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

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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.**

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.

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	High Moderate	Quality of evidence Balance of benefits and harms Patient values and preferences	Strong • Most people would want course • Most people should take course • Can be adapted as policy in most cases
Observational	Low Very low	Resources and costs Feasibility Acessibility Equity	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

Supplementary Table 1

Systematic Review (SR) Questions

	Questions Related to Treatment of AIH
SR1	Should patients with newly diagnosed AIH be treated with prednisone or prednisolone alone or in combination with azathioprine (AZA) or with budesonide in combination with AZA because outcomes are different with respect to the following? • Frequency of remission • Interval to remission (rapidity of response) • Frequency and type of medication-associated side effects • Frequency of death or liver transplantation
SR2	Should patients with AIH who worsen during standard therapy (treatment failure) or who fail to achieve remission during standard therapy (incomplete response) be treated with mycophenolate mofetil (in place of AZA), 6-mercaptopurine (in place of AZA), or calcineurin inhibitors (in place of or in addition to standard therapy) because of the following? • Frequency of remission • Frequency of medication-associated side effects • Frequency of death or liver transplantation
SR3	Should patients transplanted for AIH be maintained on glucocorticoids indefinitely or withdrawn from them because of the following? • Frequency of recurrent AIH • Number of episodes of acute cellular rejection • Occurrence of graft loss • Frequency of re-transplantation or death • Adverse side effects

Supplementary Table 2

Original Revised and Simplified Diagnostic Scoring Systems

REVISED ORIGINAL DIAGNOSTIC SCORING SYSTEM (56, 122, 635)			SIMPLIFIED DIAGNOSTIC SCORING SYSTEM (636)		
Feature	**Score**		**Feature**	**Value**	**Score**
Female sex	+2		ANA or SMA	≥1:40 titer	+1
	+2		ANA or SMA	≥1:80 titer	+1
ALP:AST (or ALT)	+2		LKM-1	≥1:40 titer	+2
<1.5	0		SLA	Positive	+2
1.5-3.0	-2		IgG	>ULN	+1
>3.0				>1.1 x ULN	+2
Serum globulins or IgG >ULN			Liver histology	Compatible	+1
>2.0	+3			Typical	+2
1.5-2.0	+2				
1.0-1.5	+1		Negative viral markers	Yes	+2
<1.0	0				
ANA, SMA or LKM-1 (titers)					
>1:80	+3		**Diagnostic Scores**		
1:80	+2				
1:40	+1				
<1:40	0		**≥6**	**Probable AIH**	
			≥7	**Definite AIH**	
AMA+	-4				
Hepatitis viral markers					
Positive	-3				
Negative	+3				
Drug history					
Positive	-4				
Negative	+1				
Average alcohol intake					
<25 g/day	+2				
>60 g/day	-2				
Liver histology					
Interface hepatitis	+3				
Lymphoplasmacytic infiltrate	+1				
Rosetting of hepatocytes	+1				

None of above	-5				
Biliary changes	-3				
Other changes	-3				
Concurrent autoimmune diseases	+2				
Additional findings					
Other defined autoantibodies	+2				
HLA DRB1*03 or DRB1*04	+1				
Response to therapy					
Complete	+2				
Relapse	+3				
Diagnostic Scores					
Pre-treatment score					
Definite AIH	**>15**				
Probable AIH	**10-15**				
Not AIH	**<10**				
Post-treatment score					
Definite AIH	**>17**				
Probable AIH	**12-17**				
Not AIH	**<17**				

AIH, autoimmune hepatitis; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AMA, antimitochondrial antibodies; ANA, antibuclear antibodies; AST, aspartate aminotransferase; IgG, immunoglobulin G; LKM-1, liver kidney microsome type 1; SLA, soluble liver antigen; ULN, upper limit of normal range.

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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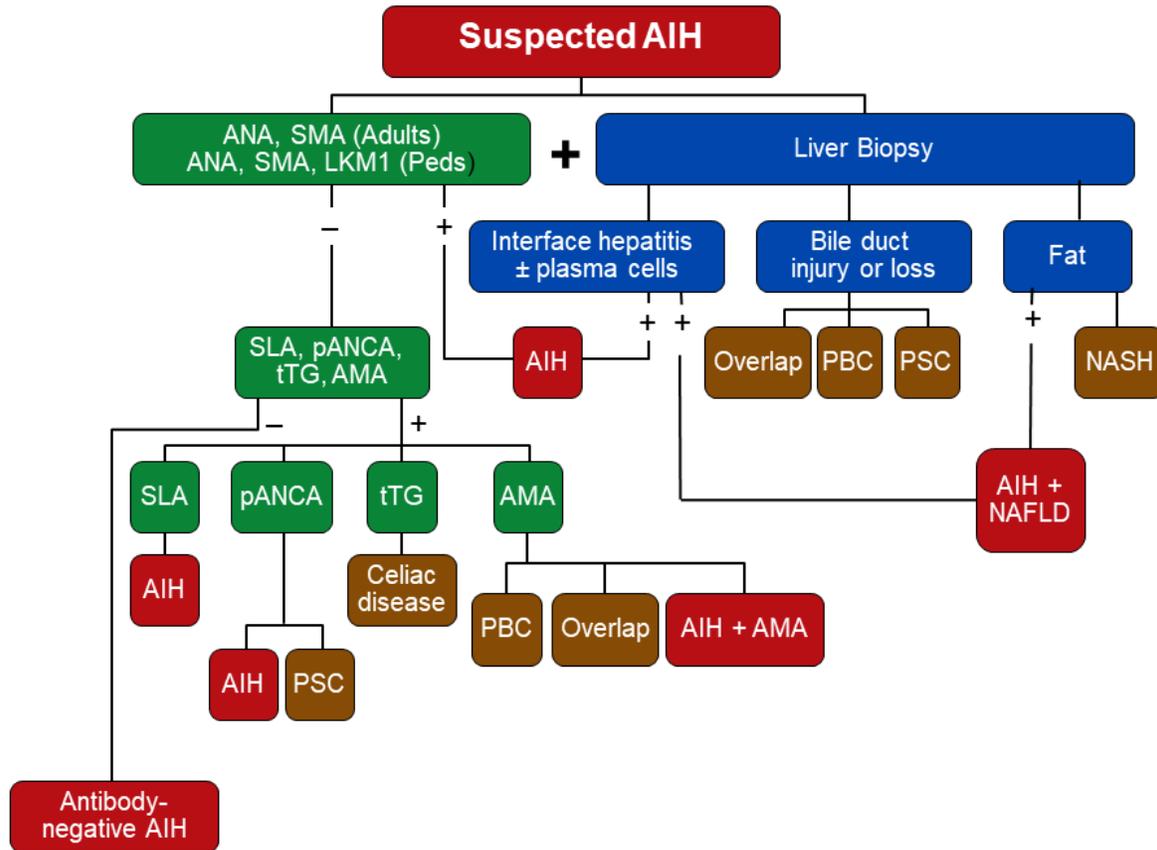
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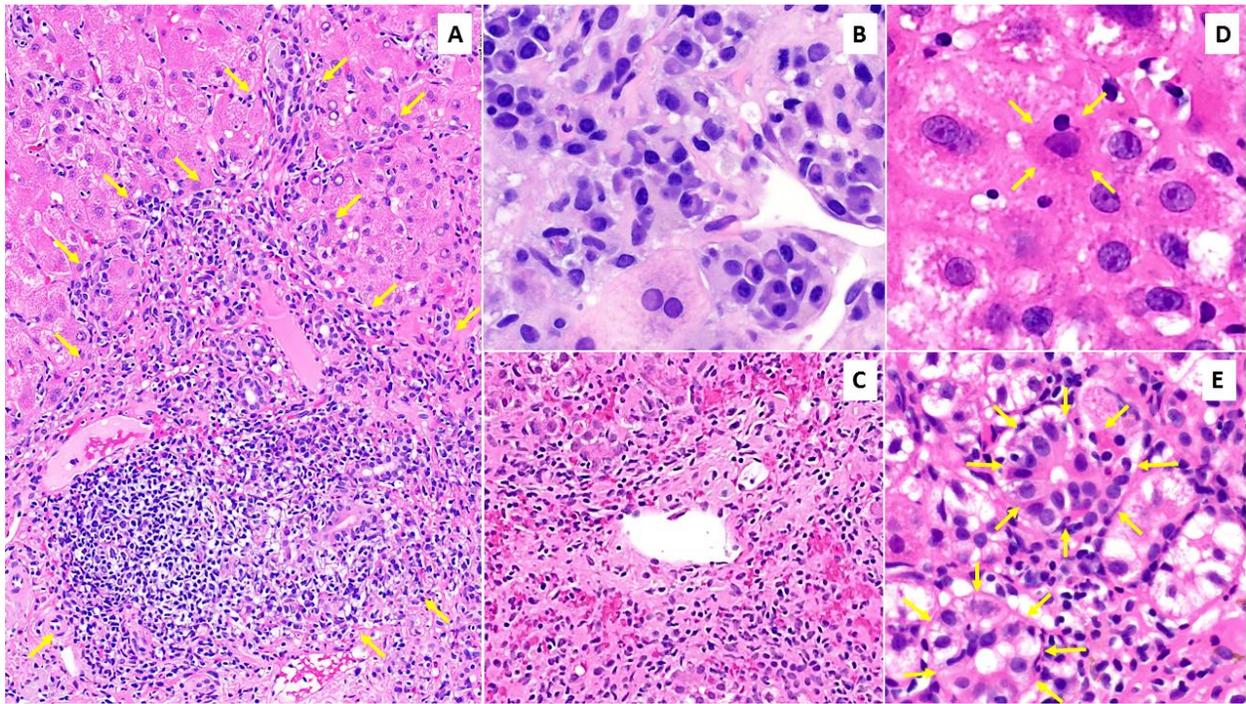
Figure 1.

Figure 2.

Figure 3.

Figure 4.

First-Line Treatment of AIH

AIH	AIH with Cirrhosis	Acute Severe AIH

Induction

STEROIDS
Adults: Prednisone (20-40 mg/d)
Pediatrics: Prednisone (1-2 mg/kg/d)
OR Budesonide (9 mg daily)
AZATHIOPRINE (AZA)
Check TPMT. After 2 weeks add AZA (50-150 mg/d)
Laboratory testing every 1-2 weeks

STEROIDS
Do not use Budesonide
Adults: Prednisone (20-40 mg/d)
Pediatrics: Prednisone (1-2 mg/kg/d)
AZATHIOPRINE (AZA)
Do not use in decompensated cirrhosis
Compensated Cirrhosis: Check TPMT.
After 2 weeks add AZA (50-150 mg/d)
Laboratory testing every 1-2 weeks

STEROIDS
Do not use Budesonide
Do not use Azathioprine (AZA)
Adults: Prednisone (60 mg/d)
Pediatrics: Prednisone (2 mg/kg/d)
OR I.V. steroids
Laboratory testing every 12-24 hours

Assess Response by 4-8 weeks:
(+) Biochemical Response
• Taper prednisone to 5-10 mg daily (budesonide 3 mg daily) over the next 6 months
• Maintain AZA
• Laboratory testing every 2-4 weeks
(-) Biochemical Response
• Re-evaluate diagnosis
• Consider second-line drugs

Assess Response by 4-8 weeks:
(+) Biochemical Response
• Taper prednisone to 5-10 mg daily over the next 6 months
• If started, maintain AZA
• Laboratory testing every 2-4 weeks
(-) Biochemical Response
• Re-evaluate diagnosis
• Consider second-line drugs

Assess Response by 7-14 days:
(+) Biochemical Response
• Cautiously reduce prednisone
• Consider AZA after cholestasis is resolved (check TPMT first)
• Laboratory testing every 1-2 weeks
(-) Biochemical Response
• Re-evaluate Diagnosis
• Consider second-line drugs
• Initiate Transplant Evaluation
If Hepatic Encephalopathy develops:
• Urgent Transplant Evaluation

Maintenance

Once Biochemical Remission is achieved:
• Laboratory testing every 3-4 months
• May attempt a steroid withdrawal while continuing AZA
After Prolonged Biochemical Remission (24 months):
• Laboratory testing every 4-6 months
• Consider immunosuppression withdrawal if appropriate (+/-biopsy)

Once Biochemical Remission is achieved:
• Laboratory testing every 3-4 months
• Use lowest immunosuppression doses to maintain remission
• *Do not withdraw immunosuppression*