. Am J Med 1998;105:484-487.

79. Czaja AJ. Cryptogenic chronic hepatitis and its changing guise in adults. Dig. Dis. Sci. 2011;56:3421-3438.
80. Zachou K, Rigopoulou E, Dalekos GN. Autoantibodies and autoantigens in autoimmune hepatitis: important tools in clinical practice and to study pathogenesis of the disease. J Autoimmune Dis 2004;1:2.
81. Czaja AJ, Cassani F, Cataleta M, Valentini P, Bianchi FB. Frequency and significance of antibodies to actin in type 1 autoimmune hepatitis. Hepatology 1996;24:1068-1073.
82. Chretien-Leprince P, Ballot E, Andre C, Olsson NO, Fabien N, Escande A, Oksman F, et al. Diagnostic value of anti-F-actin antibodies in a French multicenter study. Ann N Y Acad Sci 2005;1050:266-273.
83. Frenzel C, Herkel J, Luth S, Galle PR, Schramm C, Lohse AW. Evaluation of F-actin ELISA for the diagnosis of autoimmune hepatitis. Am J Gastroenterol 2006;101:2731-2736.
84. Gueguen P, Dalekos G, Nousbaum JB, Zachou K, Putterman C, Youinou P, Renaudineau Y. Double reactivity against actin and alpha-actinin defines a severe form of autoimmune hepatitis type 1. J Clin Immunol 2006;26:495-505.
85. Zachou K, Oikonomou K, Renaudineau Y, Chauveau A, Gatselis N, Youinou P, Dalekos GN. Anti-alpha actinin antibodies as new predictors of response to treatment in autoimmune hepatitis type 1. Aliment. Pharmacol. Ther. 2012;35:116-125.
86. Renaudineau Y, Dalekos GN, Gueguen P, Zachou K, Youinou P. Anti-alpha-actinin antibodies cross-react with anti-ssDNA antibodies in active autoimmune hepatitis. Clin Rev Allergy Immunol 2008;34:321-325.
87. 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.
88. Abuaf N, Johanet C, Chretien P, Martini E, Soulier E, Laperche S, Homberg JC. Characterization of the liver cytosol antigen type 1 reacting with autoantibodies in chronic active hepatitis. Hepatology 1992;16:892-898.
89. Bachrich T, Thalhammer T, Jager W, Haslmayer P, Alihodzic B, Bakos S, Hitchman E, et al. Characterization of autoantibodies against uridine-diphosphate glucuronosyltransferase in patients with inflammatory liver diseases. Hepatology 2001;33:1053-1059.
90. Obermayer-Straub P, Manns MP. Cytochromes P450 and UDP-glucuronosyl-transferases as hepatocellular autoantigens. Baillieres Clin Gastroenterol 1996;10:501-532.
91. Strassburg CP, Obermayer-Straub P, Alex B, Durazzo M, Rizzetto M, Tukey RH, Manns MP. Autoantibodies against glucuronosyltransferases differ between viral hepatitis and autoimmune hepatitis. Gastroenterology 1996;111:1576-1586.
92. Obermayer-Straub P, Manns MP. Cytochrome P450 enzymes and UDP-glucuronosyltransferases as hepatocellular autoantigens. Mol Biol Rep 1996;23:235-242.
93. Fabien N, Desbos A, Bienvenu J, Magdalou J. Autoantibodies directed against the UDP-glucuronosyltransferases in human autoimmune hepatitis. Autoimmun Rev 2004;3:1-9.
94. Czaja AJ, Shums Z, Norman GL. Nonstandard antibodies as prognostic markers in autoimmune hepatitis. Autoimmunity 2004;37:195-201.
95. Czaja AJ, Carpenter HA. Sensitivity, specificity, and predictability of biopsy interpretations in chronic hepatitis. Gastroenterology 1993;105:1824-1832.
96. Pratt DS, Fawaz KA, Rabson A, Dellelis R, Kaplan MM. A novel histological lesion in glucocorticoid-responsive chronic hepatitis. Gastroenterology 1997;113:664-668.
97. 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.
98. Misdraji J, Thiim M, Graeme-Cook FM. Autoimmune hepatitis with centrilobular necrosis. Am J Surg Pathol 2004;28:471-478.

99. Miyake Y, Iwasaki Y, Terada R, Onishi T, Okamoto R, Takaguchi K, Ikeda H, et al. Clinical features of Japanese type 1 autoimmune hepatitis patients with zone III necrosis. Hepatol Res 2007;37:801-805.
100. Stravitz RT, Lefkowitch JH, Fontana RJ, Gershwin ME, Leung PS, Sterling RK, Manns MP, et al. Autoimmune acute liver failure: proposed clinical and histological criteria. Hepatology 2011;53:517-526.
101. Humble JG, Jayne WH, Pulvertaft RJ. Biological interaction between lymphocytes and other cells. Br J Haematol 1956;2:283-294.
102. Rastogi V, Sharma R, Misra SR, Yadav L, Sharma V. Emperipolesis - a review. J Clin Diagn Res 2014;8:ZM01-02.
103. Balitzer D, Shafizadeh N, Peters MG, Ferrell LD, Alshak N, Kakar S. Autoimmune hepatitis: review of histologic features included in the simplified criteria proposed by the international autoimmune hepatitis group and proposal for new histologic criteria. Mod Pathol 2017;30:773-783.
104. 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.
105. Roberts SK, Therneau TM, Czaja AJ. Prognosis of histological cirrhosis in type 1 autoimmune hepatitis. Gastroenterology 1996;110:848-857.
106. 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.
107. Liberal R, Grant CR. Cirrhosis and autoimmune liver disease: Current understanding. World J Hepatol 2016;8:1157-1168.
108. Mieli-Vergani G, Vergani D, Baumann U, Czubkowski P, Debray D, Dezsofi A, Fischler B, et al. Diagnosis and management of pediatric autoimmune liver disease: ESPGHAN Hepatology Committee position statement. J Pediatr Gastroenterol Nutr 2018;66:345-360.
109. 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.
110. 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.
111. Wang KK, Czaja AJ. Hepatocellular carcinoma in corticosteroid-treated severe autoimmune chronic active hepatitis. Hepatology 1988;8:1679-1683.
112. Park SZ, Nagorney DM, Czaja AJ. Hepatocellular carcinoma in autoimmune hepatitis. Dig Dis Sci 2000;45:1944-1948.
113. Montano-Loza AJ, Carpenter HA, Czaja AJ. Predictive factors for hepatocellular carcinoma in type 1 autoimmune hepatitis. Am J Gastroenterol 2008;103:1944-1951.
114. Yeoman AD, Al-Chalabi T, Karani JB, Quaglia A, Devlin J, Mieli-Vergani G, Bomford A, 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.
115. Chung H, Watanabe T, Kudo M, Maenishi O, Wakatsuki Y, Chiba T. Identification and characterization of IgG4-associated autoimmune hepatitis. Liver Int 2010;30:222-231.
116. Umemura T, Zen Y, Hamano H, Joshita S, Ichijo T, Yoshizawa K, Kiyosawa K, et al. Clinical significance of immunoglobulin G4-associated autoimmune hepatitis. J Gastroenterol 2011;46 Suppl 1:48-55.
117. Yada N, Kudo M, Chung H, Watanabe T. Autoimmune hepatitis and immunoglobulin g4-associated autoimmune hepatitis. Dig Dis 2013;31:415-420.
118. De Luca-Johnson J, Wangensteen KJ, Hanson J, Krawitt E, Wilcox R. Natural history of patients presenting with autoimmune hepatitis and coincident nonalcoholic fatty liver disease. Dig Dis Sci 2016;61:2710-2720.

119. Takahashi A, Arinaga-Hino T, Ohira H, Abe K, Torimura T, Zeniya M, Abe M, et al. Non-alcoholic fatty liver disease in patients with autoimmune hepatitis. JGH Open 2018;2:54-58.
120. Johnson PJ, McFarlane IG. Meeting report: International Autoimmune Hepatitis Group. Hepatology 1993;18:998-1005.
121. Hennes EM, Zeniya M, Czaja AJ, Pares A, Dalekos GN, Krawitt EL, Bittencourt PL, et al. Simplified criteria for the diagnosis of autoimmune hepatitis. Hepatology 2008;48:169-176.
122. Czaja AJ. Performance parameters of the diagnostic scoring systems for autoimmune hepatitis. Hepatology 2008;48:1540-1548.
123. Arcos-Machancoses JV, Molera Busoms C, Julio Tatis E, Bovo MV, Martin de Carpi J. Accuracy of the simplified criteria for autoimmune hepatitis in children: systematic review and decision analysis. J Clin Exp Hepatol 2019;9:147-155.
124. 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.
125. Yatsuji S, Hashimoto E, Kaneda H, Taniai M, Tokushige K, Shiratori K. Diagnosing autoimmune hepatitis in nonalcoholic fatty liver disease: is the International Autoimmune Hepatitis Group scoring system useful? J Gastroenterol 2005;40:1130-1138.
126. Boberg KM, Chapman RW, Hirschfield GM, Lohse AW, Manns MP, Schrumpf E, International Autoimmune Hepatitis G. Overlap syndromes: the International Autoimmune Hepatitis Group (IAIHG) position statement on a controversial issue. J Hepatol 2011;54:374-385.
127. 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.
128. Czaja AJ. Natural history, clinical features, and treatment of autoimmune hepatitis. Semin Liver Dis 1984;4:1-12.
129. Muratori P, Fabbri A, Lalanne C, Lenzi M, Muratori L. Autoimmune liver disease and concomitant extrahepatic autoimmune disease. Eur J Gastroenterol Hepatol 2015;27:1175-1179.
130. 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.
131. Czaja AJ. Features and consequences of untreated type 1 autoimmune hepatitis. Liver Int. 2009;29:816-823.
132. Muratori P, Lalanne C, Barbato E, Fabbri A, Cassani F, Lenzi M, Muratori L. Features and progression of asymptomatic autoimmune hepatitis in Italy. Clin Gastroenterol Hepatol 2016;14:139-146.
133. Nikias GA, Batts KP, Czaja AJ. The nature and prognostic implications of autoimmune hepatitis with an acute presentation. J. Hepatol. 1994;21:866-871.
134. Ferrari R, Pappas G, Agostinelli D, Muratori P, Muratori L, Lenzi M, Verucchi G, et al. Type 1 autoimmune hepatitis: patterns of clinical presentation and differential diagnosis of the 'acute' type. QJM 2004;97:407-412.
135. 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.
136. Czaja AJ. Acute and acute severe (fulminant) autoimmune hepatitis. Dig Dis Sci 2013;58:897-914.
137. Lee WS, McKiernan P, Kelly DA. Etiology, outcome and prognostic indicators of childhood fulminant hepatic failure in the United kingdom. J. Pediatr. Gastroenterol. Nutr. 2005;40:575-581.
138. 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.
139. Anand L, Choudhury A, Bihari C, Sharma BC, Kumar M, Maiwall R, Siam Tan S, et al. Flare of autoimmune hepatitis causing acute on chronic liver failure: diagnosis and response to corticosteroid therapy. Hepatology 2019;70:587-596.

140. Yasui S, Fujiwara K, Yonemitsu Y, Oda S, Nakano M, Yokosuka O. Clinicopathological features of severe and fulminant forms of autoimmune hepatitis. J. Gastroenterol. 2011;46:378-390.
141. Fujiwara K, Fukuda Y, Yokosuka O. Precise histological evaluation of liver biopsy specimen is indispensable for diagnosis and treatment of acute-onset autoimmune hepatitis. J Gastroenterol 2008;43:951-958.
142. Yasui S, Fujiwara K, Okitsu K, Yonemitsu Y, Ito H, Yokosuka O. Importance of computed tomography imaging features for the diagnosis of autoimmune acute liver failure. Hepatol. Res. 2012;42:42-50.
143. Heringlake S, Schutte A, Flemming P, Schmiegel W, Manns MP, Tillmann HL. Presumed cryptogenic liver disease in Germany: High prevalence of autoantibody-negative autoimmune hepatitis, low prevalence of NASH, no evidence for occult viral etiology. Z Gastroenterol 2009;47:417-423.
144. Mehendiratta V, Mitroo P, Bombonati A, Navarro VJ, Rossi S, Rubin R, Herrine SK. Serologic markers do not predict histologic severity or response to treatment in patients with autoimmune hepatitis. Clin Gastroenterol Hepatol 2009;7:98-103.
145. Miyake Y, Yamamoto K. Current status of autoimmune hepatitis in Japan. Acta Med Okayama 2008;62:217-226.
146. 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.
147. 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.
148. Czaja AJ. Autoantibody-negative autoimmune hepatitis. Dig. Dis. Sci. 2012;57:610-624.
149. Bittencourt PL, Farias AQ, Porta G, Cancado EL, Miura I, Pugliese R, Kalil J, 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.
150. Teufel A, Weinmann A, Kahaly GJ, Centner C, Piendl A, Worns M, Lohse AW, et al. Concurrent autoimmune diseases in patients with autoimmune hepatitis. J Clin Gastroenterol 2010;44:208-213.
151. Efe C, Wahlin S, Ozaslan E, Berlot AH, Purnak T, Muratori L, Quarneti C, et al. Autoimmune hepatitis/primary biliary cirrhosis overlap syndrome and associated extrahepatic autoimmune diseases. Eur J Gastroenterol Hepatol 2012;24:531-534.
152. Wong GW, Yeong T, Lawrence D, Yeoman AD, Verma S, Heneghan MA. Concurrent extrahepatic autoimmunity in autoimmune hepatitis: implications for diagnosis, clinical course and long-term outcomes. Liver Int 2017;37:449-457.
153. Homberg JC, Abuaf N, Bernard O, Islam S, Alvarez F, Khalil SH, Poupon R, et al. Chronic active hepatitis associated with antiliver/kidney microsome antibody type 1: a second type of "autoimmune" hepatitis. Hepatology 1987;7:1333-1339.
154. 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.
155. Lankisch TO, Jaeckel E, Strassburg CP. The autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy or autoimmune polyglandular syndrome type 1. Semin Liver Dis 2009;29:307-314.
156. Czaja AJ, Carpenter HA. Distinctive clinical phenotype and treatment outcome of type 1 autoimmune hepatitis in the elderly. Hepatology 2006;43:532-538.
157. Czaja AJ, Carpenter HA, Santrach PJ, Moore SB. Significance of HLA DR4 in type 1 autoimmune hepatitis. Gastroenterology 1993;105:1502-1507.
158. Czaja AJ, Strettell MD, Thomson LJ, Santrach PJ, Moore SB, Donaldson PT, Williams R. Associations between alleles of the major histocompatibility complex and type 1 autoimmune hepatitis. Hepatology 1997;25:317-323.

159. Fogel R, Comerford M, Chilukuri P, Orman E, Chalasani N, Lammert C. Extrahepatic Autoimmune Diseases are Prevalent in Autoimmune Hepatitis Patients and Their First-Degree Relatives: Survey Study. Interact J Med Res 2018;7:e18.
160. Volta U, De Franceschi L, Molinaro N, Cassani F, Muratori L, Lenzi M, Bianchi FB, et al. Frequency and significance of anti-gliadin and anti-endomysial antibodies in autoimmune hepatitis. Dig Dis Sci 1998;43:2190-2195.
161. van Gerven NM, Bakker SF, de Boer YS, Witte BI, Bontkes H, van Nieuwkerk CM, Mulder CJ, et al. Seroprevalence of celiac disease in patients with autoimmune hepatitis. Eur J Gastroenterol Hepatol 2014;26:1104-1107.
162. Caprai S, Vajro P, Ventura A, Sciveres M, Maggiore G, Disease SSGfALDiC. Autoimmune liver disease associated with celiac disease in childhood: a multicenter study. Clin Gastroenterol Hepatol 2008;6:803-806.
163. Volta U, De Franceschi L, Lari F, Molinaro N, Zoli M, Bianchi FB. Coeliac disease hidden by cryptogenic hypertransaminasaemia. Lancet 1998;352:26-29.
164. Volta U, Granito A, De Franceschi L, Petrolini N, Bianchi FB. Anti tissue transglutaminase antibodies as predictors of silent coeliac disease in patients with hypertransaminasaemia of unknown origin. Dig Liver Dis 2001;33:420-425.
165. Volta U. Pathogenesis and clinical significance of liver injury in celiac disease. Clin Rev Allergy Immunol 2009;36:62-70.
166. Nastasio S, Sciveres M, Riva S, Filippeschi IP, Vajro P, Maggiore G. Celiac disease-associated autoimmune hepatitis in childhood: long-term response to treatment. J Pediatr Gastroenterol Nutr 2013;56:671-674.
167. Marciano F, Savoia M, Vajro P. Celiac disease-related hepatic injury: Insights into associated conditions and underlying pathomechanisms. Dig Liver Dis 2016;48:112-119.
168. Domschke W, Klein R, Terracciano LM, Jung P, Kirchner T, Berg PA, Bianchi L. Sequential occurrence of primary sclerosing cholangitis and autoimmune hepatitis type III in a patient with ulcerative colitis: a follow up study over 14 years. Liver 2000;20:340-345.
169. Abdo AA, Bain VG, Kichian K, Lee SS. Evolution of autoimmune hepatitis to primary sclerosing cholangitis: A sequential syndrome. Hepatology 2002;36:1393-1399.
170. Poupon R, Chazouilleres O, Corpechot C, Chretien Y. Development of autoimmune hepatitis in patients with typical primary biliary cirrhosis. Hepatology 2006;44:85-90.
171. Gossard AA, Lindor KD. Development of autoimmune hepatitis in primary biliary cirrhosis. Liver Int. 2007;27:1086-1090.
172. Lindgren S, Glaumann H, Almer S, Bergquist A, Bjornsson E, Broome U, Danielsson A, et al. Transitions between variant forms of primary biliary cirrhosis during long-term follow-up. Eur J Intern Med 2009;20:398-402.
173. Czaja AJ. Cholestatic phenotypes of autoimmune hepatitis. Clin Gastroenterol Hepatol 2014;12:1430-1438.
174. Czaja AJ. The variant forms of autoimmune hepatitis. Ann Intern Med 1996;125:588-598.
175. Czaja AJ. Frequency and nature of the variant syndromes of autoimmune liver disease. Hepatology 1998;28:360-365.
176. Czaja AJ, Carpenter HA. Autoimmune hepatitis overlap syndromes and liver pathology. Gastroenterol Clin North Am 2017;46:345-364.
177. 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.

178. Farias AQ, Goncalves LL, Bittencourt PL, De Melo ES, Abrantes-Lemos CP, Porta G, Nakhle MC, 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.
179. Beuers U, Boberg KM, Chapman RW, Chazouilleres O, Invernizzi P, Jones DEJ, Lammert F, et al. EASL Clinical Practice Guidelines: management of cholestatic liver diseases. J Hepatol 2009;51:237-267.
180. Beuers U, Gershwin ME, Gish RG, Invernizzi P, Jones DE, Lindor K, Ma X, et al. Changing nomenclature for PBC: From 'cirrhosis' to 'cholangitis'. Hepatology 2015;62:1620-1622.
181. Kuiper EM, Zondervan PE, van Buuren HR. Paris criteria are effective in diagnosis of primary biliary cirrhosis and autoimmune hepatitis overlap syndrome. Clin Gastroenterol Hepatol 2010;8:530-534.
182. Bonder A, Retana A, Winston DM, Leung J, Kaplan MM. Prevalence of primary biliary cirrhosis-autoimmune hepatitis overlap syndrome. Clin Gastroenterol Hepatol 2011;9:609-612.
183. 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.
184. 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.
185. Olsson R, Glaumann H, Almer S, Broome U, Lebrun B, Bergquist A, Bjornsson E, et al. High prevalence of small duct primary sclerosing cholangitis among patients with overlapping autoimmune hepatitis and primary sclerosing cholangitis. Eur J Intern Med 2009;20:190-196.
186. Muratori P, Muratori L, Gershwin ME, Czaja AJ, Pappas G, MacCariello S, Granito A, et al. 'True' antimitochondrial antibody-negative primary biliary cirrhosis, low sensitivity of the routine assays, or both? Clin Exp Immunol 2004;135:154-158.
187. Bjornsson E, Talwalkar J, Treeprasertsuk S, Kamath PS, Takahashi N, Sanderson S, Neuhauser M, et al. Drug-induced autoimmune hepatitis: clinical characteristics and prognosis. Hepatology 2010;51:2040-2048.
188. Czaja AJ. Drug-induced autoimmune-like hepatitis. Dig Dis Sci 2011;56:958-976.
189. Castiella A, Lucena MI, E.M. Z, Otazua P, Andrade RJ. Drug-induced autoimmune-like hepatitis: a diagnostic challenge. Dig Dis Sci 2011;56:2501-2502.
190. deLemos AS, Foureau DM, Jacobs C, Ahrens W, Russo MW, Bonkovsky HL. Drug-induced liver injury with autoimmune features. Semin Liver Dis 2014;34:194-204.
191. Licata A, Maida M, Cabibi D, Butera G, Macaluso FS, Alessi N, Caruso C, et al. Clinical features and outcomes of patients with drug-induced autoimmune hepatitis: a retrospective cohort study. Dig Liver Dis 2014;46:1116-1120.
192. 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.
193. 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.
194. Bhat G, Jordan J, Jr., Sokalski S, Bajaj V, Marshall R, Berkelhammer C. Minocycline-induced hepatitis with autoimmune features and neutropenia. J Clin Gastroenterol 1998;27:74-75.
195. Teitelbaum JE, Perez-Atayde AR, Cohen M, Bousvaros A, Jonas MM. Minocycline-related autoimmune hepatitis: case series and literature review. Arch Pediatr Adolesc Med 1998;152:1132-1136.
196. Goldstein NS, Bayati N, Silverman AL, Gordon SC. Minocycline as a cause of drug-induced autoimmune hepatitis. Report of four cases and comparison with autoimmune hepatitis. Am J Clin Pathol 2000;114:591-598.
197. Abe M, Furukawa S, Takayama S, Michitaka K, Minami H, Yamamoto K, Horiike N, et al. Drug-induced hepatitis with autoimmune features during minocycline therapy. Intern Med 2003;42:48-52.

198. Ramakrishna J, Johnson AR, Banner BF. Long-term minocycline use for acne in healthy adolescents can cause severe autoimmune hepatitis. J Clin Gastroenterol 2009;43:787-790.
199. Hatoff DE, Cohen M, Schweigert BF, Talbert WM. Nitrofurantoin: another cause of drug-induced chronic active hepatitis? A report of a patient with HLA-B8 antigen. Am J Med 1979;67:117-121.
200. Sharp JR, Ishak KG, Zimmerman HJ. Chronic active hepatitis and severe hepatic necrosis associated with nitrofurantoin. Ann Intern Med 1980;92:14-19.
201. Stricker BH, Blok AP, Claas FH, Van Parys GE, Desmet VJ. Hepatic injury associated with the use of nitrofurans: a clinicopathological study of 52 reported cases. Hepatology 1988;8:599-606.
202. Paiva LA, Wright PJ, Koff RS. Long-term hepatic memory for hypersensitivity to nitrofurantoin. Am J Gastroenterol 1992;87:891-893.
203. Amit G, Cohen P, Ackerman Z. Nitrofurantoin-induced chronic active hepatitis. Isr Med Assoc J 2002;4:184-186.
204. Fontana RJ, Seeff LB, Andrade RJ, Bjornsson E, Day CP, Serrano J, Hoofnagle JH. Standardization of nomenclature and causality assessment in drug-induced liver injury: summary of a clinical research workshop. Hepatology 2010;52:730-742.
205. Appleyard S, Saraswati R, Gorard DA. Autoimmune hepatitis triggered by nitrofurantoin: a case series. J Med Case Rep 2010;4:311.
206. Germano V, Picchianti Diamanti A, Baccano G, Natale E, Onetti Muda A, Priori R, Valesini G. Autoimmune hepatitis associated with infliximab in a patient with psoriatic arthritis. Ann Rheum Dis 2005;64:1519-1520.
207. Tobon GJ, Canas C, Jaller JJ, Restrepo JC, Anaya JM. Serious liver disease induced by infliximab. Clin Rheumatol 2007;26:578-581.
208. Ozorio G, McGarity B, Bak H, Jordan AS, Lau H, Marshall C. Autoimmune hepatitis following infliximab therapy for ankylosing spondylitis. Med J Aust 2007;187:524-526.
209. Marques M, Magro F, Cardoso H, Carneiro F, Portugal R, Lopes J, Costa Santos C. Infliximab-induced lupus-like syndrome associated with autoimmune hepatitis. Inflamm Bowel Dis 2008;14:723-725.
210. Carlsen KM, Riis L, Madsen OR. Toxic hepatitis induced by infliximab in a patient with rheumatoid arthritis with no relapse after switching to etanercept. Clin Rheumatol 2009;28:1001-1003.
211. Fairhurst DA, Sheehan-Dare R. Autoimmune hepatitis associated with infliximab in a patient with palmoplantar pustular psoriaisis. Clin Exp Dermatol 2009;34:421-422.
212. Subramaniam K, Chitturi S, Brown M, Pavli P. Infliximab-induced autoimmune hepatitis in Crohn's disease treated with budesonide and mycophenolate. Inflammatory bowel diseases 2011;17:E149-150.
213. Goldfeld DA, Verna EC, Lefkowitch J, Swaminath A. Infliximab-induced autoimmune hepatitis with successful switch to adalimumab in a patient with Crohn's disease: the index case. Dig Dis Sci 2011;56:3386-3388.
214. Bjornsson ES, Bergmann OM, Bjornsson HK, Kvaran RB, Olafsson S. Incidence, presentation, and outcomes in patients with drug-induced liver injury in the general population of Iceland. Gastroenterology 2013;144:1419-1425.
215. Efe C. Drug induced autoimmune hepatitis and TNF-alpha blocking agents: is there a real relationship? Autoimmun Rev 2013;12:337-339.
216. Ghabril M, Bonkovsky HL, Kum C, Davern T, Hayashi PH, Kleiner DE, Serrano J, et al. Liver injury from tumor necrosis factor-alpha antagonists: analysis of thirty-four cases. Clin Gastroenterol Hepatol 2013;11:558-564 e553.
217. Dang LJ, Lubel JS, Gunatheesan S, Hosking P, Su J. Drug-induced lupus and autoimmune hepatitis secondary to infliximab for psoriasis. Australas J Dermatol 2014;55:75-79.

218. Bjornsson ES, Gunnarsson BI, Grondal G, Jonasson JG, Einarsdottir R, Ludviksson BR, Gudbjornsson B, et al. Risk of drug-induced liver injury from tumor necrosis factor antagonists. Clin Gastroenterol Hepatol 2015;13:602-608.
219. Rodrigues S, Lopes S, Magro F, Cardoso H, Horta e Vale AM, Marques M, Mariz E, et al. Autoimmune hepatitis and anti-tumor necrosis factor alpha therapy: A single center report of 8 cases. World J Gastroenterol 2015;21:7584-7588.
220. French JB, Bonacini M, Ghabril M, Foureau D, Bonkovsky HL. Hepatotoxicity associated with the use of anti-TNF-alpha agents. Drug Saf 2016;39:199-208.
221. Ricciuto A, Kamath BM, Walters TD, Frost K, Carman N, Church PC, Ling SC, et al. New onset autoimmune hepatitis during anti-tumor necrosis factor-alpha treatment in children. J Pediatr 2018;194:128-135 e121.
222. Young A, Quandt Z, Bluestone JA. The balancing act between cancer immunity and autoimmunity in response to immunotherapy. Cancer Immunol Res 2018;6:1445-1452.
223. Myers G. Immune-related adverse events of immune checkpoint inhibitors: a brief review. Curr Oncol 2018;25:342-347.
224. Czaja AJ. Immune inhibitory proteins and their pathogenic and therapeutic implications in autoimmunity and autoimmune hepatitis. Autoimmunity 2019;52:144-160.
225. Kleiner DE, Berman D. Pathologic changes in ipilimumab-related hepatitis in patients with metastatic melanoma. Dig Dis Sci 2012;57:2233-2240.
226. Reddy HG, Schneider BJ, Tai AW. Immune checkpoint inhibitor-associated colits and hepatitis. Clin Transl Gastroenterol 2018;9:180.
227. Reynolds K, Thomas M, Dougan M. Diagnosis and management of hepatitis in patients on checkpoint blockade. Oncologist 2018;23:991-997.
228. Zen Y, Yeh MM. Hepatotoxicity of immune checkpoint inhibitors: a histology study of seven cases in comparison with autoimmune hepatitis and idiosyncratic drug-induced liver injury. Mod Pathol 2018;31:965-973.
229. Nishida N, Kudo M. Liver damage related to immune checkpoint inhibitors. Hepatol Int 2019:DOI: 10.1007/s12072-12018-19921-12077.
230. Doherty GJ, Duckworth AM, Davies SE, Mells GF, Brais R, Harden SV, Parkinson CA, et al. Severe steroid-resistant anti-PD1 T-cell checkpoint inhibitor-induced hepatotoxicity driven by biliary injury. ESMO Open 2017;2:e000268.
231. Lewis JH, Zimmerman HJ: Drug-induced autoimmune liver disease. In: Krawitt EL, Wiesner RH, Nishioka K, eds. Autoimmune Liver Diseases. 2nd edition ed. Amsterdam: Elsevier Science BV, 1998; 627-649.
232. Liu ZX, Kaplowitz N. Immune-mediated drug-induced liver disease. Clin Liver Dis 2002;6:755-774.
233. Watkins PB, Seeff LB. Drug-induced liver injury: summary of a single topic clinical research conference. Hepatology 2006;43:618-631.
234. Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN prospective study. Gastroenterology 2015;148:1340-1352 e1347.
235. Ramachandran R, Kakar S. Histological patterns in drug-induced liver disease. J Clin Pathol 2009;62:481-492.
236. de Boer YS, Kosinski AS, Urban TJ, Zhao Z, Long N, Chalasani N, Kleiner DE, et al. Features of autoimmune hepatitis in patients with drug-induced liver injury. Clin Gastroenterol Hepatol 2017;15:103-112.
237. Suzuki A, Brunt EM, Kleiner DE, Miquel R, Smyrk TC, Andrade RJ, Lucena MI, et al. The use of liver biopsy evaluation in discrimination of idiopathic autoimmune hepatitis versus drug-induced liver injury. Hepatology 2011;54:931-939.

238. Bjornsson E, Kalaitzakis E, Av Klinteberg V, Alem N, Olsson R. Long-term follow-up of patients with mild to moderate drug-induced liver injury. Aliment Pharmacol Ther 2007;26:79-85.
239. Bjornsson E, Davidsdottir L. The long-term follow-up after idiosyncratic drug-induced liver injury with jaundice. J Hepatol 2009;50:511-517.
240. Bjornsson E, Olsson R. Outcome and prognostic markers in severe drug-induced liver disease. Hepatology 2005;42:481-489.
241. Andrade RJ, Lucena MI, Fernandez MC, Pelaez G, Pachkoria K, Garcia-Ruiz E, Garcia-Munoz B, et al. Drug-induced liver injury: an analysis of 461 incidences submitted to the Spanish registry over a 10-year period. Gastroenterology 2005;129:512-521.
242. Robles-Diaz M, Lucena MI, Kaplowitz N, Stephens C, Medina-Caliz I, Gonzalez-Jimenez A, Ulzurrun E, et al. Use of Hy's law and a new composite algorithm to predict acute liver failure in patients with drug-induced liver injury. Gastroenterology 2014;147:109-118 e105.
243. Montano-Loza AJ, Carpenter HA, Czaja AJ. Consequences of treatment withdrawal in type 1 autoimmune hepatitis. Liver Int. 2007;27:507-515.
244. van Gerven NM, Verwer BJ, Witte BI, van Hoek B, Coenraad MJ, van Erpecum KJ, Beuers U, et al. Relapse is almost universal after withdrawal of immunosuppressive medication in patients with autoimmune hepatitis in remission. J Hepatol 2013;58:141-147.
245. Castiella A, Zapata E, Lucena MI, Andrade RJ. Drug-induced autoimmune liver disease: A diagnostic dilemma of an increasingly reported disease. World J Hepatol 2014;6:160-168.
246. Fontana RJ, Hayashi PH, Gu J, Reddy KR, Barnhart H, Watkins PB, Serrano J, et al. Idiosyncratic drug-induced liver injury is associated with substantial morbidity and mortality within 6 months from onset. Gastroenterology 2014;147:96-108 e104.
247. Ngo Y, Munteanu M, Messous D, Charlotte F, Imbert-Bismut F, Thabut D, Lebray P, et al. A prospective analysis of the prognostic value of biomarkers (FibroTest) in patients with chronic hepatitis C. Clin Chem 2006;52:1887-1896.
248. Poynard T, Ngo Y, Perazzo H, Munteanu M, Lebray P, Moussalli J, Thabut D, et al. Prognostic value of liver fibrosis biomarkers: a meta-analysis. Gastroenterol Hepatol (N Y) 2011;7:445-454.
249. Poynard T, de Ledinghen V, Zarski JP, Stanciu C, Munteanu M, Vergniol J, France J, et al. Relative performances of FibroTest, Fibroscan, and biopsy for the assessment of the stage of liver fibrosis in patients with chronic hepatitis C: a step toward the truth in the absence of a gold standard. J Hepatol 2012;56:541-548.
250. Wai CT, Greenson JK, Fontana RJ, Kalbfleisch JD, Marrero JA, Conjeevaram HS, Lok AS. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Hepatology 2003;38:518-526.
251. Sterling RK, Lissen E, Clumeck N, Sola R, Correa MC, Montaner J, M SS, et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatology 2006;43:1317-1325.
252. Shah AG, Lydecker A, Murray K, Tetri BN, Contos MJ, Sanyal AJ. Comparison of noninvasive markers of fibrosis in patients with nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol 2009;7:1104-1112.
253. Parkes J, Roderick P, Harris S, Day C, Mutimer D, Collier J, Lombard M, et al. Enhanced liver fibrosis test can predict clinical outcomes in patients with chronic liver disease. Gut 2010;59:1245-1251.
254. Parkes J, Guha IN, Roderick P, Harris S, Cross R, Manos MM, Irving W, et al. Enhanced Liver Fibrosis (ELF) test accurately identifies liver fibrosis in patients with chronic hepatitis C. J Viral Hepat 2011;18:23-31.
255. Poynard T, Morra R, Ingiliz P, Imbert-Bismut F, Thabut D, Messous D, Munteanu M, et al. Biomarkers of liver fibrosis. Adv Clin Chem 2008;46:131-160.

256. Czaja AJ. Review article: Prevention and reversal of hepatic fibrosis in autoimmune hepatitis. Aliment Pharmacol Ther 2014;39:385-406.
257. Guha IN, Parkes J, Roderick P, Chattopadhyay D, Cross R, Harris S, Kaye P, et al. Noninvasive markers of fibrosis in nonalcoholic fatty liver disease: Validating the European Liver Fibrosis Panel and exploring simple markers. Hepatology 2008;47:455-460.
258. Mayo MJ, Parkes J, Adams-Huet B, Combes B, Mills AS, Markin RS, Rubin R, et al. Prediction of clinical outcomes in primary biliary cirrhosis by serum enhanced liver fibrosis assay. Hepatology 2008;48:1549-1557.
259. Wu S, Yang Z, Zhou J, Zeng N, He Z, Zhan S, Jia J, et al. Systematic review: diagnostic accuracy of non-invasive tests for staging liver fibrosis in autoimmune hepatitis. Hepatol Int 2019;13:91-101.
260. Hartl J, Denzer U, Ehlken H, Zenouzi R, Peiseler M, Sebode M, Hubener S, et al. Transient elastography in autoimmune hepatitis: Timing determines the impact of inflammation and fibrosis. J Hepatol 2016;65:769-775.
261. Xu Q, Sheng L, Bao H, Chen X, Guo C, Li H, Ma X, et al. Evaluation of transient elastography in assessing liver fibrosis in patients with autoimmune hepatitis. J Gastroenterol Hepatol 2017;32:639-644.
262. Guo L, Zheng L, Hu L, Zhou H, Yu L, Liang W. Transient Elastography (FibroScan) Performs Better Than Non-Invasive Markers in Assessing Liver Fibrosis and Cirrhosis in Autoimmune Hepatitis Patients. Med Sci Monit 2017;23:5106-5112.
263. Sagir A, Erhardt A, Schmitt M, Haussinger D. Transient elastography is unreliable for detection of cirrhosis in patients with acute liver damage. Hepatology 2008;47:592-595.
264. Romanque P, Stickel F, Dufour JF. Disproportionally high results of transient elastography in patients with autoimmune hepatitis. Liver Int 2008;28:1177-1178.
265. Hartl J, Ehlken H, Sebode M, Peiseler M, Krech T, Zenouzi R, von Felden J, et al. Usefulness of biochemical remission and transient elastography in monitoring disease course in autoimmune hepatitis. J Hepatol 2018;68:754-763.
266. Huwart L, Sempoux C, Vicaut E, Salameh N, Annet L, Danse E, Peeters F, et al. Magnetic resonance elastography for the noninvasive staging of liver fibrosis. Gastroenterology 2008;135:32-40.
267. Venkatesh SK, Yin M, Ehman RL. Magnetic resonance elastography of liver: technique, analysis, and clinical applications. J Magn Reson Imaging 2013;37:544-555.
268. Loomba R, Wolfson T, Ang B, Hooker J, Behling C, Peterson M, Valasek M, et al. Magnetic resonance elastography predicts advanced fibrosis in patients with nonalcoholic fatty liver disease: a prospective study. Hepatology 2014;60:1920-1928.
269. Wang J, Malik N, Yin M, Smyrk TC, Czaja AJ, Ehman RL, Venkatesh SK. Magnetic resonance elastography is accurate in detecting advanced fibrosis in autoimmune hepatitis. World J Gastroenterol 2017;23:859-868.
270. Talwalkar JA, Yin M, Venkatesh S, Rossman PJ, Grimm RC, Manduca A, Romano A, et al. Feasibility of in vivo MR elastographic splenic stiffness measurements in the assessment of portal hypertension. Am J Roentgenol 2009;193:122-127.
271. Shi Y, Guo Q, Xia F, Dzyubak B, Glaser KJ, Li Q, Li J, et al. MR elastography for the assessment of hepatic fibrosis in patients with chronic hepatitis B infection: does histologic necroinflammation influence the measurement of hepatic stiffness? Radiology 2014;273:88-98.
272. D'Onofrio M, Crosara S, De Robertis R, Canestrini S, Demozzi E, Gallotti A, Pozzi Mucelli R. Acoustic radiation force impulse of the liver. World J Gastroenterol 2013;19:4841-4849.
273. Bruno C, Minniti S, Bucci A, Pozzi Mucelli R. ARFI: from basic principles to clinical applications in diffuse chronic disease-a review. Insights Imaging 2016;7:735-746.
274. Piscaglia F, Salvatore V, Di Donato R, D'Onofrio M, Gualandi S, Gallotti A, Peri E, et al. Accuracy of VirtualTouch Acoustic Radiation Force Impulse (ARFI) imaging for the diagnosis of cirrhosis during liver ultrasonography. Ultraschall Med 2011;32:167-175.

275. Bota S, Herkner H, Sporea I, Salzl P, Sirli R, Neghina AM, Peck-Radosavljevic M. Meta-analysis: ARFI elastography versus transient elastography for the evaluation of liver fibrosis. Liver Int 2013;33:1138-1147.
276. Ye XP, Ran HT, Cheng J, Zhu YF, Zhang DZ, Zhang P, Zheng YY. Liver and spleen stiffness measured by acoustic radiation force impulse elastography for noninvasive assessment of liver fibrosis and esophageal varices in patients with chronic hepatitis B. J Ultrasound Med 2012;31:1245-1253.
277. Morishita N, Hiramatsu N, Oze T, Harada N, Yamada R, Miyazaki M, Yakushijin T, et al. Liver stiffness measurement by acoustic radiation force impulse is useful in predicting the presence of esophageal varices or high-risk esophageal varices among patients with HCV-related cirrhosis. J Gastroenterol 2014;49:1175-1182.
278. Karlas TF, Pfrepper C, Rosendahl J, Benckert C, Wittekind C, Jonas S, Moessner J, et al. Acoustic radiation force impulse (ARFI) elastography in acute liver failure: necrosis mimics cirrhosis. Z Gastroenterol 2011;49:443-448.
279. Bacon BR, Treuhaft WH, Goodman AM. Azathioprine-induced pancytopenia. Occurrence in two patients with connective-tissue diseases. Arch. Intern. Med. 1981;141:223-226.
280. 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.
281. Szumlanski CL, Honchel R, Scott MC, Weinshilboum RM. Human liver thiopurine methyltransferase pharmacogenetics: biochemical properties, liver-erythrocyte correlation and presence of isozymes. Pharmacogenetics 1992;2:148-159.
282. Otterness D, Szumlanski C, Lennard L, Klemetsdal B, Aarbakke J, Park-Hah JO, Iven H, et al. Human thiopurine methyltransferase pharmacogenetics: gene sequence polymorphisms. Clin Pharmacol Ther 1997;62:60-73.
283. Yates CR, Krynetski EY, Loennechen T, Fessing MY, Tai HL, Pui CH, Relling MV, et al. Molecular diagnosis of thiopurine S-methyltransferase deficiency: genetic basis for azathioprine and mercaptopurine intolerance. Ann Intern Med 1997;126:608-614.
284. Sahasranaman S, Howard D, Roy S. Clinical pharmacology and pharmacogenetics of thiopurines. Eur J Clin Pharmacol 2008;64:753-767.
285. Regueiro M, Mardini H. Determination of thiopurine methyltransferase genotype or phenotype optimizes initial dosing of azathioprine for the treatment of Crohn's disease. J Clin Gastroenterol 2002;35:240-244.
286. Lichtenstein GR. Use of laboratory testing to guide 6-mercaptopurine/azathioprine therapy. Gastroenterology 2004;127:1558-1564.
287. Richard VS, Al-Ismail D, Salamat A. Should we test TPMT enzyme levels before starting azathioprine? Hematology 2007;12:359-360.
288. Czaja AJ. Review article: the management of autoimmune hepatitis beyond consensus guidelines. Aliment Pharmacol Ther 2013;38:343-364.
289. 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.
290. 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.
291. Czaja AJ, Carpenter HA. Thiopurine methyltransferase deficiency and azathioprine intolerance in autoimmune hepatitis. Dig. Dis. Sci. 2006;51:968-975.

292. Ferucci ED, Hurlburt KJ, Mayo MJ, Livingston S, Deubner H, Gove J, Plotnik J, et al. Azathioprine metabolite measurements are not useful in following treatment of autoimmune hepatitis in Alaska Native and other non-Caucasian people. Can. J. Gastroenterol. 2011;25:21-27.
293. CDC. Vaccines and immunization. Centers for Disease Control and Prevention 2018;www.cdc.gov/vaccines.
294. Worns MA, Teufel A, Kanzler S, Shrestha A, Victor A, Otto G, Lohse AW, et al. Incidence of HAV and HBV infections and vaccination rates in patients with autoimmune liver diseases. Am J Gastroenterol 2008;103:138-146.
295. Danziger-Isakov L, Kumar D, Practice AICo. Vaccination of solid organ transplant candidates and recipients: Guidelines from the American society of transplantation infectious diseases community of practice. Clin Transplant 2019:e13563.
296. Perrillo RP, Gish R, Falck-Ytter YT. American Gastroenterological Association Institute technical review on prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. Gastroenterology 2015;148:221-244.
297. Reddy KR, Beavers KL, Hammond SP, Lim JK, Falck-Ytter YT. American Gastroenterological Association Institute guideline on the prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. Gastroenterology 2015;148:215-219.
298. Loomba R, Liang TJ. Hepatitis B reactivation associated with immune suppressive and biological modifier therapies: current concepts, management strategies, and future directions. Gastroenterology 2017;152:1297-1309.
299. Terrault NA, Lok ASF, McMahon BJ, Chang KM, Hwang JP, Jonas MM, Brown RS, Jr., et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology 2018;67:1560-1599.
300. Pattullo V. Prevention of hepatitis B reactivation in the setting of immunosuppression. Clin Mol Hepatol 2016;22:219-237.
301. American Gastroenterological Association medical position statement: osteoporosis in hepatic disorders. Gastroenterology 2003;125:937-940.
302. Bernstein CN, Katz S. Guidelines for osteoporosis and inflammatory bowel disease. A guide to diagnosis and management for the gastroenterologist. Monograph of the American College of Gastroenterology 2003.
303. Kornbluth A, Hayes M, Feldman S, Hunt M, Fried-Boxt E, Lichtiger S, Legnani P, et al. Do guidelines matter? Implementation of the ACG and AGA osteoporosis screening guidelines in inflammatory bowel disease (IBD) patients who meet the guidelines' criteria. Am J Gastroenterol 2006;101:1546-1550.
304. Long MD, Thiny MT, Sandler RS, Gangarosa LM. Bone health in a tertiary-care gastroenterology and hepatology population. Dig Dis Sci 2010;55:2263-2269.
305. Efe C, Kav T, Aydin C, Cengiz M, Imga NN, Purnak T, Smyk DS, et al. Low serum vitamin D levels are associated with severe histological features and poor response to therapy in patients with autoimmune hepatitis. Dig Dis Sci 2014;59:3035-3042.
306. Ebadi M, Bhanji RA, Mazurak VC, Lytvyak E, Mason A, Czaja AJ, Montano-Loza AJ. Severe vitamin D deficiency is a prognostic biomarker in autoimmune hepatitis. Aliment Pharmacol Ther 2019;49:173-182.
307. Czaja AJ, Montano-Loza AJ. Evolving role of vitamin D in immune-mediated disease and its implications in autoimmune hepatitis. Dig Dis Sci 2019;64:324-344.
308. Pares A, Guanabens N. Treatment of bone disorders in liver disease. J Hepatol 2006;45:445-453.
309. Collier J. Bone disorders in chronic liver disease. Hepatology 2007;46:1271-1278.
310. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, Fruchart JC, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes

Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 2009;120:1640-1645.
311. Rochlani Y, Pothineni NV, Kovelamudi S, Mehta JL. Metabolic syndrome: pathophysiology, management, and modulation by natural compounds. Ther Adv Cardiovasc Dis 2017;11:215-225.
312. Weiler-Normann C, Lohse AW. Treatment adherence - room for improvement, not only in autoimmune hepatitis. J. Hepatol. 2012;57:1168-1170.
313. Wusk B, Kullak-Ublick GA, Rammert C, von Eckardstein A, Fried M, Rentsch KM. Therapeutic drug monitoring of thiopurine drugs in patients with inflammatory bowel disease or autoimmune hepatitis. Eur. J. Gastroenterol. Hepatol. 2004;16:1407-1413.
314. Sockalingam S, Blank D, Abdelhamid N, Abbey SE, Hirschfield GM. Identifying opportunities to improve management of autoimmune hepatitis: evaluation of drug adherence and psychosocial factors. J Hepatol 2012;57:1299-1304.
315. Janik MK, Wunsch E, Raszeja-Wyszomirska J, Moskwa M, Kruk B, Krawczyk M, Milkiewicz P. Autoimmune hepatitis exerts a profound, negative effect on health-related quality of life: A prospective, single-centre study. Liver Int 2019;39:215-221.
316. Schramm C, Wahl I, Weiler-Normann C, Voigt K, Wiegard C, Glaubke C, Brahler E, et al. Health-related quality of life, depression, and anxiety in patients with autoimmune hepatitis. J Hepatol 2014;60:618-624.
317. Mieli-Vergani G, Vergani D, Czaja AJ, Manns MP, Krawitt EL, Vierling JM, Lohse AW, et al. Autoimmune hepatitis. Nature Reviews Disease Primers 2018;4:18017.
318. Takahashi A, Moriya K, Ohira H, Arinaga-Hino T, Zeniya M, Torimura T, Abe M, et al. Health-related quality of life in patients with autoimmune hepatitis: A questionnaire survey. PLoS One 2018;13:e0204772.
319. Gulati R, Radhakrishnan KR, Hupertz V, Wyllie R, Alkhouri N, Worley S, Feldstein AE. Health-related quality of life in children with autoimmune liver disease. J Pediatr Gastroenterol Nutr 2013;57:444-450.
320. Trevizoli IC, Pinedo CS, Teles VO, Seixas R, de Carvalho E. Autoimmune hepatitis in children and adolescents: effect on quality of life. J Pediatr Gastroenterol Nutr 2018;66:861-865.
321. Wong LL, Fisher HF, Stocken DD, Rice S, Khanna A, Heneghan MA, Oo YH, et al. The impact of autoimmune hepatitis and its treatment on health utility. Hepatology 2018;68:1487-1497.
322. Bozzini AB, Neder L, Silva CA, Porta G. Decreased health-related quality of life in children and adolescents with autoimmune hepatitis. J Pediatr (Rio J) 2019;95:87-93.
323. Srivastava S, Boyer JL. Psychological stress is associated with relapse in type 1 autoimmune hepatitis. Liver Int 2010;30:1439-1447.
324. Mieli-Vergani G, Vergani D, Czaja AJ, Manns MP, Krawitt EL, Vierling JM, Lohse AW, et al. Autoimmune hepatitis. Nat Rev Dis Primers. 2018;4:18017.
325. Westbrook RH, Yeoman AD, Kriese S, Heneghan MA. Outcomes of pregnancy in women with autoimmune hepatitis. J Autoimmun 2012;38:J239-244.
326. Terrabuio DR, Abrantes-Lemos CP, Carrilho FJ, Cancado EL. Follow-up of pregnant women with autoimmune hepatitis: the disease behavior along with maternal and fetal outcomes. J Clin Gastroenterol 2009;43:350-356.
327. 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.
328. 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.
329. Waldenstrom J. Leber, Blutproteine und Nahrungseiweiss. Dtsch Gesellsch Verdau Stoffwechselkr 1950;15:113-121.

330. Barnea ER, Kirk D, Ramu S, Rivnay B, Roussev R, Paidas MJ. PreImplantation Factor (PIF) orchestrates systemic antiinflammatory response by immune cells: effect on peripheral blood mononuclear cells. Am J Obstet Gynecol 2012;207:313 e311-311.
331. Barnea ER, Lubman DM, Liu YH, Absalon-Medina V, Hayrabedyan S, Todorova K, Gilbert RO, et al. Insight into PreImplantation Factor (PIF*) mechanism for embryo protection and development: target oxidative stress and protein misfolding (PDI and HSP) through essential RIKP [corrected] binding site. PLoS One 2014;9:e100263.
332. Tran TT, Ahn J, Reau NS. ACG Clinical Guideline: Liver Disease and Pregnancy. Am J Gastroenterol 2016;111:176-194; quiz 196.
333. CDC. National birth defects prevention study (NBDPS). 2017:https://www.cdc.gov/ncbddd/birthdefects/nbdps.html.
334. Rosenkrantz JG, Githens JH, Cox SM, Kellum DL. Azathioprine (Imuran) and pregnancy. Am J Obstet Gynecol 1967;97:387-394.
335. Akbari M, Shah S, Velayos FS, Mahadevan U, Cheifetz AS. Systematic review and meta-analysis on the effects of thiopurines on birth outcomes from female and male patients with inflammatory bowel disease. Inflamm Bowel Dis. 2013;19:15-22.
336. 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.
337. Coscia LA, Armenti DP, King RW, Sifontis NM, Constantinescu S, Moritz MJ. Update on the teratogenicity of maternal mycophenolate mofetil. J Pediatr Genet 2015;4:42-55.
338. Montano-Loza AJ, Czaja AJ. Current therapy for autoimmune hepatitis. Nat Clin Pract Gastroenterol Hepatol 2007;4:202-214.
339. 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.
340. Curtis JJ, Galla JH, Woodford SY, Saykaly RJ, Luke RG. Comparison of daily and alternate-day prednisone during chronic maintenance therapy: a controlled crossover study. Am J Kidney Dis 1981;1:166-171.
341. Summerskill WH, Korman MG, Ammon HV, Baggenstoss AH. Prednisone for chronic active liver disease: dose titration, standard dose, and combination with azathioprine compared. Gut 1975;16:876-883.
342. Czaja AJ. Safety issues in the management of autoimmune hepatitis. Expert Opin. Drug Saf. 2008;7:319-333.
343. Rumbo C, Emerick KM, Emre S, Shneider BL. Azathioprine metabolite measurements in the treatment of autoimmune hepatitis in pediatric patients: a preliminary report. J. Pediatr. Gastroenterol. Nutr. 2002;35:391-398.
344. Nguyen TM, Daubard M, Le Gall C, Larger M, Lachaux A, Boulieu R. Monitoring of azathioprine metabolites in pediatric patients with autoimmune hepatitis. Ther Drug Monit 2010;32:433-437.
345. Hindorf U, Jahed K, Bergquist A, Verbaan H, Prytz H, Wallerstedt S, Werner M, et al. Characterisation and utility of thiopurine methyltransferase and thiopurine metabolite measurements in autoimmune hepatitis. J. Hepatol. 2010;52:106-111.
346. Sheiko MA, Sundaram SS, Capocelli KE, Pan Z, McCoy AM, Mack CL. Outcomes in pediatric autoimmune hepatitis and significance of azathioprine metabolites. J Pediatr Gastroenterol Nutr 2017;65:80-85.
347. Rumbo C, Shneider BL, Emre SH. Utility of azathioprine metabolite measurements in post-transplant recurrent autoimmune and immune-mediated hepatitis. Pediatr. Transplant. 2004;8:571-575.

348. Miloh T, Annunziato R, Arnon R, Warshaw J, Parkar S, Suchy FJ, Iyer K, et al. Improved adherence and outcomes for pediatric liver transplant recipients by using text messaging. Pediatrics 2009;124:e844-850.
349. Kerkar N, Annunziato RA, Foley L, Schmeidler J, Rumbo C, Emre S, Shneider B, et al. Prospective analysis of nonadherence in autoimmune hepatitis: a common problem. J Pediatr Gastroenterol Nutr 2006;43:629-634.
350. Inman GJ, Wang J, Nagano A, Alexandrov LB, Purdie KJ, Taylor RG, Sherwood V, et al. The genomic landscape of cutaneous SCC reveals drivers and a novel azathioprine associated mutational signature. Nat Commun 2018;9:3667.
351. Manns MP, Woynarowski M, Kreisel W, Lurie Y, Rust C, Zuckerman E, Bahr MJ, et al. Budesonide induces remission more effectively than prednisone in a controlled trial of patients with autoimmune hepatitis. Gastroenterology 2010;139:1198-1206.
352. Manns MP, Jaeckel E, Taubert R. Budesonide in autoimmune hepatitis: The right drug at the right time for the right patient. Clin Gastroenterol Hepatol 2018;16:186-189.
353. Czaja AJ, Lindor KD. Failure of budesonide in a pilot study of treatment-dependent autoimmune hepatitis. Gastroenterology 2000;119:1312-1316.
354. Geier A, Gartung C, Dietrich CG, Wasmuth HE, Reinartz P, Matern S. Side effects of budesonide in liver cirrhosis due to chronic autoimmune hepatitis: influence of hepatic metabolism versus portosystemic shunts on a patient complicated with HCC. World J. Gastroenterol. 2003;9:2681-2685.
355. Efe C, Ozaslan E, Kav T, Purnak T, Shorbagi A, Ozkayar O, Berlot AH, et al. Liver fibrosis may reduce the efficacy of budesonide in the treatment of autoimmune hepatitis and overlap syndrome. Autoimmun. Rev. 2012;11:330-334.
356. Hempfling W, Grunhage F, Dilger K, Reichel C, Beuers U, Sauerbruch T. Pharmacokinetics and pharmacodynamic action of budesonide in early- and late-stage primary biliary cirrhosis. Hepatology 2003;38:196-202.
357. Peiseler M, Liebscher T, Sebode M, Zenouzi R, Hartl J, Ehlken H, Pannicke N, et al. Efficacy and limitations of budesonide as a second-line treatment for patients with autoimmune hepatitis. Clin Gastroenterol Hepatol 2018;16:260-267.
358. Woynarowski M, Nemeth A, Baruch Y, Koletzko S, Melter M, Rodeck B, Strassburg CP, et al. Budesonide versus prednisone with azathioprine for the treatment of autoimmune hepatitis in children and adolescents. J Pediatr 2013;163:1347-1353.
359. Dyson JK, Wong LL, Bigirumurame T, Hirschfield GM, Kendrick S, Oo YH, Lohse AW, et al. Inequity of care provision and outcome disparity in autoimmune hepatitis in the United Kingdom. Aliment Pharmacol Ther 2018;48:951-960.
360. Niederau C, Herden D, van Thiel I, Kautz A, Bemba G, Wohn HP, Bertram T, et al. Prospective survey of health and socioeconomical characteristics of 249 patients with autoimmune hepatitis. Verdauungskrankheiten 2013;31:55-65.
361. Zachou K, Gatselis N, Papadamou G, Rigopoulou EI, Dalekos GN. Mycophenolate for the treatment of autoimmune hepatitis: prospective assessment of its efficacy and safety for induction and maintenance of remission in a large cohort of treatment-naive patients. J Hepatol 2011;55:636-646.
362. Zachou K, Gatselis NK, Arvaniti P, Gabeta S, Rigopoulou EI, Koukoulis GK, Dalekos GN. A real-world study focused on the long-term efficacy of mycophenolate mofetil as first-line treatment of autoimmune hepatitis. Aliment Pharmacol Ther 2016;43:1035-1047.
363. Yu ZJ, Zhang LL, Huang TT, Zhu JS, He ZB. Comparison of mycophenolate mofetil with standard treatment for autoimmune hepatitis: a meta-analysis. Eur J Gastroenterol Hepatol 2019;31:873-877.
364. Van Thiel DH, Wright H, Carroll P, Abu-Elmagd K, Rodriguez-Rilo H, McMichael J, Irish W, 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.

365. Alvarez F, Ciocca M, Canero-Velasco C, Ramonet M, de Davila MT, Cuarterolo M, Gonzalez T, et al. Short-term cyclosporine induces a remission of autoimmune hepatitis in children. J. Hepatol. 1999;30:222-227.
366. 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.
367. Marlaka JR, Papadogiannakis N, Fischler B, Casswall TH, Beijer E, Nemeth A. Tacrolimus without or with the addition of conventional immunosuppressive treatment in juvenile autoimmune hepatitis. Acta Paediatr 2012;101:993-999.
368. Nasseri-Moghaddam S, Nikfam S, Karimiam S, Khashayar P, Malekzadeh R. Cyclosporine-A versus prednisolone for induction of remission in auto-immune hepatitis: interim analysis report of a randomized controlled trial. Middle East J Dig Dis 2013;5:193-200.
369. Nastasio S, Sciveres M, Matarazzo L, Malaventura C, Cirillo F, Riva S, Maggiore G. Long-term follow-up of children and young adults with autoimmune hepatitis treated with cyclosporine. Dig Liver Dis 2019;51:712-718.
370. Cuarterolo M, Ciocca M, Velasco CC, Ramonet M, Gonzalez T, Lopez S, Garsd A, et al. Follow-up of children with autoimmune hepatitis treated with cyclosporine. J. Pediatr. Gastroenterol. Nutr. 2006;43:635-639.
371. Yeoman AD, Westbrook RH, Zen Y, Bernal W, Al-Chalabi T, Wendon JA, O'Grady JG, et al. Prognosis of acute severe autoimmune hepatitis (AS-AIH): the role of corticosteroids in modifying outcome. J Hepatol 2014;61:876-882.
372. Karkhanis J, Verna EC, Chang MS, Stravitz RT, Schilsky M, Lee WM, Brown RS, Jr., et al. Steroid use in acute liver failure. Hepatology 2014;59:612-621.
373. Ichai P, Duclos-Vallee JC, Guettier C, Hamida SB, Antonini T, Delvart V, Saliba F, et al. Usefulness of corticosteroids for the treatment of severe and fulminant forms of autoimmune hepatitis. Liver Transpl 2007;13:996-1003.
374. 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.
375. Rahim MN, Liberal R, Miquel R, Heaton ND, Heneghan MA. Acute severe sutoimmune hepatitis: corticosteroids or liver transplantation? Liver Transpl 2019;25:946-959.
376. Takikawa Y, Suzuki K. Clinical epidemiology of fulminant hepatitis in Japan. Hepatol. Res. 2008;38 Suppl 1:S14-18.
377. Yeoman AD, Westbrook RH, Zen Y, Maninchedda P, Portmann BC, Devlin J, O'Grady JG, et al. Early predictors of corticosteroid treatment failure in icteric presentations of autoimmune hepatitis. Hepatology 2011;53:926-934.
378. Sugawara K, Nakayama N, Mochida S. Acute liver failure in Japan: definition, classification, and prediction of the outcome. J. Gastroenterol. 2012;47:849-861.
379. Czaja AJ, Rakela J, Ludwig J. Features reflective of early prognosis in corticosteroid-treated severe autoimmune chronic active hepatitis. Gastroenterology 1988;95:448-453.
380. Czaja AJ. Rapidity of treatment response and outcome in type 1 autoimmune hepatitis. J. Hepatol. 2009;51:161-167.
381. Chen J, Eslick GD, Weltman M. Systematic review with meta-analysis: clinical manifestations and management of autoimmune hepatitis in the elderly. Aliment Pharmacol Ther 2014;39:117-124.
382. Couto CA, Bittencourt PL, Porta G, Abrantes-Lemos CP, Carrilho FJ, Guardia BD, Cancado EL. Antismooth muscle and antiactin antibodies are indirect markers of histological and biochemical activity of autoimmune hepatitis. Hepatology 2014;59:592-600.

383. Taubert R, Hardtke-Wolenski M, Noyan F, Lalanne C, Jonigk D, Schlue J, Krech T, et al. Hyperferritinemia and hypergammaglobulinemia predict the treatment response to standard therapy in autoimmune hepatitis. PLoS One 2017;12:e0179074.
384. Efe C, Cengiz M, Kahramanoglu-Aksoy E, Yilmaz B, Ozseker B, Beyazt Y, Tanoglu A, et al. Angiotensin-converting enzyme for noninvasive assessment of liver fibrosis in autoimmune hepatitis. Eur J Gastroenterol Hepatol 2015;27:649-654.
385. EASL Clinical Practice Guidelines: Autoimmune hepatitis. J Hepatol 2015;63:971-1004.
386. Hartl J, Ehlken H, Weiler-Normann C, Sebode M, Kreuels B, Pannicke N, Zenouzi R, et al. Patient selection based on treatment duration and liver biochemistry increases success rates after treatment withdrawal in autoimmune hepatitis. J Hepatol 2015;62:642-646.
387. Czaja AJ, Davis GL, Ludwig J, Taswell HF. Complete resolution of inflammatory activity following corticosteroid treatment of HBsAg-negative chronic active hepatitis. Hepatology 1984;4:622-627.
388. Czaja AJ, Menon KV, Carpenter HA. Sustained remission after corticosteroid therapy for type 1 autoimmune hepatitis: a retrospective analysis. Hepatology 2002;35:890-897.
389. Czaja AJ, Carpenter HA. Histological features associated with relapse after corticosteroid withdrawal in type 1 autoimmune hepatitis. Liver Int. 2003;23:116-123.
390. Guirguis J, Alonso Y, Lopez R, Carey W. Well-controlled autoimmune hepatitis treatment withdrawal may be safely accomplished without liver-biopsy guidance. Gastroenterol Rep (Oxf) 2018;6:284-290.
391. Czaja AJ. Late relapse of type 1 autoimmune hepatitis after corticosteroid withdrawal. Dig. Dis. Sci. 2010;55:1761-1769.
392. Czaja AJ. Review article: permanent drug withdrawal is desirable and achievable for autoimmune hepatitis. Aliment Pharmacol Ther 2014;39:1043-1058.
393. Deneau M, Book LS, Guthery SL, Jensen MK. Outcome after discontinuation of immunosuppression in children with autoimmune hepatitis: a population-based study. J Pediatr 2014;164:714-719.
394. 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.
395. 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.
396. 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.
397. Dhaliwal HK, Anderson R, Thornhill EL, Schneider S, McFarlane E, Gleeson D, Lennard L. Clinical significance of azathioprine metabolites for the maintenance of remission in autoimmune hepatitis. Hepatology 2012;56:1401-1408.
398. Stellon AJ, Hegarty JE, Portmann B, Williams R. Randomised controlled trial of azathioprine withdrawal in autoimmune chronic active hepatitis. Lancet 1985;1:668-670.
399. Johnson PJ, McFarlane IG, Williams R. Azathioprine for long-term maintenance of remission in autoimmune hepatitis. N. Engl. J. Med. 1995;333:958-963.
400. Harrison L, Gleeson D. Stopping immunosuppressive treatment in autoimmune hepatitis (AIH): Is it justified (and in whom and when)? Liver Int 2019;39:610-620.
401. Czaja AJ. Low-dose corticosteroid therapy after multiple relapses of severe HBsAg-negative chronic active hepatitis. Hepatology 1990;11:1044-1049.
402. Seela S, Sheela H, Boyer JL. Autoimmune hepatitis type 1: safety and efficacy of prolonged medical therapy. Liver Int 2005;25:734-739.
403. Parker R, Oo YH, Adams DH. Management of patients with difficult autoimmune hepatitis. Ther Adv Gastroenterol 2012;5:421-437.

404. Selvarajah V, Montano-Loza AJ, Czaja AJ. Systematic review: managing suboptimal treatment responses in autoimmune hepatitis with conventional and nonstandard drugs. Aliment. Pharmacol. Ther. 2012;36:691-707.
405. 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.
406. 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.
407. Inductivo-Yu I, Adams A, Gish RG, Wakil A, Bzowej NH, Frederick RT, Bonacini M. Mycophenolate mofetil in autoimmune hepatitis patients not responsive or intolerant to standard immunosuppressive therapy. Clin. Gastroenterol. Hepatol. 2007;5:799-802.
408. Hlivko JT, Shiffman ML, Stravitz RT, Luketic VA, Sanyal AJ, Fuchs M, Sterling RK. A single center review of the use of mycophenolate mofetil in the treatment of autoimmune hepatitis. Clin. Gastroenterol. Hepatol. 2008;6:1036-1040.
409. Hennes EM, Oo YH, Schramm C, Denzer U, Buggisch P, Wiegard C, Kanzler S, et al. Mycophenolate mofetil as second line therapy in autoimmune hepatitis? Am. J. Gastroenterol. 2008;103:3063-3070.
410. Baven-Pronk AM, Coenraad MJ, van Buuren HR, de Man RA, van Erpecum KJ, Lamers MM, Drenth JP, et al. The role of mycophenolate mofetil in the management of autoimmune hepatitis and overlap syndromes. Aliment. Pharmacol. Ther.. 2011;34:335-343.
411. Fallatah HI, Akbar HO. Mycophenolate mofetil as a rescue therapy for autoimmune hepatitis patients who are not responsive to standard therapy. Expert Rev Gastroenterol Hepatol 2011;5:517-522.
412. Hyams JS, Ballow M, Leichtner AM. Cyclosporine treatment of autoimmune chronic active hepatitis. Gastroenterology 1987;93:890-893.
413. Person JL, McHutchison JG, Fong TL, Redeker AG. A case of cyclosporine-sensitive, steroid-resistant, autoimmune chronic active hepatitis. J. Clin. Gastroenterol. 1993;17:317-320.
414. Sherman KE, Narkewicz M, Pinto PC. Cyclosporine in the management of corticosteroid-resistant type I autoimmune chronic active hepatitis. J. Hepatol. 1994;21:1040-1047.
415. Jackson LD, Song E. Cyclosporin in the treatment of corticosteroid resistant autoimmune chronic active hepatitis. Gut 1995;36:459-461.
416. Debray D, Maggiore G, Girardet JP, Mallet E, Bernard O. Efficacy of cyclosporin A in children with type 2 autoimmune hepatitis. J. Pediatr. 1999;135:111-114.
417. Zizzo AN, Valentino PL, Shah PS, Kamath BM. Second-line agents in pediatric patients with autoimmune hepatitis: a systematic review and meta-analysis. J Pediatr Gastroenterol Nutr 2017;65:6-15.
418. 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.
419. Efe C, Hagstrom H, Ytting H, Bhanji RA, Muller NF, Wang Q, Purnak T, et al. Efficacy and safety of mycophenolate mofetil and tacrolimus as second-line therapy for patients with autoimmune hepatitis. Clin Gastroenterol Hepatol 2017;15:1950-1956 e1951.
420. Efe C, Taii HA, Ytting H, Aehling N, Bhanji RA, Hagstrom H, Purnak T, et al. Tacrolimus and mycophenolate mofetil as second-line therapies for pediatric patients with autoimmune hepatitis. Dig Dis Sci 2018;63:1348-1354.
421. Than NN, Wiegard C, Weiler-Normann C, Fussel K, Mann J, Hodson J, Hirschfield GM, et al. Long-term follow-up of patients with difficult to treat type 1 autoimmune hepatitis on Tacrolimus therapy. Scand J Gastroenterol 2016;51:329-336.
422. Pratt DS, Flavin DP, Kaplan MM. The successful treatment of autoimmune hepatitis with 6-mercaptopurine after failure with azathioprine. Gastroenterology 1996;110:271-274.

423. Hubener S, Oo YH, Than NN, Hubener P, Weiler-Normann C, Lohse AW, Schramm C. Efficacy of 6-mercaptopurine as second-line treatment for patients with autoimmune hepatitis and azathioprine intolerance. Clin Gastroenterol Hepatol 2016;14:445-453.
424. Burak KW, Swain MG, Santodomingo-Garzon T, Lee SS, Urbanski SJ, Aspinall AI, Coffin CS, et al. Rituximab for the treatment of patients with autoimmune hepatitis who are refractory or intolerant to standard therapy. Can J Gastroenterol 2013;27:273-280.
425. Weiler-Normann C, Schramm C, Quaas A, Wiegard C, Glaubke C, Pannicke N, Moller S, et al. Infliximab as a rescue treatment in difficult-to-treat autoimmune hepatitis. J Hepatol 2013;58:529-534.
426. Santiago P, Schwartz I, Tamariz L, Levy C. Systematic review with meta-analysis: mycophenolate mofetil as a second-line therapy for autoimmune hepatitis. Aliment Pharmacol Ther 2019;49:830-839.
427. De Lemos-Bonotto M, Valle-Tovo C, Costabeber AM, Mattos AA, Azeredo-da-Silva ALF. A systematic review and meta-analysis of second-line immunosuppressants for autoimmune hepatitis treatment. Eur J Gastroenterol Hepatol 2018;30:212-216.
428. Nicoll AJ, Roberts SK, Lim R, Mitchell J, Weltman M, George J, Wigg A, et al. Beneficial response to mycophenolate mofetil by patients with autoimmune hepatitis, who have failed standard therapy, is predicted by older age and lower immunoglobulin G and INR levels. Aliment Pharmacol Ther 2019;49:1314-1322.
429. Tannous MM, Cheng J, Muniyappa K, Farooq I, Bharara A, Kappus M, Luketic V, et al. Use of tacrolimus in the treatment of autoimmune hepatitis: a single centre experience. Aliment Pharmacol Ther 2011;34:405-407.
430. Hanouneh M, Ritchie MM, Ascha M, Ascha MS, Chedid A, Sanguankeo A, Zein NN, et al. A review of the utility of tacrolimus in the management of adults with autoimmune hepatitis. Scand J Gastroenterol 2019;54:76-80.
431. Chatur N, Ramji A, Bain VG, Ma MM, Marotta PJ, Ghent CN, Lilly LB, 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.
432. Cravo M, Silva R, Serrano M. Autoimmune hepatitis induced by infliximab in a patient with Crohn's disease with no relapse after switching to adalimumab. BioDrugs 2010;24 Suppl 1:25-27.
433. Harada K, Akai Y, Koyama S, Ikenaka Y, Saito Y. A case of autoimmune hepatitis exacerbated by the administration of etanercept in the patient with rheumatoid arthritis. Clin Rheumatol 2008;27:1063-1066.
434. Averbukh LD, Wu GY. Role of biologics in the development of autoimmune hepatitis: A review. J Clin Transl Hepatol 2018;6:402-409.
435. Nedelkopoulou N, Vadamalayan B, Vergani D, Mieli-Vergani G. Anti-TNFalpha treatment in children and adolescents with combined inflammatory bowel disease and autoimmune liver disease. J Pediatr Gastroenterol Nutr 2018;66:100-105.
436. D'Agostino D, Costaguta A, Alvarez F. Successful treatment of refractory autoimmune hepatitis with rituximab. Pediatrics 2013;132:e526-530.
437. Elion GB. The pharmacology of azathioprine. Ann N Y Acad Sci 1993;685:400-407.
438. Weinshilboum R. Thiopurine pharmacogenetics: clinical and molecular studies of thiopurine methyltransferase. Drug Metab Dispos 2001;29:601-605.
439. Legue C, Legros L, Kammerer-Jacquet S, Jezequel C, Houssel-Debry P, Uguen T, Le Lan C, et al. Safety and efficacy of 6-thioguanine as a second-line treatment for autoimmune hepatitis. Clin Gastroenterol Hepatol 2018;16:290-291.
440. van den Brand FF, van Nieuwkerk CMJ, Verwer BJ, de Boer YS, de Boer NKH, Mulder CJJ, Bloemena E, et al. Biochemical efficacy of tioguanine in autoimmune hepatitis: a retrospective review of practice in the Netherlands. Aliment Pharmacol Ther 2018;48:761-767.

441. de Boer NK, van Nieuwkerk CM, Aparicio Pages MN, de Boer SY, Derijks LJ, Mulder CJ. Promising treatment of autoimmune hepatitis with 6-thioguanine after adverse events on azathioprine. Eur. J. Gastroenterol. Hepatol. 2005;17:457-461.
442. Dubinsky MC, Vasiliauskas EA, Singh H, Abreu MT, Papadakis KA, Tran T, Martin P, et al. 6-thioguanine can cause serious liver injury in inflammatory bowel disease patients. Gastroenterology 2003;125:298-303.
443. Seinen ML, van Asseldonk DP, Mulder CJ, de Boer NK. Dosing 6-thioguanine in inflammatory bowel disease: expert-based guidelines for daily practice. J. Gastrointestin. Liver Dis. 2010;19:291-294.
444. Trivedi PJ, Hirschfield GM. Review article: overlap syndromes and autoimmune liver disease. Aliment Pharmacol Ther 2012;36:517-533.
445. Joshi S, Cauch-Dudek K, Wanless IR, Lindor KD, Jorgensen R, Batts K, Heathcote EJ. Primary biliary cirrhosis with additional features of autoimmune hepatitis: response to therapy with ursodeoxycholic acid. Hepatology 2002;35:409-413.
446. 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.
447. 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.
448. Floreani A, Rizzotto ER, Ferrara F, Carderi I, Caroli D, Blasone L, Baldo V. Clinical course and outcome of autoimmune hepatitis/primary sclerosing cholangitis overlap syndrome. Am J Gastroenterol 2005;100:1516-1522.
449. Chapman R, Fevery J, Kalloo A, Nagorney DM, Boberg KM, Shneider B, Gores GJ, et al. Diagnosis and management of primary sclerosing cholangitis. Hepatology 2010;51:660-678.
450. 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.
451. Czaja AJ. The overlap syndromes of autoimmune hepatitis. Dig Dis Sci 2013;58:326-343.
452. Hoeroldt B, McFarlane E, Dube A, Basumani P, Karajeh M, Campbell MJ, Gleeson D. Long-term outcomes of patients with autoimmune hepatitis managed at a nontransplant center. Gastroenterology 2011;140:1980-1989.
453. Verma S, Torbenson M, Thuluvath PJ. The impact of ethnicity on the natural history of autoimmune hepatitis. Hepatology 2007;46:1828-1835.
454. Wong RJ, Gish R, Frederick T, Bzowej N, Frenette C. The impact of race/ethnicity on the clinical epidemiology of autoimmune hepatitis. J. Clin. Gastroenterol. 2012;46:155-161.
455. 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.
456. Czaja AJ. Clinical features, differential diagnosis and treatment of autoimmune hepatitis in the elderly. Drugs Aging 2008;25:219-239.
457. Czaja AJ. Autoimmune hepatitis in diverse ethnic populations and geographical regions. Expert Rev Gastroenterol Hepatol 2013 7:365-385.
458. 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.
459. Wen JW, Kohn MA, Wong R, Somsouk M, Khalili M, Maher J, Tana MM. Hospitalizations for autoimmune hepatitis disproportionately affect Black and Latino Americans. Am J Gastroenterol 2018;113:243-253.

460. de Boer YS, Gerussi A, van den Brand FF, Wong GW, Halliday N, Liberal R, Drenth JPH, et al. Association between black race and presentation and liver-related outcomes of patients with autoimmune hepatitis. Clin Gastroenterol Hepatol 2019;17:1616-1624 e1612.
461. Wong RJ, Gish R, Frederick T, Bzowej N, Frenette C. Development of hepatocellular carcinoma in autoimmune hepatitis patients: a case series. Dig. Dis. Sci. 2011;56:578-585.
462. Czaja AJ. Hepatocellular cancer and other malignancies in autoimmune hepatitis. Dig Dis Sci 2013;58:1459-1476.
463. Werner M, Almer S, Prytz H, Lindgren S, Wallerstedt S, Bjornsson E, Bergquist A, et al. Hepatic and extrahepatic malignancies in autoimmune hepatitis. A long-term follow-up in 473 Swedish patients. J. Hepatol. 2009;50:388-393.
464. Ngu JH, Gearry RB, Frampton CM, Stedman CA. Mortality and the risk of malignancy in autoimmune liver diseases: a population-based study in Canterbury, New Zealand. Hepatology 2012;55:522-529.
465. 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.
466. Leung J, Dowling L, Obadan I, Davis J, Bonis PA, Kaplan MM, Casey D, et al. Risk of non-melanoma skin cancer in autoimmune hepatitis. Dig Dis Sci 2010;55:3218-3223.
467. Singal A, Volk ML, Waljee A, Salgia R, Higgins P, Rogers MA, Marrero JA. Meta-analysis: surveillance with ultrasound for early-stage hepatocellular carcinoma in patients with cirrhosis. Aliment Pharmacol Ther 2009;30:37-47.
468. Gleeson D, Heneghan MA. British Society of Gastroenterology (BSG) guidelines for management of autoimmune hepatitis. Gut 2011;60:1611-1629.
469. Marrero JA, Kulik LM, Sirlin CB, Zhu AX, Finn RS, Abecassis MM, Roberts LR, et al. Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology 2018;68:723-750.
470. Adam R, Karam V, Delvart V, O'Grady J, Mirza D, Klempnauer J, Castaing D, et al. Evolution of indications and results of liver transplantation in Europe. A report from the European Liver Transplant Registry (ELTR). J Hepatol 2012;57:675-688.
471. Carbone M, Neuberger JM. Autoimmune liver disease, autoimmunity and liver transplantation. J Hepatol 2014;60:210-223.
472. Mendes F, Couto CA, Levy C. Recurrent and de novo autoimmune liver diseases. Clin Liver Dis 2011;15:859-878.
473. Webb GJ, Rana A, Hodson J, Akhtar MZ, Ferguson JW, Neuberger JM, Vierling JM, et al. Twenty-year comparative analysis of patients with autoimmune liver diseases on transplant waitlists. Clin Gastroenterol Hepatol 2018;16:278-287
474. Jossen J, Annunziato R, Kim HS, Chu J, Arnon R. Liver transplantation for children with primary sclerosing cholangitis and autoimmune hepatitis: UNOS database analysis. J Pediatr Gastroenterol Nutr 2017;64:e83-e87.
475. Futagawa Y, Terasaki PI. An analysis of the OPTN/UNOS Liver Transplant Registry. Clin. Transpl. 2004:315-329.
476. Schramm C, Bubenheim M, Adam R, Karam V, Buckels J, O'Grady JG, Jamieson N, et al. Primary liver transplantation for autoimmune hepatitis: a comparative analysis of the European Liver Transplant Registry. Liver Transpl 2010;16:461-469.
477. Baganate F, Beal EW, Tumin D, Azoulay D, Mumtaz K, Black SM, Washburn K, et al. Early mortality after liver transplantation: Defining the course and the cause. Surgery 2018;164:694-704.
478. Hayashi M, Keeffe EB, Krams SM, Martinez OM, Ojogho ON, So SK, Garcia G, et al. Allograft rejection after liver transplantation for autoimmune liver diseases. Liver Transpl. Surg. 1998;4:208-214.

479. Milkiewicz P, Gunson B, Saksena S, Hathaway M, Hubscher SG, Elias E. Increased incidence of chronic rejection in adult patients transplanted for autoimmune hepatitis: assessment of risk factors. Transplantation 2000;70:477-480.
480. Thurairajah PH, Carbone M, Bridgestock H, Thomas P, Hebbar S, Gunson BK, Shah T, et al. Late acute liver allograft rejection; a study of its natural history and graft survival in the current era. Transplantation 2013;95:955-959.
481. Vogel A, Heinrich E, Bahr MJ, Rifai K, Flemming P, Melter M, Klempnauer J, et al. Long-term outcome of liver transplantation for autoimmune hepatitis. Clin. Transplant. 2004;18:62-69.
482. Jain A, Kashyap R, Marsh W, Rohal S, Khanna A, Fung JJ. Reasons for long-term use of steroid in primary adult liver transplantation under tacrolimus. Transplantation 2001;71:1102-1106.
483. Pelletier SJ, Nadig SN, Lee DD, Ammori JB, Englesbe MJ, Sung RS, Magee JC, et al. A prospective, randomized trial of complete avoidance of steroids in liver transplantation with follow-up of over 7 years. HPB (Oxford) 2013;15:286-293.
484. Krishnamoorthy TL, Miezynska-Kurtycz J, Hodson J, Gunson BK, Neuberger J, Milkiewicz P, Oo YH. Longterm corticosteroid use after liver transplantation for autoimmune hepatitis is safe and associated with a lower incidence of recurrent disease. Liver Transpl 2016;22:34-41.
485. Theocharidou E, Heneghan MA. Con: Steroids should not be withdrawn in transplant recipients with autoimmune hepatitis. Liver Transpl 2018;24:1113-1118.
486. Everson GT, Trouillot T, Wachs M, Bak T, Steinberg T, Kam I, Shrestha R, et al. Early steroid withdrawal in liver transplantation is safe and beneficial. Liver Transpl Surg 1999;5:S48-57.
487. Trouillot TE, Shrestha R, Kam I, Wachs M, Everson GT. Successful withdrawal of prednisone after adult liver transplantation for autoimmune hepatitis. Liver Transpl Surg 1999;5:375-380.
488. Adams RW, Chapman RL, Smallwood GA. Steroid withdrawal in liver transplant recipients. Prog Transplant 2001;11:217-223.
489. Heffron TG, Smallwood GA, Oakley B, Pillen T, Welch D, Martinez E, Romero R, et al. Autoimmune hepatitis following liver transplantation: relationship to recurrent disease and steroid weaning. Transplant Proc 2002;34:3311-3312.
490. Junge G, Neuhaus R, Schewior L, Klupp J, Guckelberger O, Langrehr JM, Tullius S, et al. Withdrawal of steroids: a randomized prospective study of prednisone and tacrolimus versus mycophenolate mofetil and tacrolimus in liver transplant recipients with autoimmune hepatitis. Transplant Proc 2005;37:1695-1696.
491. Llado L, Xiol X, Figueras J, Ramos E, Memba R, Serrano T, Torras J, et al. Immunosuppression without steroids in liver transplantation is safe and reduces infection and metabolic complications: results from a prospective multicenter randomized study. J Hepatol 2006;44:710-716.
492. Campsen J, Zimmerman MA, Trotter JF, Wachs M, Bak T, Steinberg T, Kaplan M, et al. Liver transplantation for autoimmune hepatitis and the success of aggressive corticosteroid withdrawal. Liver Transpl. 2008;14:1281-1286.
493. Sgourakis G, Radtke A, Fouzas I, Mylona S, Goumas K, Gockel I, Lang H, et al. Corticosteroid-free immunosuppression in liver transplantation: a meta-analysis and meta-regression of outcomes. Transpl Int 2009;22:892-905.
494. Sgourakis G, Dedemadi G. Corticosteroid-free immunosuppression in liver transplantation: an evidence-based review. World J Gastroenterol 2014;20:10703-10714.
495. Fairfield C, Penninga L, Powell J, Harrison EM, Wigmore SJ. Glucocorticosteroid-free versus glucocorticosteroid-containing immunosuppression for liver transplanted patients. Cochrane Database Syst Rev 2015:CD007606.
496. Satapathy SK, Jones OD, Vanatta JM, Kamal F, Kedia SK, Jiang Y, Nair SP, et al. Outcomes of liver transplant recipients with autoimmune liver disease using long-term dual immunosuppression regimen without corticosteroid. Transplant Direct 2017;3:e178.

497. Kalra A, Burton JR, Jr., Forman LM. Pro: Steroids can be withdrawn after transplant in recipients with autoimmune hepatitis. Liver Transpl 2018;24:1109-1112.
498. Prados E, Cuervas-Mons V, de la Mata M, Fraga E, Rimola A, Prieto M, Clemente G, et al. Outcome of autoimmune hepatitis after liver transplantation. Transplantation 1998;66:1645-1650.
499. Czaja AJ. Diagnosis, pathogenesis, and treatment of autoimmune hepatitis after liver transplantation. Dig. Dis. Sci. 2012;57:2248-2266.
500. Montano-Loza AJ, Bhanji RA, Wasilenko S, Mason AL. Systematic review: recurrent autoimmune liver diseases after liver transplantation. Aliment Pharmacol Ther 2017;45:485-500.
501. Puustinen L, Boyd S, Arkkila P, Isoniemi H, Arola J, Farkkila M. Histologic surveillance after liver transplantation due to autoimmune hepatitis. Clin Transplant 2017;31:e12936.
502. Stirnimann G, Ebadi M, Czaja AJ, Montano-Loza AJ. Recurrent and de novo autoimmune hepatitis. Liver Transpl 2019;25:152-166.
503. Aravinthan AD, Doyle AC, Issachar A, Dib M, Peretz D, Cattral MS, Ghanekar A, et al. First-degree living-related donor liver transplantation in autoimmune liver diseases. Am J Transplant 2016;16:3512-3521.
504. Kerkar N, Hadzic N, Davies ET, Portmann B, Donaldson PT, Rela M, Heaton ND, et al. De-novo autoimmune hepatitis after liver transplantation. Lancet 1998;351:409-413.
505. 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.
506. 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.
507. Miyagawa-Hayashino A, Haga H, Egawa H, Hayashino Y, Sakurai T, Minamiguchi S, Tanaka K, et al. Outcome and risk factors of de novo autoimmune hepatitis in living-donor liver transplantation. Transplantation 2004;78:128-135.
508. Gibelli NE, Tannuri U, Mello ES, Cancado ER, Santos MM, Ayoub AA, Maksoud-Filho JG, et al. Successful treatment of de novo autoimmune hepatitis and cirrhosis after pediatric liver transplantation. Pediatr Transplant 2006;10:371-376.
509. Venick RS, McDiarmid SV, Farmer DG, Gornbein J, Martin MG, Vargas JH, Ament ME, 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.
510. Cho JM, Kim KM, Oh SH, Lee YJ, Rhee KW, Yu E. De novo autoimmune hepatitis in Korean children after liver transplantation: a single institution's experience. Transplant Proc 2011;43:2394-2396.
511. Heneghan MA, Portmann BC, Norris SM, Williams R, Muiesan P, Rela M, Heaton ND, et al. Graft dysfunction mimicking autoimmune hepatitis following liver transplantation in adults. Hepatology 2001;34:464-470.
512. 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.
513. 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.
514. 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.
515. Rodriguez-Diaz Y, Reyes-Rodriguez R, Dorta-Francisco MC, Aguilera I, Perera-Molinero A, Moneva-Arce E, Aviles-Ruiz JF. De novo autoimmune hepatitis following liver transplantation for primary biliary cirrhosis. Transplant Proc 2006;38:1467-1470.

516. Yoshizawa K, Shirakawa H, Ichijo T, Umemura T, Tanaka E, Kiyosawa K, Imagawa E, et al. De novo autoimmune hepatitis following living-donor liver transplantation for primary biliary cirrhosis. Clin Transplant 2008;22:385-390.
517. Zhang Y, Wang B, Wang T. De novo autoimmune hepatitis with centrilobular necrosis following liver transplantation for primary biliary cirrhosis: a case report. Transplant Proc 2010;42:3854-3857.
518. Aguilera I, Wichmann I, Sousa JM, Bernardos A, Franco E, Garcia-Lozano JR, Nunez-Roldan A. Antibodies against glutathione S-transferase T1 (GSTT1) in patients with de novo immune hepatitis following liver transplantation. Clin Exp Immunol 2001;126:535-539.
519. Berardi S, Lodato F, Gramenzi A, D'Errico A, Lenzi M, Bontadini A, Morelli MC, et al. High incidence of allograft dysfunction in liver transplanted patients treated with pegylated-interferon alpha-2b and ribavirin for hepatitis C recurrence: possible de novo autoimmune hepatitis? Gut 2007;56:237-242.
520. Guido M, Burra P. De novo autoimmune hepatitis after liver transplantation. Semin Liver Dis 2011;31:71-81.
521. Montano-Loza AJ, Vargas-Vorackova F, Ma M, Bain VG, Burak K, Kumar T, Mason AL. Incidence and risk factors associated with de novo autoimmune hepatitis after liver transplantation. Liver Int. 2012;32:1426-1433.
522. Kerkar N, Vergani D. De novo autoimmune hepatitis -is this different in adults compared to children? J Autoimmun 2018;95:26-33.
523. Fiel MI, Agarwal K, Stanca C, Elhajj N, Kontorinis N, Thung SN, Schiano TD. Posttransplant plasma cell hepatitis (de novo autoimmune hepatitis) is a variant of rejection and may lead to a negative outcome in patients with hepatitis C virus. Liver Transpl 2008;14:861-871.
524. Castillo-Rama M, Sebagh M, Sasatomi E, Randhawa P, Isse K, Salgarkar AD, Ruppert K, et al. "Plasma cell hepatitis" in liver allografts: identification and characterization of an IgG4-rich cohort. Am J Transplant 2013;13:2966-2977.
525. Demetris AJ, Bellamy C, Hubscher SG, O'Leary J, Randhawa PS, Feng S, Neil D, et al. 2016 comprehensive update of the Banff Working Group on liver allograft pathology: introduction of antibody-mediated rejection. Am J Transplant 2016;16:2816-2835.
526. Demetris AJ, Sebagh M. Plasma cell hepatitis in liver allografts: Variant of rejection or autoimmune hepatitis? Liver Transpl 2008;14:750-755.
527. Fiel MI, Schiano TD. Plasma cell hepatitis (de-novo autoimmune hepatitis) developing post liver transplantation. Curr Opin Organ Transplant 2012;17:287-292.
528. Levitsky J, Fiel MI, Norvell JP, Wang E, Watt KD, Curry MP, Tewani S, et al. Risk for immune-mediated graft dysfunction in liver transplant recipients with recurrent HCV infection treated with pegylated interferon. Gastroenterology 2012;142:1132-1139.
529. Jones D, Manns MP, Terracciano L, Torbenson M, Vierling JM. Unmet needs and new models for future trials in autoimmune hepatitis. Lancet Gastroenterol Hepatol 2018;3:363-370.
530. Czaja AJ. Review article: Chemokines as orchestrators of autoimmune hepatitis and potential therapeutic targets. Aliment Pharmacol Ther 2014;40:261-279.
531. Czaja AJ. Evolving paradigm for treatment of autoimmune hepatitis. Expert Rev Clin Immunol 2017;13:781-798.
532. Czaja AJ. Review article: next-generation transformative advances in the pathogenesis and management of autoimmune hepatitis. Aliment Pharmacol Ther 2017;46:920-937.
533. Czaja AJ. Immune inhibitory proteins and their pathogenic and therapeutic implications in autoimmunity and autoimmune hepatitis. Autoimmunity 2019:10.1080/08916934.08912019.01641200.
534. Czaja AJ. Nature and implications of oxidative and nitrosative stresses in autoimmune hepatitis. Dig Dis Sci 2016;61:2784-2803.

535. Montano-Loza AJ, Thandassery RB, Czaja AJ. Targeting hepatic fibrosis in autoimmune hepatitis. Dig Dis Sci 2016;61:3118-3139.
536. Czaja AJ. Adoptive cell transfer in autoimmune hepatitis. Expert Rev Gastroenterol Hepatol 2015;9:821-836.
537. Lapierre P, Beland K, Yang R, Alvarez F. Adoptive transfer of ex vivo expanded regulatory T cells in an autoimmune hepatitis murine model restores peripheral tolerance. Hepatology 2013;57:217-227.
538. Czaja AJ. Emerging therapeutic biomarkers of autoimmune hepatitis and their impact on current and future management. Expert Rev Gastroenterol Hepatol 2018;12:547-564.
539. Matsumoto K, Miyake Y, Matsushita H, Ohnishi A, Ikeda F, Shiraha H, Takaki A, et al. Anti-programmed cell death-1 antibody as a new serological marker for type 1 autoimmune hepatitis. J Gastroenterol Hepatol 2014;29:110-115.
540. Aarslev K, Dige A, Greisen SR, Kreutzfeldt M, Jessen N, Vilstrup H, Deleuran B, et al. Soluble programmed death-1 levels are associated with disease activity and treatment response in patients with autoimmune hepatitis. Scand J Gastroenterol 2017;52:93-99.
541. Assis DN, Leng L, Du X, Zhang CK, Grieb G, Merk M, Garcia AB, et al. The role of macrophage migration inhibitory factor in autoimmune liver disease. Hepatology 2014;59:580-591.
542. Assis DN, Takahashi H, Leng L, Zeniya M, Boyer JL, Bucala R. A macrophage migration inhibitory factor polymorphism is associated with autoimmune hepatitis severity in US and Japanese patients. Dig Dis Sci 2016;61:3506-3512.
543. Migita K, Komori A, Kozuru H, Jiuchi Y, Nakamura M, Yasunami M, Furukawa H, et al. Circulating microRNA profiles in patients with type-1 autoimmune hepatitis. PLoS One 2015;10:e0136908.
544. Gronbaek H, Kreutzfeldt M, Kazankov K, Jessen N, Sandahl T, Hamilton-Dutoit S, Vilstrup H, et al. Single-centre experience of the macrophage activation marker soluble (s)CD163 - associations with disease activity and treatment response in patients with autoimmune hepatitis. Aliment Pharmacol Ther 2016;44:1062-1070.
545. Wang JB, Pu SB, Sun Y, Li ZF, Niu M, Yan XZ, Zhao YL, et al. Metabolomic profiling of autoimmune hepatitis: the diagnostic utility of nuclear magnetic resonance spectroscopy. J Proteome Res 2014;13:3792-3801.
546. Lian JS, Liu W, Hao SR, Chen DY, Wang YY, Yang JL, Jia HY, et al. A serum metabolomic analysis for diagnosis and biomarker discovery of primary biliary cirrhosis and autoimmune hepatitis. Hepatobiliary Pancreat Dis Int 2015;14:413-421.
547. Lytton SD, Osiecki M, MalgorzataWozniak, Cukrowska B, Wierzbicka A, Goliszek M, Socha P, et al. Tryptophan-kynurenine profile in pediatric autoimmune hepatitis. Immunol Res 2019;67:39-47.
548. Czaja AJ. Epigenetic changes and their implications in autoimmune hepatitis. Eur J Clin Invest 2018;48:e12899.
549. Czaja AJ. Factoring the intestinal microbiome into the pathogenesis of autoimmune hepatitis. World J Gastroenterol 2016;22:9257-9278.
550. Lin R, Zhou L, Zhang J, Wang B. Abnormal intestinal permeability and microbiota in patients with autoimmune hepatitis. Int J Clin Exp Pathol 2015;8:5153-5160.
551. Yuksel M, Wang Y, Tai N, Peng J, Guo J, Beland K, Lapierre P, et al. A novel "humanized mouse" model for autoimmune hepatitis and the association of gut microbiota with liver inflammation. Hepatology 2015;62:1536-1550.
552. Markle JG, Frank DN, Mortin-Toth S, Robertson CE, Feazel LM, Rolle-Kampczyk U, von Bergen M, et al. Sex differences in the gut microbiome drive hormone-dependent regulation of autoimmunity. Science 2013;339:1084-1088.
553. Yurkovetskiy L, Burrows M, Khan AA, Graham L, Volchkov P, Becker L, Antonopoulos D, et al. Gender bias in autoimmunity is influenced by microbiota. Immunity 2013;39:400-412.

554. Markle JG, Frank DN, Adeli K, von Bergen M, Danska JS. Microbiome manipulation modifies sex-specific risk for autoimmunity. Gut Microbes 2014;5:485-493.
555. Czaja AJ. Under-evaluated or unassessed pathogenic pathways in autoimmune hepatitis and implications for future management. Dig Dis Sci 2018;63:1706-1725.
556. Czaja AJ, Manns MP, Homburger HA. Frequency and significance of antibodies to liver/kidney microsome type 1 in adults with chronic active hepatitis. Gastroenterology 1992;103:1290-1295.
557. Mieli-Vergani G, Vergani D. Autoimmune hepatitis in children: what is different from adult AIH? Semin Liver Dis 2009;29:297-306.
558. Narkewicz MR, Horslen S, Belle SH, Rudnick DA, Ng VL, Rosenthal P, Romero R, et al. Prevalence and significance of autoantibodies in children with acute liver failure. J Pediatr Gastroenterol Nutr 2017;64:210-217.
559. Czaja AJ, Nishioka M, Morshed SA, Hachiya T. Patterns of nuclear immunofluorescence and reactivities to recombinant nuclear antigens in autoimmune hepatitis. Gastroenterology 1994;107:200-207.
560. Toh BH. Smooth muscle autoantibodies and autoantigens. Clin Exp Immunol 1979;38:621-628.
561. 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.
562. 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.
563. Wies I, Brunner S, Henninger J, Herkel J, Kanzler S, Meyer zum Buschenfelde KH, Lohse AW. Identification of target antigen for SLA/LP autoantibodies in autoimmune hepatitis. Lancet 2000;355:1510-1515.
564. Volkmann M, Martin L, Baurle A, Heid H, Strassburg CP, Trautwein C, Fiehn W, 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.
565. Volkmann M, Luithle D, Zentgraf H, Schnolzer M, Fiedler S, Heid H, Schulze-Bergkamen A, et al. SLA/LP/tRNP((Ser)Sec) antigen in autoimmune hepatitis: identification of the native protein in human hepatic cell extract. J Autoimmun 2010;34:59-65.
566. 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.
567. Terjung B, Herzog V, Worman HJ, Gestmann I, Bauer C, Sauerbruch T, Spengler U. 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.
568. Terjung B, Bogsch F, Klein R, Sohne J, Reichel C, Wasmuth JC, Beuers U, et al. Diagnostic accuracy of atypical p-ANCA in autoimmune hepatitis using ROC- and multivariate regression analysis. Eur J Med Res 2004;9:439-448.
569. Schwarze C, Terjung B, Lilienweiss P, Beuers U, Herzog V, Sauerbruch T, Spengler U. IgA class antineutrophil cytoplasmic antibodies in primary sclerosing cholangitis and autoimmune hepatitis. Clin Exp Immunol 2003;133:283-289.
570. Oikonomou KG, Zachou K, Dalekos GN. Alpha-actinin: a multidisciplinary protein with important role in B-cell driven autoimmunity. Autoimmun Rev 2011;10:389-396.
571. Lapierre P, Hajoui O, Homberg JC, Alvarez F. Formiminotransferase cyclodeaminase is an organ-specific autoantigen recognized by sera of patients with autoimmune hepatitis. Gastroenterology 1999;116:643-649.

572. Muratori L, Sztul E, Muratori P, Gao Y, Ripalti A, Ponti C, Lenzi M, et al. Distinct epitopes on formiminotransferase cyclodeaminase induce autoimmune liver cytosol antibody type 1. Hepatology 2001;34:494-501.
573. Lenzi M, Manotti P, Muratori L, Cataleta M, Ballardini G, Cassani F, Bianchi FB. Liver cytosolic 1 antigen-antibody system in type 2 autoimmune hepatitis and hepatitis C virus infection. Gut 1995;36:749-754.
574. Manns MP, Griffin KJ, Quattrochi LC, Sacher M, Thaler H, Tukey RH, Johnson EF. Identification of cytochrome P450IA2 as a human autoantigen. Arch Biochem Biophys 1990;280:229-232.
575. Belloc C, Gauffre A, Andre C, Beaune PH. Epitope mapping of human CYP1A2 in dihydralazine-induced autoimmune hepatitis. Pharmacogenetics 1997;7:181-186.
576. Bourdi M, Gautier JC, Mircheva J, Larrey D, Guillouzo A, Andre C, Belloc C, et al. Anti-liver microsomes autoantibodies and dihydralazine-induced hepatitis: specificity of autoantibodies and inductive capacity of the drug. Mol Pharmacol 1992;42:280-285.
577. Clemente MG, Obermayer-Straub P, Meloni A, Strassburg CP, Arangino V, Tukey RH, De Virgiliis S, et al. Cytochrome P450 1A2 is a hepatic autoantigen in autoimmune polyglandular syndrome type 1. J Clin Endocrinol Metab 1997;82:1353-1361.
578. Van de Water J, Cooper A, Surh CD, Coppel R, Danner D, Ansari A, Dickson R, et al. Detection of autoantibodies to recombinant mitochondrial proteins in patients with primary biliary cirrhosis. N Engl J Med 1989;320:1377-1380.
579. 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.
580. 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.
581. Maggiore G, Larizza D, Lorini R, De Giacomo C, Scotta MS, Severi F. Propylthiouracil hepatotoxicity mimicking autoimmune chronic active hepatitis in a girl. J Pediatr Gastroenterol Nutr 1989;8:547-548.
582. Fedotin MS, Lefer LG. Liver disease caused by propylthiouracil. Arch Intern Med 1975;135:319-321.
583. Jennings JJ, Mandaliya R, Nakshabandi A, Lewis JH. Hepatotoxicity induced by immune checkpoint inhibitors: a comprehensive review including current and alternative management strategies. Expert Opin Drug Metab Toxicol 2019;15:231-244.
584. Black M, Mitchell JR, Zimmerman HJ, Ishak KG, Epler GR. Isoniazid-associated hepatitis in 114 patients. Gastroenterology 1975;69:289-302.
585. Aithal GP, Ramsay L, Daly AK, Sonchit N, Leathart JB, Alexander G, Kenna JG, et al. Hepatic adducts, circulating antibodies, and cytokine polymorphisms in patients with diclofenac hepatotoxicity. Hepatology 2004;39:1430-1440.
586. 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.
587. Maddrey WC, Boitnott JK. Severe hepatitis from methyldopa. Gastroenterology 1975;68:351-360.
588. Rodman JS, Deutsch DJ, Gutman SI. Methyldopa Hepatitis. A report of six cases and review of the literature. Am J Med 1976;60:941-948.
589. Shalev O, Mosseri M, Ariel I, Stalnikowicz R. Methyldopa-induced immune hemolytic anemia and chronic active hepatitis. Arch Intern Med 1983;143:592-593.
590. Kwok G, Yau TC, Chiu JW, Tse E, Kwong YL. Pembrolizumab (Keytruda). Hum Vaccin Immunother 2016;12:2777-2789.
591. Adar T, Mizrahi M, Pappo O, Scheiman-Elazary A, Shibolet O. Adalimumab-induced autoimmune hepatitis. J Clin Gastroenterol 2010;44:e20-22.

592. Efe C, Purnak T, Ozaslan E, Wahlin S. Drug-induced autoimmune hepatitis caused by anti-tumor necrosis factor alpha agents. Hepatology 2010;52:2246-2247.
593. Grasland A, Sterpu R, Boussoukaya S, Mahe I. Autoimmune hepatitis induced by adalimumab with successful switch to abatacept. Eur J Clin Pharmacol 2012;68:895-898.
594. Graziadei IW, Obermoser GE, Sepp NT, Erhart KH, Vogel W. Drug-induced lupus-like syndrome associated with severe autoimmune hepatitis. Lupus 2003;12:409-412.
595. Pelli N, Setti M, Ceppa P, Toncini C, Indiveri F. Autoimmune hepatitis revealed by atorvastatin. Eur J Gastroenterol Hepatol 2003;15:921-924.
596. Noel B. Lupus erythematosus and other autoimmune diseases related to statin therapy: a systematic review. J Eur Acad Dermatol Venereol 2007;21:17-24.
597. Russo MW, Scobey M, Bonkovsky HL. Drug-induced liver injury associated with statins. Semin Liver Dis 2009;29:412-422.
598. Neuberger J, Kenna JG. Halothane hepatitis: a model of immune mediated drug hepatotoxicity. Clin Sci (Lond) 1987;72:263-270.
599. Eliasson E, Gardner I, Hume-Smith H, de Waziers I, Beaune P, Kenna JG. Interindividual variability in P450-dependent generation of neoantigens in halothane hepatitis. Chem Biol Interact 1998;116:123-141.
600. Wolters LM, Van Buuren HR. Rosuvastatin-associated hepatitis with autoimmune features. Eur J Gastroenterol Hepatol 2005;17:589-590.
601. 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.
602. Guzman G, Kallwitz ER, Wojewoda C, Chennuri R, Berkes J, Layden TJ, Cotler SJ. Liver injury with features mimicking autoimmune hepatitis following the use of black cohosh. Case Report Med 2009;2009:918156.
603. Reynolds TB, Peters RL, Yamada S. Chronic active and lupoid hepatitis caused by a laxative, oxyphenisatin. N Engl J Med 1971;285:813-820.
604. Pessayre D, Degos F, Feldmann G, Degott C, Bernuau J, Benhamou JP. Chronic active hepatitis and giant multinucleated hepatocytes in adults treated with clometacin. Digestion 1981;22:66-72.
605. Pariente EA, Hamoud A, Goldfain D, Latrive JP, Gislon J, Cassan P, Morin T, et al. [Hepatitis caused by clometacin (Duperan). Retrospective study of 30 cases. A model of autoimmune drug-induced hepatitis?]. Gastroenterol Clin Biol 1989;13:769-774.
606. 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.
607. Bourdi M, Larrey D, Nataf J, Bernuau J, Pessayre D, Iwasaki M, Guengerich FP, et al. Anti-liver endoplasmic reticulum autoantibodies are directed against human cytochrome P-450IA2. A specific marker of dihydralazine-induced hepatitis. J Clin Invest 1990;85:1967-1973.
608. Larrey D, Vial T, Pauwels A, Castot A, Biour M, David M, Michel H. Hepatitis after germander (Teucrium chamaedrys) administration: another instance of herbal medicine hepatotoxicity. Ann Intern Med 1992;117:129-132.
609. Homberg JC, Andre C, Abuaf N. A new anti-liver-kidney microsome antibody (anti-LKM2) in tienilic acid-induced hepatitis. Clin Exp Immunol 1984;55:561-570.
610. Fong TL, Klontz KC, Canas-Coto A, Casper SJ, Durazo FA, Davern TJ, 2nd, Hayashi P, et al. Hepatotoxicity due to hydroxycut: a case series. Am J Gastroenterol 2010;105:1561-1566.
611. Gilbert KM, Przybyla B, Pumford NR, Han T, Fuscoe J, Schnackenberg LK, Holland RD, et al. Delineating liver events in trichloroethylene-induced autoimmune hepatitis. Chem Res Toxicol 2009;22:626-632.
612. Poncin E, Silvain C, Touchard G, Barbier J, Beauchant M. Papaverine-induced chronic liver disease. Gastroenterology 1986;90:1051-1053.

613. Abraham C, Hart J, Locke SM, Baker AL. A case of indometacin-induced acute hepatitis developing into chronic autoimmune hepatitis. Nat Clin Pract Gastroenterol Hepatol 2008;5:172-176.
614. Aliberti S, Grignani G, Allione P, Fizzotti M, Galatola G, Pisacane A, Aglietta M. An acute hepatitis resembling autoimmune hepatitis occurring during imatinib therapy in a gastrointestinal stromal tumor patient. Am J Clin Oncol 2009;32:640-641.
615. Elkayam O, Yaron M, Caspi D. Minocycline-induced autoimmune syndromes: an overview. Semin Arthritis Rheum 1999;28:392-397.
616. Ratziu V, Samuel D, Sebagh M, Farges O, Saliba F, Ichai P, Farahmand H, et al. Long-term follow-up after liver transplantation for autoimmune hepatitis: evidence of recurrence of primary disease. J Hepatol 1999;30:131-141.
617. Reich DJ, Fiel I, Guarrera JV, Emre S, Guy SR, Schwartz ME, Miller CM, et al. Liver transplantation for autoimmune hepatitis. Hepatology 2000;32:693-700.
618. Duclos-Vallee JC, Sebagh M, Rifai K, Johanet C, Ballot E, Guettier C, Karam V, 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.
619. Gonzalez-Koch A, Czaja AJ, Carpenter HA, Roberts SK, Charlton MR, Porayko MK, Rosen CB, et al. Recurrent autoimmune hepatitis after orthotopic liver transplantation. Liver Transpl. 2001;7:302-310.
620. Andries S, Casamayou L, Sempoux C, Burlet M, Reding R, Bernard Otte J, Buts JP, et al. Posttransplant immune hepatitis in pediatric liver transplant recipients: incidence and maintenance therapy with azathioprine. Transplantation 2001;72:267-272.
621. Duclos-Vallee JC. Recurrence of autoimmune hepatitis, primary biliary cirrhosis and primary sclerosing cholangitis after liver transplantation. Acta Gastroenterol Belg 2005;68:331-336.
622. Sempoux C, Horsmans Y, Lerut J, Rahier J, Geubel A. Acute lobular hepatitis as the first manifestation of recurrent autoimmune hepatitis after orthotopic liver transplantation. Liver 1997;17:311-315.
623. Ayata G, Gordon FD, Lewis WD, Pomfret E, Pomposelli JJ, Jenkins RL, Khettry U. Liver transplantation for autoimmune hepatitis: a long-term pathologic study. Hepatology 2000;32:185-192.
624. Hubscher SG. Recurrent autoimmune hepatitis after liver transplantation: diagnostic criteria, risk factors, and outcome. Liver Transpl 2001;7:285-291.
625. Banff Working G, Demetris AJ, Adeyi O, Bellamy CO, Clouston A, Charlotte F, Czaja AJ, et al. Liver biopsy interpretation for causes of late liver allograft dysfunction. Hepatology 2006;44:489-501.
626. Liberal R, Longhi MS, Grant CR, Mieli-Vergani G, Vergani D. Autoimmune hepatitis after liver transplantation. Clin. Gastroenterol. Hepatol. 2012;10:346-353.
627. Hurtova M, Duclos-Vallee JC, Johanet C, Emile JF, Roque-Afonso AM, Feray C, Bismuth H, 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.
628. Salcedo M, Vaquero J, Banares R, Rodriguez-Mahou M, Alvarez E, Vicario JL, Hernandez-Albujar A, et al. Response to steroids in de novo autoimmune hepatitis after liver transplantation. Hepatology 2002;35:349-356.
629. Pfitzmann R, Klupp J, Langrehr JM, Uhl M, Neuhaus R, Settmacher U, Steinmuller T, et al. Mycophenolatemofetil for immunosuppression after liver transplantation: a follow-up study of 191 patients. Transplantation 2003;76:130-136.
630. Kerkar N, Dugan C, Rumbo C, Morotti RA, Gondolesi G, Shneider BL, Emre S. Rapamycin successfully treats post-transplant autoimmune hepatitis. Am. J. Transplant. 2005;5:1085-1089.
631. Gibelli NE, Tannuri U, Pinho-Apezzato ML, Tannuri AC, Maksoud-Filho JG, Andrade WC, Velhote MC, et al. Sirolimus in pediatric liver transplantation: a single-center experience. Transplant. Proc. 2009;41:901-903.

632. Milkiewicz P, Hubscher SG, Skiba G, Hathaway M, Elias E. Recurrence of autoimmune hepatitis after liver transplantation. Transplantation 1999;68:253-256.
633. 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.
634. Gelson W, Hoare M, Dawwas MF, Vowler S, Gibbs P, Alexander G. The pattern of late mortality in liver transplant recipients in the United Kingdom. Transplantation 2011;91:1240-1244.
635. Czaja AJ. Comparability of probable and definite autoimmune hepatitis by international diagnostic scoring criteria. Gastroenterology 2011;140:1472-1480.
636. Hennes EM, Zeniya M, Czaja AJ, Pares A, Dalekos GN, Krawitt EL, Bittencourt PL, et al. Simplified criteria for the diagnosis of autoimmune hepatitis. Hepatology 2008;48:169-176.

Figure 1.

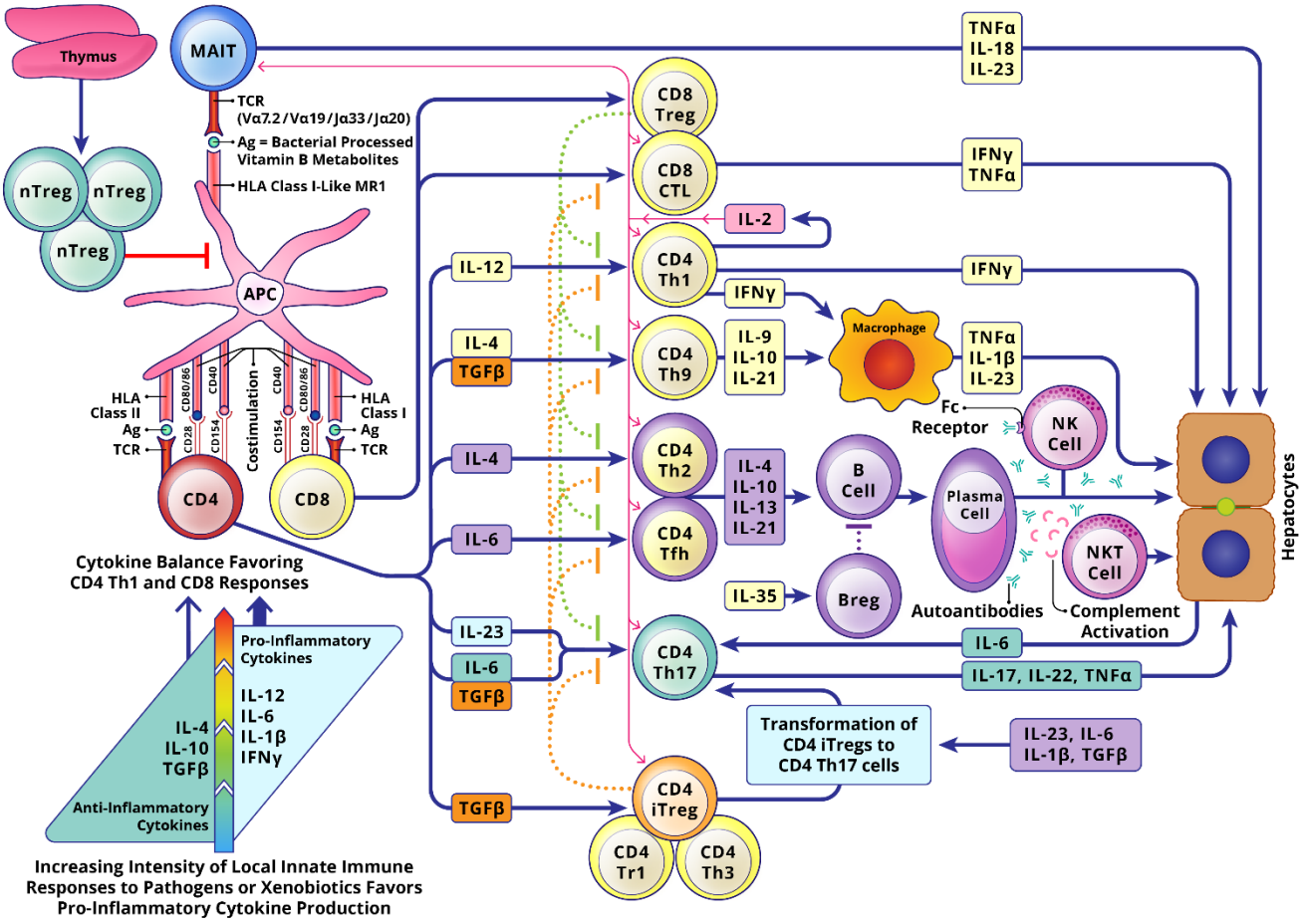

Figure 2.

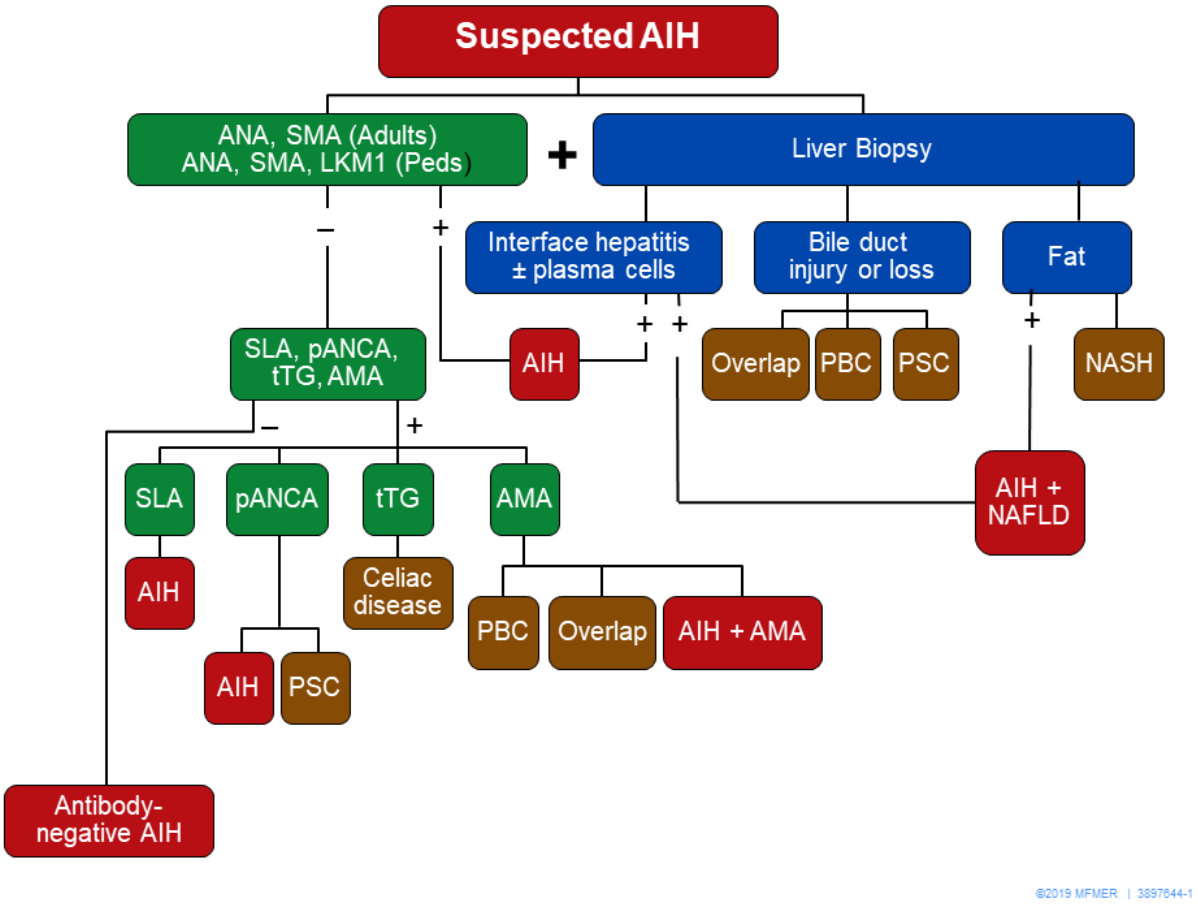

Figure 3.

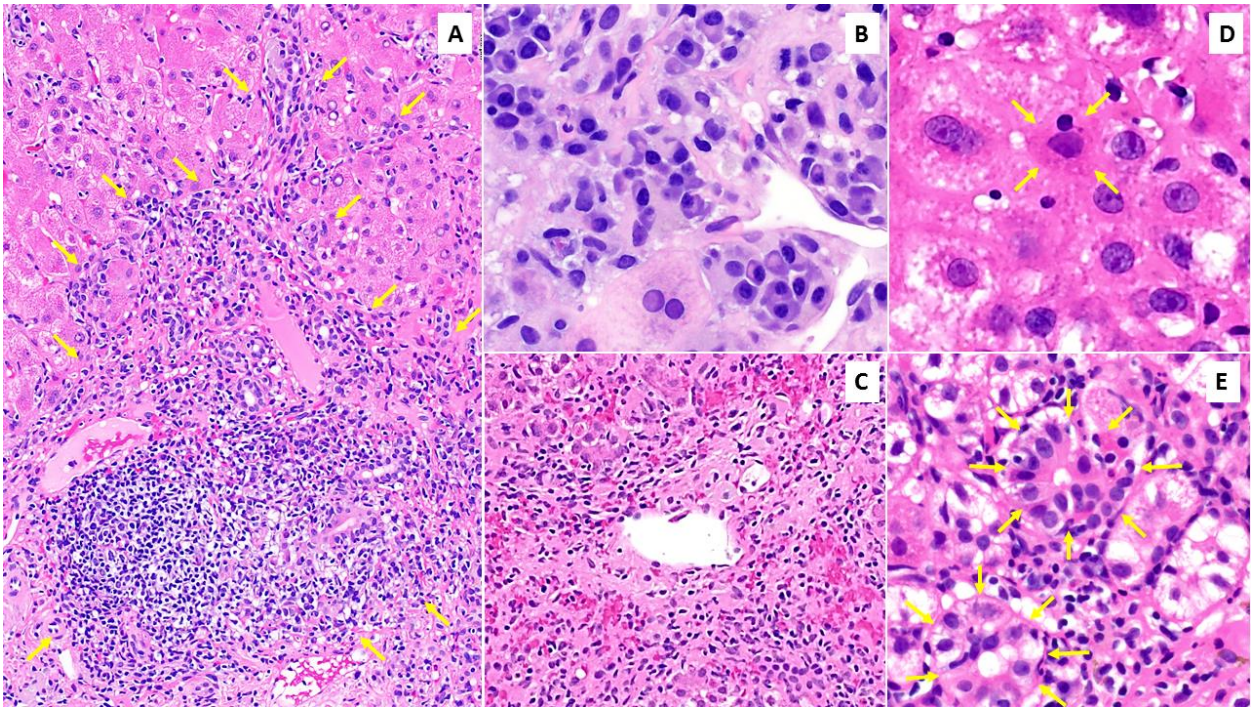

Figure 4.