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Hellenic Association for the Study of the Liver (HASL): revised clinical practice guidelines for autoimmune hepatitis

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Abstract

Autoimmune hepatitis (AIH) is a rare liver disease, of unknown origin, characterized by considerable heterogeneity. AIH can affect both sexes, of all ages, ethnicities and races. The revised Clinical Practice Guidelines (CPGs) of the Hellenic Association for the Study of the Liver aim to provide updated guidance to clinicians. The diagnosis of AIH is based on clinicopathological characteristics, such as elevation of immunoglobulin G (IgG) levels, detection of autoantibodies, portal or lobular hepatitis at the histological level, absence of viral hepatitis markers, and a favorable response to immunosuppressive treatment. Clinical manifestations at onset vary, from no symptoms to the fulminant form of the disease. Aminotransferases and bilirubin levels also vary, while liver biopsy is a prerequisite to establish a firm diagnosis. Investigation for detection of autoantibodies is the cornerstone for diagnosis, if it is performed according to the CPGs. Treatment of AIH should aim towards the achievement of complete biochemical response (CBR; normalization of aminotransferases and IgG) no later than 6-12 months after treatment initiation, and also histological remission of the disease. All patients with active disease, irrespective of the presence of cirrhosis, should receive personalized and response-guided first-line induction treatment with predniso(lo)ne combined with mycophenolate mofetil or azathioprine. Treatment should be given for at least 3-5 years, and for at least 2 years after the achievement of CBR, while liver biopsy should be considered before treatment cessation. The updated CPGs also provide guidance for the management of difficult-to-treat patients, including those with variants and specific forms of AIH.

Keywords Autoimmune hepatitis, clinical practice guidelines, corticosteroids, azathioprine, mycophenolate mofetil

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Introduction

In 2019, the Hellenic Association for the Study of the Liver (HASL) published the first Clinical Practice Guidelines (CPGs) for the diagnosis and management of autoimmune hepatitis (AIH) [1]. Since then, there has been considerable progress in terms of disease pathogenesis, serological, histological and response criteria, and endpoints, along with treatment schedules for AIH; this has resulted in an unmet need for updating the CPGs [2-7].

The revised CPGs aim to provide updated recommendations and statements designed to improve the care of AIH patients. Thus, the HASL Governing Board appointed a panel of experts who were responsible for literature research and writing. Searching was performed through PubMed, Embase, Google Scholar and Scopus.

The quality of evidence was assessed according to the criteria of the Oxford Centre for Evidence-based Medicine (OCEBM), while the strength of recommendations and statements was assessed using the OCEBM criteria (strong or weak/open) [8] (Table 1). All statements and recommendations, including grading and the level of evidence, underwent thorough discussion and approval by all panel members during an in-person meeting and many email communications.

Epidemiological aspects

AIH is an autoimmune liver disease characterized by a distinct increase of immunoglobulin G (IgG) levels, detection of autoantibodies, portal or lobular hepatitis at the histological level, absence of viral hepatitis markers, and a favorable response to immunosuppression [1,9-11]. Although predominantly found in females (ratio 3-4:1), AIH is now recognized to affect people from all ethnic groups, irrespective of race, age and sex [1,9-14]. The worldwide annual prevalence and incidence in adults and children varies from 4-42.7/100,000 and 2.4-9.9/100,000 population, and from 0.67-2.2/100,000 and 0.23-0.4/100,000 per year, respectively [9,12,13,15-17]. Apart from genetic differences, these disparities could be attributed to external (medications, infections, toxins, and personal habits) or internal (microbiome) factors, socioeconomic status, and healthcare access [12,13,17]. The net result suggests that, in most countries, the incidence of AIH is increasing significantly, as was recently shown by an English population-based study between 1997 and 2015 (from 1.27 to 2.56/100,000 population per year) [18]. Notably, in that study, the 10-year cumulative all-cause mortality was 31.9% and the 10-year cumulative liver-related mortality, including hepatocellular carcinoma (HCC), was 10.5% [18].

Ethnicity and race seem important, as AIH patients of Asian, African American, or Latino-American origin demonstrate poor outcomes [19,20]. Again, genetic predisposition, triggering and socioeconomic factors, along with problems in healthcare access, could explain these differences [19,20].

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Statements 1-2

- AIH is a very heterogeneous disease, with increasing incidence and prevalence worldwide, which affects women and men of all ages, and all ethnic groups and races **(Evidence 1, Strong statement)**
- Race and ethnicity may affect disease presentation and outcome **(Evidence 2, Weak statement)**

Clinical presentation

In the appropriate clinical and laboratory background, the possibility of AIH should be seriously taken into consideration under any circumstances [1,9-11,14,21-24]. Male patients with AIH seem to be younger, more likely to present advanced disease at first evaluation, and may experience worse outcomes compared to females [20,25,26]. Sex-related comorbidities, sex hormones that may influence the activity of AIH and its progression, sex-associated dissimilarities in immunogenetics, and differences in medical adherence could explain these disparities, at least in part [27].

AIH is commonly associated with several extrahepatic autoimmune diseases, such as Hashimoto thyroiditis (the strongest association), Grave's disease, celiac disease, rheumatoid arthritis, vitiligo, alopecia, psoriasis, systemic lupus erythematosus (SLE), diabetes mellitus type 1, inflammatory bowel disease (IBD), and Sjögren's syndrome [21,24,28,29]. A large study in 2479 AIH patients showed that the presence of other autoimmune diseases negatively affects not only the quality of life, but also mortality, which was higher in those with multiple extrahepatic autoimmune diseases (Table 2) [28]. As in most chronic diseases, AIH is also characterized by high rates of anxiety and depression [30-32].

Manifestations of the disease vary considerably, from entirely asymptomatic to acute liver failure (ALF) [1,9-11,18,22,33,34]. Acute presentation occurs in about 30% of patients and is indistinguishable from viral or other causes of hepatitis [34,35]. Acute AIH, either icteric or non-icteric, can present as an acute flare of chronic AIH that had not been diagnosed previously, or as a genuine episode of acute hepatitis without lesions of chronic disease on liver histology [9,22,33-36]. Some of these patients can present an acute–severe type of AIH (AS-AIH) (Table 2) [11,34-37].

Most patients (65%-70%) are either completely asymptomatic or present with general symptoms of various severity, such as weakness, fatigue, malaise, amenorrhea, lethargy, anorexia, weight loss, upper right quadrant pain, nausea, low-grade fever and polyarthralgia, usually involving the small joints, without arthritis, dating back even for years [9,13-15,19,20,22,38]. Almost a third of adults and 40-50% of children already have cirrhosis at baseline [15,38], even though these figures seem to be declining in recent studies from several countries, including Greece, probably reflecting improvements in early diagnosis and treatment [13,22,39,40].

Table 1 Levels of evidence (A) and grades of recommendations (B) based on the Oxford Centre for Evidence-based Medicine (adapted from: [8])

A

Level	Criteria	Simple model for high, intermediate, and low evidence
1	Systematic reviews (SR) (with homogeneity) of randomized-controlled trials (RCT)	Further research is unlikely to change our confidence in the estimate of benefit and risk
2	RCT or observational studies with dramatic effects; SR of lower quality studies (i.e. non-randomized, retrospective)	
3	SR of lower quality studies (i.e. non-randomized, retrospective)	Further research (if performed) is likely to have an impact on our confidence in the estimate of benefit and risk and may change the estimate
4	Case-series, case-control, or historically controlled studies (SR are generally better than individual studies)	
5	Expert opinion (mechanism-based reasoning)	Any estimate of effect is uncertain

B

Grade	Wording	Criteria
Strong	Must, shall, should, is recommended Shall not, should not, is not recommended	Evidence, consistency of studies, risk-benefit ratio, patient preferences, ethical obligations, feasibility
Weak or open	Can, may, is suggested May not, is not suggested	

Table 2 Common and uncommon variants and specific forms of autoimmune hepatitis (AIH)

Common	Uncommon
AIH with normal IgG - *10%-15% of AIH patients; no differences in terms of liver biochemistry, serology, histology, and treatment response rates to those with high IgG; possible higher chance of long-term remission after treatment withdrawal*	Autoantibodies-negative AIH - *Extremely rare if guidelines for autoantibodies detection are followed strictly*
DI-ALH - *Histologically and clinically indistinguishable from classical AIH; often resolves after stopping the causative agent or short-term immunosuppression*	AIH with concurrent HBV, HCV or HIV infection - *Rare; difficult to diagnose; treat first HBV or HCV or simultaneously for HIV*
AIH-PBC – *About 10%; for criteria of diagnosis see Suppl. Tables 1 and 2; association with severe disease and worse outcome compared to PBC alone; treat with combination with UDCA*	AIH coexistence with alcohol-associated liver disease - *Rare; difficult to diagnose; follow the related guidelines for both diseases*
AIH-PSC – *6.5-14%; MRCP in all children; in adults only when cholestasis is present and PBC-specific antibodies are negative; better outcome compared to PSC but worse compared to AIH*	SLA/LP-positive AIH – *Concurrent with Ro52 antibodies in 98% of SLA/LP positive patients; Permanent immunosuppression is needed*
AS-AIH - *≤26 weeks, jaundice, INR ≥1.5 but <2 without hepatic encephalopathy; INR >2 and encephalopathy denotes AS-AIH with ALF*	Plasma cell rich–rejection (previous *de-novo* AIH in liver transplant recipients) - *Rare; difficult to diagnose; treat like genuine AIH*
AIH coexistence with other autoimmune diseases – *Very common (Hashimoto thyroiditis by far the strongest association); first-degree relatives also; appears to negatively affect mortality, being higher in those with multiple extrahepatic autoimmune diseases*	AIH in pregnancy - *Rare but does occur; frequently postpartum as it attenuates during pregnancy; high rates of hypertensive disorders, gestational diabetes mellitus, preterm birth, and fetal growth restriction but congenital malformations, neonatal mortality and stillbirth are not affected*
AIH coexistence with MASLD – *Difficult to treat; may affect outcome and prognosis; close surveillance and follow up is justified*	AIH with AMA seropositivity - *About 5%; no association with disease severity, treatment response and outcome*
AIH in elderly - *a third ≥65 years (10% ≥70 years); 30% already cirrhotic at diagnosis; more frequent treatment response; higher frequency of autoimmune diseases compared to youngers*	Viral induced AIH – *Rare; molecular mimicry and IFNα therapies have been implicated; might be a result of bias*

ALF, acute liver failure; AMA, antimitochondrial antibodies; AS-AIH, acute severe autoimmune hepatitis; DI-ALH, drug-induced autoimmune-like hepatitis; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IgG, immunoglobulin G; IFNα, interferon-alpha; MASLD, metabolic dysfunction-associated steatotic liver disease; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; SLA/LP, soluble liver antigens/ liver pancreas; UDCA, ursodeoxycholic acid

AIH is classified in 2 subtypes, AIH-type 1 (AIH-1) and AIH-type 2 (AIH-2), according to the circulating autoantibodies, although the importance of this distinction is still uncertain. Indeed, a recent long-term observational study in children with AIH showed that disease severity, treatment response and outcomes were not associated with the type of AIH [41]. Patients with AIH-1 have seropositivity for antinuclear autoantibodies (ANA), smooth muscle autoantibodies (SMA) and/or soluble liver antigens/liver pancreas antibodies (anti-SLA/LP), while those with AIH-2 have seropositivity for anti-liver/kidney microsomal antibody type-1 (anti-LKM1) and/or antibodies against liver cytosol type-1 antigen (anti-LC1) or rarely anti-LKM-type 3 (anti-LKM3) [1,10,42,43].

Statements 3-7

- Early diagnosis is of utmost importance, as it positively affects the patient's outcome **(Evidence 1, Strong statement)**
- Males may represent a subgroup with advanced disease at diagnosis and worse outcome **(Evidence 3, Weak statement)**
- Almost a third of adults and 40-50% of children already have cirrhosis at diagnosis, because of undiagnosed or misdiagnosed disease **(Evidence 2, Strong statement)**
- Acute AIH presents as an acute flare of undiagnosed AIH, or as a genuine episode of acute hepatitis **(Evidence 2, Strong statement)**
- AS-AIH is defined by the presence of jaundice, prolongation of international normalized ratio (INR ≥1.5 and <2) and no hepatic encephalopathy **(Evidence 2, Strong statement)**

Recommendations 1-4

- Thorough investigation for suspected AIH should be performed in all cases of unexplained hepatitis, especially when IgG levels are elevated **(Evidence 2, Strong recommendation)**
- AIH patients should be screened at diagnosis and during follow up for the presence of Hashimoto thyroiditis, the most common concurrent extrahepatic autoimmune disease **(Evidence 2, Strong recommendation)**
- Patients with AIH can be screened according to symptoms for other extrahepatic autoimmune diseases, as they may affect mortality, being higher in those with more than one autoimmune disease **(Evidence 2, Weak recommendation)**
- Sub-classification of AIH into AIH-1 and AIH-2 is not recommended **(Evidence 4, Strong recommendation)**

Specific forms of AIH

AIH may present in the context of any other hepatic and non-hepatic disease or syndromes (Table 2). In this regard, some of the uncommon specific forms of AIH include seronegative AIH, coexistence of AIH with hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV) or alcohol-associated liver disease, plasma cell rich–rejection hepatitis (known also as *de-novo* AIH), anti-SLA/LP-positive AIH, AIH in pregnancy, AIH with anti-mitochondrial antibodies (AMA), and AIH development after viral infections (Table 2) [44-53].

Considering AMA, the specific autoantibody for the diagnosis of primary biliary cholangitis (PBC) [54,55], a recent large study from the International AIH Group (IAIHG) showed that AMA can be detected in about 5% of patients, either at diagnosis or during the course of AIH, even though this finding was not associated with liver biochemistry, bile duct injury, disease severity at diagnosis, response to treatment or liver-related mortality [56]. However, AMA positivity in AIH patients with incidental findings of bile duct injury on baseline liver biopsy may be of significance, as they may bear a higher risk of disease progression [56]. Rarely, development of AIH has also been reported in association with previous viral infections [1,10,57], including HCV after treatment with interferon alpha [58], and acute HCV infection irrespective of viral clearance [59]. The recent acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has also been proposed as a potential trigger of AIH development in a few case reports [60]. However, all the above associations might be a result of bias, as previous undiagnosed AIH can be unmasked during an incidental episode of acute viral infection, or because the diagnosis of the supposed viral hepatitis could rely on serology only (possible false-positive result due to the considerable hypergammaglobulinemia of AIH).

More common specific forms of AIH include AS-AIH, AIH with normal IgG, drug-induced autoimmune-like hepatitis (DI-ALH), the coexistence of AIH with other autoimmune diseases, or the metabolic dysfunction-associated steatotic liver disease (MASLD), previously termed nonalcoholic fatty liver disease, and AIH in the elderly (Table 2) [14,21,24,28,29,34,35,61-66].

Many drugs, including SARS-CoV-2 vaccines, dietary supplements and/or herbals, may result in a phenotype of liver injury resembling that of classical AIH, which was known as drug-induced AIH [1,10,11,67,68]. However, recently, an expert opinion meeting report, along with the CPGs of the European Association for the Study of the Liver (EASL), chose the term DI-ALH, instead of drug-induced AIH, as the preferred term to describe this quite enigmatic and problematic entity [62,67]. According to the EASL CPGs, DI-ALH is defined as an *"acute drug-induced liver injury (DILI) with serological and/or histological markers of idiopathic AIH"* [67]. Indeed, liver injury in DI-ALH is clinically and histologically indistinguishable from that observed in classical AIH, while features of hypersensitivity, such as rash, eosinophilia or fever, are usually absent [62,67]. DI-ALH often resolves either spontaneously within 6 months after withdrawal of the causative agent, or after a short course of immunosuppression with corticosteroids [62,63,69]. Recently, 5 criteria were proposed for DI-ALH definition [69], namely: 1) drug as a trigger of liver injury with markers of autoimmunity (elevation in any of SMA, ANA and IgG) and liver histology compatible with AIH, according to the simplified criteria for

AIH diagnosis [70]; 2) incomplete or no recovery, or worsening of liver biochemistry after drug discontinuation; 3) need for corticosteroid administration or spontaneous recovery; 4) lack of relapse during at least 6 months follow up after stopping corticosteroids; and 5) drugs potentially inducing DI-ALH with a chronic course. The first 4 criteria are needed to define probable, while 3 indicates possible DI-ALH [62,69]. Nevertheless, these criteria need to be validated in future prospective studies.

MASLD and metabolic dysfunction-associated steatohepatitis (MASH) represent a modern "pandemic" which affects at least a quarter of the population worldwide, making its coexistence with other liver diseases inevitable [66,71]. In this context, a large study from the IAIHG, including 640 AIH patients, investigated the clinical significance of the coexistence of MASLD or components of the metabolic syndrome (MetS) [65]. MASLD prevalence in AIH patients was similar to that in the general population. However, the coexistence of MASH denotes a more severe disease and probably low rates of treatment response, whereas the presence of even simple steatosis may underline a worse prognosis in AIH patients with established cirrhosis at baseline. Type 2 diabetes and dyslipidemia in patients with AIH were also associated with disease progression and worse prognosis [65].

Almost a third of patients are older than 65 years at diagnosis, with those older than 70 years representing about 10% of all patients [12-15,22,39]. Among them, approximately 30% have severe fibrosis or cirrhosis at baseline, even though most are asymptomatic [14,30,72]. This finding could be explained by delayed diagnosis, as physicians may not consider AIH in asymptomatic elderly subjects with unexplained transaminasemia.

Statements 8-13

- AIH can rarely be diagnosed during pregnancy (more frequently after delivery), concurrently with HBV, HCV or HIV infections, alcohol-associated liver disease or after viral infections **(Evidence 4, Weak statement)**
- AMA are detected in about 5% of patients, without affecting treatment response and mortality **(Evidence 3, Strong statement)**
- Normal IgG levels at diagnosis can be found in 10-15% of AIH patients, representing a subgroup with rather higher chance of long-term remission after treatment withdrawal **(Evidence 3, Weak statement)**
- DI-ALH is defined as an acute DILI with serological and/or histological markers of idiopathic/classical AIH, in which long-term immunosuppression is rarely needed **(Evidence 2, Strong statement)**
- Concurrent MASLD or MASH is common in AIH patients resulting in a worse prognosis **(Evidence 3, Strong statement)**
- AIH is present in the elderly (>65 years; about 30%) a third of whom already have cirrhosis at diagnosis **(Evidence 3, Strong statement)**

Recommendation 5

- In case of suspicion, investigation for AIH is recommended under any circumstances, such as other liver diseases including MASLD, pregnancy or postpartum, after administration of drugs, supplements and/or herbals, viral infections or liver transplantation, and in the elderly **(Evidence 3, Strong recommendation)**

AIH Variants

Patients with AIH may present with additional characteristics of autoimmune cholestatic diseases, namely PBC or primary sclerosing cholangitis (PSC) [1,10,11,54,73,74]. In most cases of AIH with PBC variant, the 2 diseases present simultaneously, but consecutive manifestations have also been observed, even years after PBC diagnosis, while in most cases of AIH with PSC variant, AIH and PSC development occurs sequentially, with the AIH diagnosis frequently preceding that of PSC by several years (Table 2) [1,10,11,54,73,74]. However, it is important not to overdiagnose "variant syndromes" to avoid unnecessary exposure of PBC or PSC patients to steroids [1,10,11,54,73,74].

Depending on the predominant clinical and histological phenotype, the diagnosis of AIH-PBC (and PBC-AIH) and AIH-PSC (and PSC-AIH) variants is difficult in everyday clinical practice, as no consensus diagnostic criteria exist [1,10,73,75]. Up to the present, the "Paris criteria" published 26 years ago are still in use (Supplementary Table 1) [75]. However, 20 years after the original work by Chazouillères *et al* [75], a study from the United States reported a quite complex new score (Supplementary Table 2) with high sensitivity and specificity (cutoff score ≥21; sensitivity 98.5%, specificity 92.8%, positive predictive value 81.0%, and negative predictive value 99.5%) [76]. Regardless of the score used, all international liver authorities agree and recommend liver biopsy to confirm the presence or not of moderate/severe hepatitis [1,10,11,73]. This strategy is mandatory, particularly in patients with PBC, who have an incomplete response to ursodeoxycholic acid (UDCA) and a disproportionate increase—usually >5× upper limit of normal (ULN)—of alanine aminotransferase (ALT) and/or IgG [73,77].

Robust criteria for the diagnosis of AIH-PSC variant (or PSC-AIH) are lacking [78-81]. This variant is characterized by a high prevalence of concurrent IBD, even though in a very recent large multicenter study, including 7121 PSC patients from the International PSC Study Group (IPSCSG), PSC-AIH patients appear to have concurrent ulcerative colitis less frequently compared to those with the classical PSC [81]. The diagnosis is based on the cholangiographic and/or histological characteristics of PSC, along with features of AIH, where the presence of moderate to severe interface hepatitis on liver biopsy is of fundamental importance [74,80,82]. In children, this variant, also known in childhood as *"autoimmune sclerosing*

cholangitis", has been observed in about 50% of cases with AIH, irrespective of elevated cholestatic enzymes [74,78,80,83]. Therefore, magnetic resonance cholangiopancreatography (MRCP) screening is recommended at baseline for all children and adolescents with AIH (Table 2) [1,10,11,74,78,83,84]. In contrast, this strategy is not recommended at baseline in adults with AIH, but only when there are biochemical indices of cholestasis and PBC-specific autoantibodies are negative [80,85].

Statements 14-15

- Concurrent AIH with autoimmune cholestatic diseases can be observed both at diagnosis and during follow up **(Evidence 3, Weak statement)**
- Physicians should be cautious, as overdiagnosis of variants results in unnecessary exposure of PBC or PSC patients to steroids **(Evidence 5, Strong statement)**

Recommendations 6-9

- Variant syndromes should be considered when a patient with AIH, PBC or PSC deviates from the standard clinical course, common findings in terms of biochemistry and serology, and the expected treatment response **(Evidence 4, Strong recommendation)**
- Autoimmune serology, IgG determination and liver biopsy are recommended in cases with PBC or PSC when there is disproportionate elevation of ALT and/or IgG **(Evidence 3, Strong recommendation)**
- All children and adolescents with AIH should undergo MRCP at baseline, irrespective of elevated cholestatic enzymes, to exclude AIH-PSC variant **(Evidence 2, Strong recommendation)**
- In adult AIH patients, MRCP should be performed only in cases of cholestasis with negative investigation for PBC-specific antibodies **(Evidence 2, Strong recommendation)**

Long-term complications

Development of cirrhosis, with or without decompensation, portal hypertension and HCC may occur during the disease process [86]. In terms of HCC, a recent large observational, multicentric, retrospective study, involving 1428 patients with AIH from the IAIHG, confirmed previous studies [17,87,88], indicating that HCC prevalence and incidence are low (1.7% and 1.44 cases/1000 patient-years, respectively) compared to other liver diseases, but with a significantly increasing incidence after cirrhosis development (cumulative HCC incidence: 2.6%, 4.6%, 5.6% and 6.6% at 5, 10, 15 and 20 years after cirrhosis) [89]. The risk for HCC development in patients with AIH-associated cirrhosis remains below the cutoff recently proposed for surveillance strategies (0.5% instead of 1.0% annually) [90]; therefore, surveillance with ultrasonography and α-fetoprotein (α-FP) determination every 6 months may not be cost-effective. In this subgroup of AIH patients, personalized surveillance strategies could be adopted, taking into consideration the presence of additional risk factors.

Statement 16

- The incidence and prevalence of HCC in AIH patients are extremely low compared to other liver diseases, even in cirrhotic patients **(Evidence 2, Strong statement)**

Recommendation 10

- A surveillance strategy for HCC detection with ultrasonography, with or without α-FP determination every 6 months, can be suggested in patients with AIH-related cirrhosis and additional independent risk factors, such as obesity, advanced age, alcohol consumption, and AIH-PSC variant at diagnosis **(Evidence 2, Weak recommendation)**

Laboratory testing

Liver biochemistry

Aminotransferases and bilirubin can range from just above the ULN to very high, while the cholestatic enzymes are usually normal or moderately elevated [1,9-11,13,22,38,70]. Spontaneous normalization of aspartate aminotransferase (AST) and ALT can be observed, even though there is usually ongoing inflammatory activity on liver biopsy. This can explain, at least in part, the observed delay and underestimation of AIH diagnosis, as well as the presence of cirrhosis in a fair number of patients at diagnosis, since a second hit of the disease months or years after the first hit may even be completely asymptomatic.

Most patients (approximately 85%), irrespective of the presence of cirrhosis, have high serum IgG or γ-globulins [1,9-11,22,70]. It should be emphasized however, that the *"normal"* range of IgG serum levels is abundant, because it is impractical to define its *"reliable normal"* values in every population where a patient resides. In addition, in the acute form of AIH, some patients may have negative results at first investigation for ANA or SMA and normal IgG, leading the physicians not to consider AIH as a probable diagnosis [1,9-11].

Autoimmune serology

The detection of autoantibodies remains one of the cornerstones for the diagnosis of AIH, even though they cannot support a definite AIH diagnosis on their own [42,43]. In this context, the immunofluorescence assay (IFA) on freshly frozen cryostat sections of rodent substrates (kidney, liver, and stomach) is the assay of choice for first screening (Fig. 1) [1,10,42,43,91]. In parallel, investigation for anti-SLA/LP by molecular-based techniques—enzyme-linked immunosorbent assay (ELISA), immunoblot or radioligand assays—should be performed (Fig. 1). IFA and anti-SLA/LP testing should be performed ideally before the initiation of treatment, as immunosuppressive therapy may affect the results. The clinical significance of antibodies in AIH is illustrated in Table 3.

SMA and ANA can be detected in various liver diseases, several extrahepatic autoimmune diseases concurrently with AIH, or in healthy individuals, and therefore they lack specificity [42,43,62,92]. However, SMA of VG (staining of arterial vessels and mesangium of renal glomeruli) or VGT patterns (staining of arterial vessels, glomeruli, and intracellular fibrils in renal tubule) by IFA seem quite specific for AIH (Table 3) [42,43,91]. It should be emphasized that both SMA and ANA are only useful for AIH diagnosis, as they are not associated with prognosis and outcome. Typically, SMA are detected in association with ANA in about 50% of patients (isolated ANA or SMA in approximately 15% and 35%, respectively) [42,43,91].

Anti-SLA/LP antibodies carry very high specificity for AIH diagnosis, albeit low sensitivity, but they do not characterize a specific subgroup of patients with AIH (Table 3) [42,43,48,93-95]. Patients with anti-SLA/LP may need permanent immunosuppression, as many of them relapse after treatment withdrawal [48]. A specific characteristic of anti-SLA/LP is its concurrence with autoantibodies against the ribonucleoprotein 52kDa/Sjögren's syndrome A antigen in almost all anti-SLA/LP-positive European and North American patients [94,96].

Anti-LKM1 and anti-LC1 often coexist in patients with AIH-2, but they are not specific, as they can be observed in patients with HCV (the anti-LKM3 in chronic hepatitis D) [22,42,43,58,91]. Apart from IFA, anti-LKM1, anti-LKM3 and anti-LC1 antibodies can also be detected by other validated techniques (ELISAs or immunoblotting) [42,43,91].

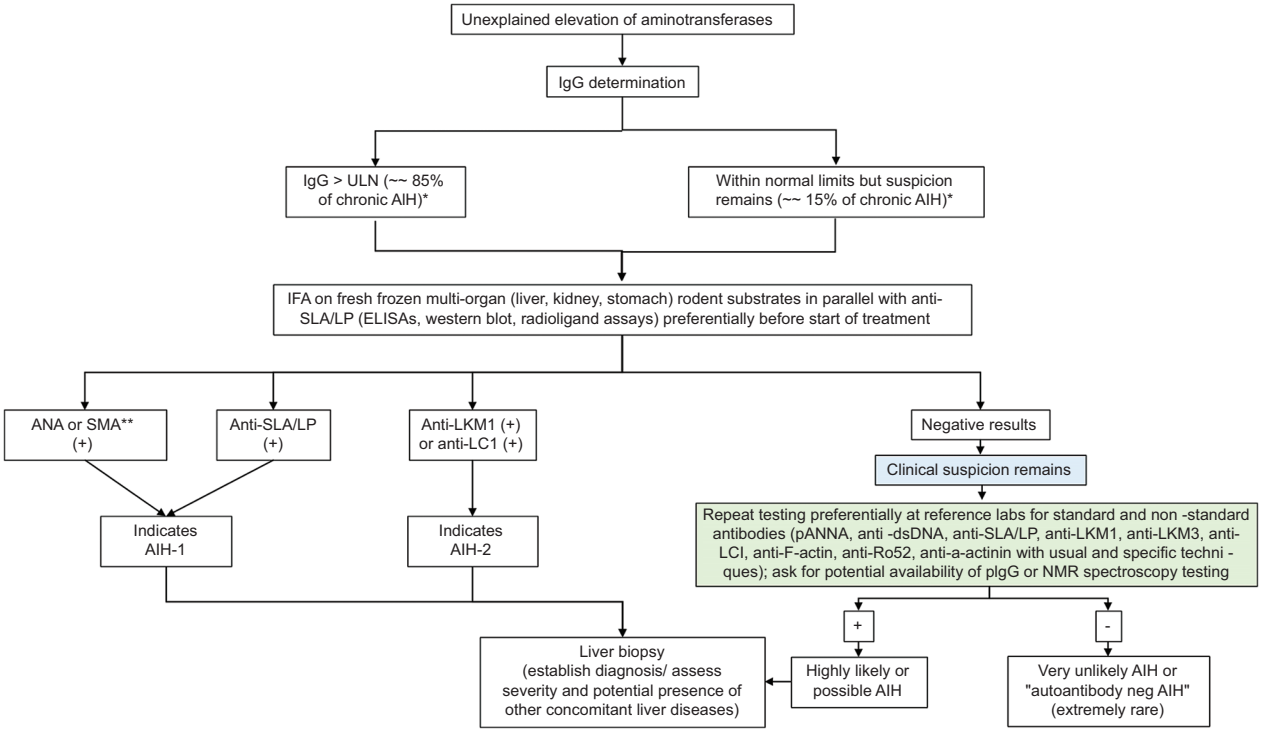

Figure 1 Proposed diagnostic algorithm for patients with suspected AIH. Antibodies are detected in >95% of patients if testing strictly adheres to the guidelines. In cases with acute severe AIH (AS-AIH), a trial with corticosteroid administration may be justified before obtaining the results, as autoimmune serology testing may be quite time-consuming.

*IgG may also be within normal levels in about 39% of AS-AIH

**ANA and SMA can also be evaluated by IFA on HEp2 cells or ELISAs (for details and rules see text and Table 6) [5]. All labs should strictly adhere to the guidelines in terms of the techniques used and the cutoffs considered for reactivity

IgG, immunoglobulin G; ULN, upper limit of normal; AIH, autoimmune hepatitis; IFA, immunofluorescence assay; anti-SLA/LP, antibodies against soluble liver antigens/liver pancreas; ELISA, enzyme-linked immunosorbent assay; ANA, antinuclear antibodies; SMA, smooth muscle antibodies; anti-LKM1, anti–liver kidney microsomal type-1 antibodies; anti-LC1, anti–liver cytosol type-1 antibodies; pANNA, perinuclear anti-neutrophil nuclear antibodies; anti-dsDNA, antibodies against double stranded DNA; anti-LKM3, anti–liver kidney microsomal type-3 antibodies; anti-F actin, antibodies against filamentous actin; anti-Ro52, antibodies against Ro52 autoantigen; pIgG, polyreactive IgG; NMR, nuclear magnetic resonance

Table 3 Major autoantibodies and their significance in autoimmune hepatitis (AIH) (adapted from: [42,43])

Autoantibody	Autoantigens/Methods	Significance
ANA	Chromatin, ribonucleoproteins, histones; single and double stranded DNA; centromere; cyclin A; undefined antigens (20-30%); IFA on multi-organ rodent substrates*	Frequent in AIH-1; not specific; Rare in AIH-2
SMA	Filamentous actin, vimentin, desmin; undefined antigens (20%); IFA on multi-organ rodent substrates*	AIH-1 frequently combined with ANA; VG/VGT patterns highly specific; Rare in AIH-2
Anti-LKM1	Cytochrome P4502D6 (MW: 50kDa); IFA on multi-organ rodent substrates; ELISA or WB	Very specific for AIH-2; present in HCV infection (10%)
Anti-LKM3	UGT1 (MW: 55kDa); IIF on multi-organ rodent substrates or by WB	Very specific but rare (AIH-2); present in HDV infection (13%)
Anti-LC1	FTCD (MW: 58-62kDa); IFA on multi-organ rodent substrates; ELISA, immunodiffusion or WB (very important in patients with concurrent anti-LKM1 by IFA)	Liver specific antibody (AIH-2); rare in HCV; usual coexistence with anti-LKM1; can be the only marker (10% of AIH-2)
Anti-SLA/LP	Synthase (S) converting *O*-phosphoseryl-tRNA (Sep) to selenocysteinyl-tRNA (Sec) (MW: 50kDa); ELISA, WB or radioligand assays	Highly specific (AIH-1, 15-30%); specificity: 99%; rare in AIH-2; concurrent with anti-Ro52 (77-98% of cases); need for permanent therapy
pANNA	Unknown autoantigen(s); IFA on fixed granulocytes	Exclusively in AIH-1 (60-96%); isolated detection in few cases; also, in IBD, PSC and AIH-PSC variant

*For updates regarding their detection by IFA on HEp2-cells or ELISAs see Table 5 and text [5]

IFA, immunofluorescence assay; ANA, antinuclear antibodies; SMA, smooth muscle antibodies; VG, staining of arterial vessels and mesangium of renal glomeruli; VGT, staining of arterial vessels, glomeruli, and intracellular fibrils in renal tubule; anti-LKM1, anti–liver kidney microsomal type-1 antibodies; CYP2D6, cytochrome P450 2D6; MW, molecular weight; ELISA, enzyme-linked immunosorbent assay; WB, western blot; HCV, hepatitis C virus; anti-LKM3, anti–liver kidney microsomal type-3 antibodies; UGT1, family 1 of uridine diphosphate glucuronosyl-transferases; HDV, hepatitis D virus; anti-LC1, anti–liver cytosol type-1 antibodies; FTCD, formiminotransferase cyclodeaminase; anti-SLA/LP, antibodies against soluble liver antigens/liver pancreas autoantigen; anti-Ro52, antibodies against Ro52 autoantigen; pANNA, perinuclear anti-neutrophil nuclear antibodies; PSC, primary sclerosing cholangitis; IBD, inflammatory bowel disease; AIH-PSC variant, autoimmune hepatitis-primary sclerosing cholangitis variant

In case of diagnostic problems between anti-LKM1/3 and AMA by IFA, complementary specific ELISAs or immunoblot are recommended.

A perinuclear pattern of anti-neutrophil nuclear antibodies (pANNA), also known as "atypical" perinuclear anti-neutrophil cytoplasmic antibodies, is detected frequently by IFA almost exclusively in AIH-1 patients [42,43,83,91]. However, very few patients with AIH-1 have isolated pANNA and therefore, it should only be performed in patients who have tested negative for ANA, SMA, and anti-SLA/LP.

Negative results, besides clinical suspicion, justify additional specific investigation and repeated testing, preferably in a reference laboratory, as the titers may vary during the disease course (Fig. 1) [42,43,91].

In adults, clinically significant titers for ANA, SMA, anti-LKM1 and anti-LC1 are ≥1:40 (≥1:20 for ANA or SMA and ≥1:10 for anti-LKM1 or anti-LC1 in children) [1,10,42,43,83]. Monitoring of autoantibody titers is not recommended in adults, but might be of clinical significance in children and adolescents [83].

The routine laboratories should comply with the guidelines in reporting the techniques and cutoffs for positivity. This information should be clearly given to physicians in order to assist them in the interpretation of the results [1,10,42,43,91]. It is also pivotal that the laboratory report should provide all patterns of renal reactivity of SMA, as SMA of VG or VGT patterns have the highest diagnostic accuracy for the diagnosis of AIH.

Other potential markers

Alpha-actinin antibodies have been detected in patients with AIH-1 and SLE [97]. They seem to characterize a more severe subgroup of AIH patients, whereas they might be used as predictors of response [98]. Antibodies against double stranded DNA (anti-dsDNA) may also be detected by ELISA in approximately 30% of patients with AIH, and in up to 60% of patients with AIH-PBC variant [42,43,99-101]. For this reason, reactivity for both ANA and anti-dsDNA should not always result in a *"superficial diagnosis"* of SLE if other criteria for its diagnosis are lacking.

Recently, a large study in 1568 adults with AIH using a protein microarray, identified several IgG antibodies with binding capacities to many human and foreign proteins [102]. As a result, a polyreactive IgG (pIgG) was quantified by reactivity against human huntingtin-interacting protein 1-related protein (HIP1R), as reactivity against HIP1R showed a significantly higher area under the curve to discriminate AIH from other liver diseases compared to reactivities against other identified proteins. This new marker showed similar sensitivity to SMA (65% vs. 63%), and lower than that of ANA (65% vs. 76%), but significantly higher specificity than SMA and ANA (74% vs. 65% and 74% vs. 59%, respectively) even though the specificity of anti-LKM and anti-SLA/LP remains very high (99% and 100%, respectively) [102]. Most importantly, reactivity against HIP1R was also observed in most patients with normal IgG, whereas after therapy

the values returned to those of patients with other liver disorders. Similar findings seem to have been obtained in a preliminary evaluation of pediatric patients with AIH [103]. Taken together, these results may suggest considering pIgG as a potential promising marker to improve the diagnostic workup of liver diseases.

The metabolomic profile has been studied in patients with diverse autoimmune diseases, such as SLE and Sjögren's syndrome [104]. In this context, the metabolomic profile by nuclear magnetic resonance (NMR) spectroscopy was recently investigated in patients with AIH, in an attempt to assess its diagnostic and pathogenetic significance in AIH compared to other autoimmune and non-autoimmune liver diseases, including MASLD [105]. After multivariate analysis, it was shown that a panel of 15 metabolites could safely discriminate AIH from healthy individuals and patients with PBC, HBV, HCV or MASLD, with 95% sensitivity and 92% specificity. To sum up, metabolomic investigation can be used as a promising additional marker for the diagnosis of AIH, considering that the NMR technique has a low cost, is highly reproducible, and there is no need for much sample handling [105].

Statements 17-18

- The levels of AST, ALT and bilirubin vary in AIH **(Evidence 1, Strong statement)**
- AIH patients with anti-SLA/LP reactivity may represent a subgroup with permanent need of immunosuppression **(Evidence 3, Weak statement)**

Recommendations 11-15

- Normal IgG should not rule out AIH diagnosis, although high IgG, particularly in the absence of IgM and IgA elevation, is an important and common feature of the disease **(Evidence 2, Strong recommendation)**
- First autoimmune serology screening for ANA, SMA, anti-LKM and anti-LC1 should ideally be performed before treatment initiation by IFA, in parallel with anti-SLA/LP testing by ELISA and/or immunoblotting **(Evidence 2, Strong recommendation)**
- In the appropriate clinical context, reactivity against 1 or more autoantibodies should lead to liver biopsy, as AIH is highly likely **(Evidence 2, Strong recommendation)**
- Routine laboratories should comply with the guidelines, regarding both the assays used and the cutoffs of reporting **(Evidence 3, Strong recommendation)**
- At present, antibodies to alpha-actinin and dsDNA, as well as pIgG and metabolomic screening, although promising, are not recommended as routine diagnostic markers of AIH **(Evidence 4, Strong recommendation)**

Liver histopathology in AIH

The presence of hepatitis in liver tissue is a prerequisite for AIH diagnosis [1,6,9-11,42,70,82]. Noninvasive scores, serum markers, liver stiffness measurements (LSMs) and imaging methods are not able to replace liver biopsy at diagnosis and before treatment discontinuation [106]. Nevertheless, repeat LSMs by vibration-controlled transient elastography (FibroScan) is a reliable tool for AIH monitoring [107-112].

Liver histopathology is best evaluated before starting treatment, as inflammatory severity and fibrosis extent do not always parallel liver biochemistry [1,6,10,11,42,70,82]. In addition, liver histopathology can provide information on AIH prognosis and management. An adequate liver biopsy sample should ideally be obtained with a 16 G or wider needle (18 G needle is also acceptable; minimum length of 1.5 cm containing at least 6-8 portal tracts) [6].

AIH has a broad histopathology spectrum and there are no pathognomonic features (Fig. 2) [82,113]. Two main histological patterns of liver injury are recognized depending on the topography of the hepatitic lesions: portal-based or lobular (Fig. 2A-C). Recently, the International AIH Pathology Group (IAIHPG) developed consensus recommendations for the histological diagnosis of both acute and chronic presentations of AIH in the native liver, based on liver injury pattern (Table 4). On this basis, a diagnosis of likely, possible, or unlikely AIH can be made [6]. Validation and generalizability studies of the IAIHPG criteria are currently ongoing, and initial results show that they can accurately identify AIH with acute onset [114]. The scores provided by the semi-quantitative evaluation of necroinflammatory activity using the modified

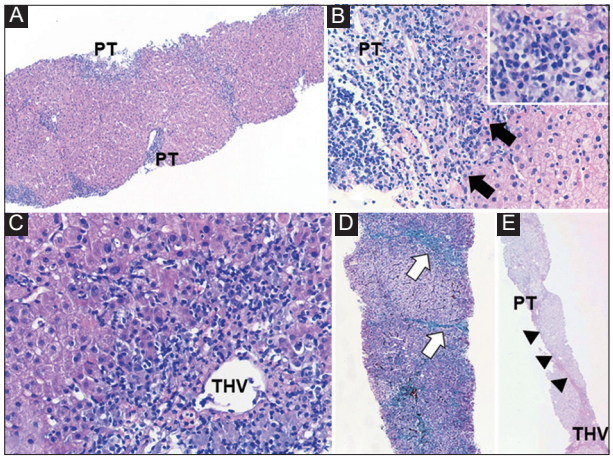

Figure 2 Representative images from needle liver biopsies with autoimmune hepatitis: (A) Chronic hepatitis pattern with portal/periportal inflammation, hematoxylin-eosin (H-E) ×40; (B) Dense portal lymphoplasmacytic inflammation with interface activity (black arrows), H-E ×100. Inset shows plasma cell clusters, H-E ×400; (C) Centrilobular lymphoplasmacytic inflammation, H-E ×200; (D) Portal/periportal fibrosis (white arrows), Masson trichrome stain for collagen (blue) ×40; (E) Portal-central bridging fibrosis (black arrowheads), Sirius red stain for collagen (red) ×10
PT, portal tract; THV, terminal hepatic venule

hepatic activity index (mHAI) [115] are helpful during therapy and follow up.

The portal-based pattern of inflammation is characterized by a mainly portal chronic lymphocytic or lymphoplasmacytic inflammatory infiltrate, that may or may not extend into the immediate periportal parenchyma, a lesion termed interface hepatitis (Figs. 2A and 2B). In the absence of histological features suggestive of another liver disease, the additional presence of more than mild interface hepatitis and/or more than mild lobular hepatitis defines a likely AIH diagnosis (Table 4). If there are features suggestive of another liver disease, or if there is no more than mild lobular or interface hepatitis, a diagnosis of possible AIH can be made.

In the lobular pattern of inflammation, the presence of more than mild lobular hepatitis, with or without centrilobular injury, and at least one of the likely histological features that include lymphoplasmacytic infiltrates, interface hepatitis or portal-based fibrosis, renders the diagnosis of likely AIH in the absence of histological features suggestive of another liver disease (Fig. 2C; Table 4). If the latter are present, then the diagnosis of possible AIH can be made. Lobular hepatitis of any severity, with or without centrilobular necroinflammation but without lymphoplasmacytic infiltrates, interface hepatitis or portal fibrosis, also suggests possible AIH, in the absence of features of another liver disease. Therefore, using the new consensus IAIHPG criteria, cases with predominantly centrilobular injury without significant portal/periportal inflammation, or cases with exclusively centrilobular necrosis, most likely representing an early stage of AIH [116], can now be diagnosed as possible AIH in the absence of another liver disease and can be treated with immunosuppressive agents [6].

Hepatocyte rosetting and emperipolesis (intracytoplasmic localization of an inflammatory cell, usually a lymphocyte, within a hepatocyte) are no longer considered typical lesions of AIH because they are non-specific [6]. However, they can still be reported if detected, as surrogate markers of AIH severity [6]. An absence of plasma cells may be seen in up to one third of AIH cases and does not rule out the diagnosis [42,82,117]. Bile duct changes with lymphocytic cholangitis have been reported in 10-28% of AIH biopsies, without any other indication of PBC [118,119]. At presentation, various fibrosis stages may be seen (Figs. 2D and 2E) [15,22,38,40]. Portal-based fibrosis provides evidence of underlying chronic liver damage and is helpful in the differential diagnosis of acute hepatitis, supporting an AIH over a drug-induced etiology [6].

Statements 19-23

- There are no pathognomonic features for the histological diagnosis of AIH **(Evidence 1, Strong statement)**
- The presence of portal-based and/or lobular hepatitis at the histological level is a prerequisite for AIH diagnosis **(Evidence 1, Strong statement)**
- The preferred terminology for the lowest, medium and highest likelihood of an AIH diagnosis in a given case is unlikely, possible and likely, respectively **(Evidence 2, Strong statement)**
- The presence of exclusive or predominant centrilobular injury is not uncommon in acute-onset AIH **(Evidence 2, Strong statement)**
- The diagnosis of possible AIH should not be excluded because of the presence of features of another liver disease **(Evidence 2, Strong statement)**

Table 4 Consensus on the histological criteria of likely, possible, or unlikely autoimmune hepatitis (AIH) by the International AIH Pathology Group (adapted from: [6])

	Portal hepatitis	Lobular hepatitis
Likely AIH	In the absence of histological features suggestive of another liver disease, presence of portal lymphoplasmacytic infiltrate with one or both of the following characteristics: a. More than mild interface hepatitis b. More than mild lobular inflammation	In the absence of histological features suggestive of another liver disease, presence of more than mild lobular hepatitis (with or without centrilobular inflammatory activity) with at least one of the following characteristics: a. Portal lymphoplasmacytic infiltrates b. Interface hepatitis c. Portal-based fibrosis
Possible AIH	Portal lymphoplasmacytic infiltrate - Without either of the likely feature "a" or "b" above in the absence of histological features suggestive of another liver disease	Any lobular hepatitis (with or without centrilobular inflammation) - Without any of the likely features "a-c" above in the absence of histological features suggestive of another liver disease
	OR	OR
	- With one or both of the likely features above in the presence of histological features suggestive of another liver disease	- With any of the likely features above in the presence of histological features suggestive of another liver disease
Unlikely AIH	Portal hepatitis - Without either of the likely features above in the presence of histological features suggestive of another liver disease	Any lobular hepatitis - Without any of the likely features above in the presence of histological features suggestive of another liver disease

Recommendations 16-20

- An adequate liver biopsy sample should be obtained with a 16 G or wider needle and have a minimum length of 1.5 cm and at least 6-8 portal tracts **(Evidence 1, Strong recommendation)**
- The consensus criteria and terminology of the IAIHPG should be applied for the histological diagnosis of AIH **(Evidence 2, Strong recommendation)**
- Predominantly or exclusively centrilobular injury should be diagnosed as possible AIH in the absence of features suggestive of another liver disease **(Evidence 2, Strong recommendation)**
- If additional features of PBC, PSC or MASLD are present, a liver biopsy should still be classified as possible AIH if likely histological features are present **(Evidence 2, Strong recommendation)**
- The pathology report should include a comment on the presence and severity of fibrosis **(Evidence 1, Strong recommendation)**

Differential diagnosis

Almost all causes of acute and chronic liver diseases are included in the differential diagnosis of AIH. As a result, HBV (including hepatitis delta), HCV, and viral hepatitis A (HAV) and E (for the acute cases), alcohol-associated liver disease, DI-ALH, Wilson's disease, MASLD, PBC, PSC, AIH-PBC and AIH-PSC variants, hemochromatosis, α1-antithrypsin deficiency, as well as celiac disease and SLE should be considered [1,9-11,42,43]. Among these, one of the most challenging is the differentiation between AIH and DI-ALH, as there is no reliable serological or histological biomarker to discriminate effectively between these 2 conditions [62,67]. A proposed management of such cases is shown in Fig. 3, even though the evidence and grading for most of the suggested options is low.

Discrimination between SLE and AIH is also a challenge. As a fair number of patients with AIH present with polyarthralgia, it is reasonable for physicians to consider SLE instead of AIH in a patient with ANA and anti-dsDNA reactivity. It should be stressed, however, that liver involvement is not a common manifestation of SLE. Concurrent viral hepatitis, MASLD (commonly induced by corticosteroids) and DILI because of SLE-associated therapies are the most frequent causes of abnormal liver enzymes in patients with SLE [42,43,120,121]. In case of uncertainty, the use of IFA on a *Crithidia luciliae* substrate, which includes high dsDNA quantities, could solve the problem, as this assay seems to detect anti-dsDNA antibodies with higher specificity than the ELISAs [42,43,100,101].

Recommendation 21

- Differential diagnosis of AIH should include all causes of liver diseases, particularly DI-ALH, along with celiac disease and SLE **(Evidence 1, Strong recommendation)**

Diagnosis of AIH

In 2008, a user-friendly, simplified score for the diagnosis of AIH was proposed by the IAIHG, with excellent sensitivity,

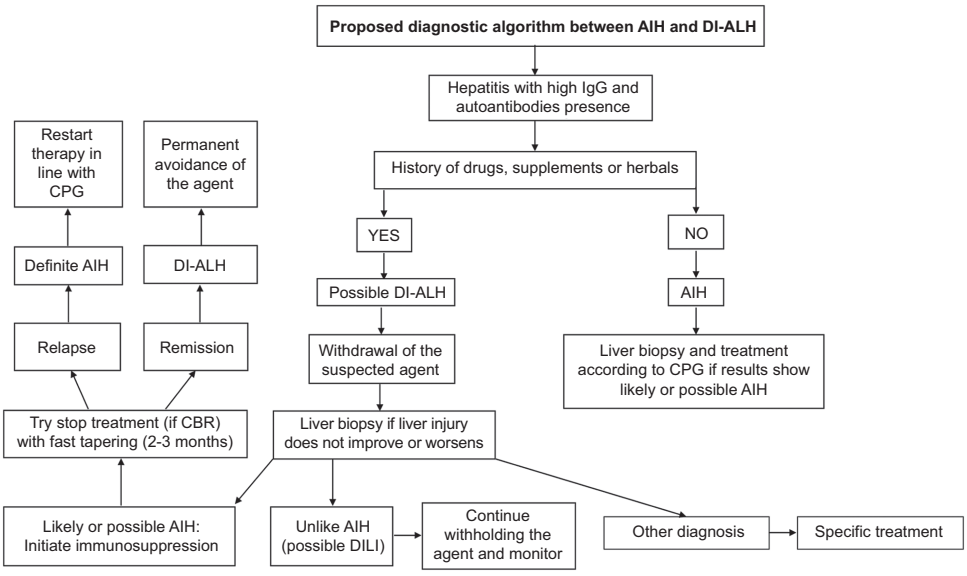

Figure 3 Suggested algorithm for the differential diagnosis between autoimmune hepatitis (AIH) and drug-induced autoimmune-like hepatitis (DI-ALH)
IgG, immunoglobulin G; CPG, clinical practice guidelines; DILI, drug induced liver injury; CBR, complete biochemical response

specificity and diagnostic accuracy (Supplementary Table 3) [70]. This score is based on only 4 parameters (serum IgG, autoantibodies, liver histology, and absence of viral hepatitis markers). However, the simplified score has not been validated extensively in patients with AS-AIH or ALF-related AIH, AIH variants, DI-ALH and children [33,34,35,65]. Subsequently, a new diagnostic score has recently been suggested for AIH and AIH-PSC in the pediatric population (Supplementary Table 4), even though external validation of this score did not reveal any statistically significant superiority compared to the simplified score [83,122,123].

Autoantibodies are detected in >95% of cases if tested according to the CPGs [42,43,91]. However, these recommendations are rarely followed by the routine clinical laboratories, and IFA on HEp2 cells and ELISAs are frequently used instead, even though the simplified score for AIH diagnosis does not account for ANA and SMA detection by the latter methods. For these reasons, a recent large multicenter study from the IAIHG, including 341 patients, was designed to assess the diagnostic validity of IFA on HEp2 and ELISAs testing and make the simplified score usable all over the world [5]. The results showed that a) IFA on HEp-2 cells is a valid alternative for AIH diagnosis when cutoff titers are increased, and b) ANA ELISAs and F-actin (the major target-autoantigen of SMA) ELISA represent potential alternatives to IFA for AIH diagnosis, but the ANA ELISA kits, apart from well recognized nuclear antigens, should also include HEp-2 nuclear extracts, while ELISA cutoffs need to be validated locally [5]. The staining pattern of ANA on HEp2 cells is not pathognomonic of AIH and does not seem to have any clinical and diagnostic significance [42,43]. In conclusion, this study suggested adaptation of the simplified score so that it could be used in everyday practice by different laboratories (Table 5) [5]. Special attention should be given, however, to the presence of specific patterns of ANA, such as the multiple nuclear dots (anti-sp100) and rim-like membranous patterns (anti-gp210) by IFA on HEp2 cells, which are highly specific for PBC but not for AIH [54,55,124].

Statements 24-25

- AIH is a clinicopathological diagnosis that is based on the presence of autoantibodies, distinct IgG elevation, and likely or possible liver histology (Evidence 1, Strong statement)
- Autoantibodies are detected in >95% of AIH cases if testing is performed according to CPGs **(Evidence 1, Strong statement)**

Recommendations 22-27

- The simplified score must be used for AIH diagnosis if rodent tissues are utilized for ANA and SMA detection by IFA **(Evidence 1, Strong recommendation)**
- The updated simplified score can be used if HEp-2 cells or ELISAs are utilized for ANA and SMA detection by IFA or ELISAs **(Evidence 3, Weak recommendation)**
- Caution is required when using ELISA testing, as ANA ELISA kits should include HEp-2 nuclear extracts for unrecognized autoantigens, while ELISA cutoffs need to be established locally **(Evidence 3, Strong recommendation)**
- The specific sp100 and gp210 ANA pattern on HEP-2 cells should not be counted in the diagnostic scores, as they represent specific markers of PBC and not of AIH **(Evidence 2, Strong recommendation)**
- In the pediatric population, a different diagnostic score may be of value for AIH and AIH-PSC diagnosis **(Evidence 3, Weak recommendation)**
- Diagnostic scores should be used with caution in the case of AS-AIH, ALF-associated AIH, AIH variants and DI-ALH **(Evidence 3, Strong recommendation)**

Table 5 Adaptation of the simplified score of the IAIHG for AIH diagnosis (adapted from: [5] and [70])

Feature	Cutoff	Points[1]
ANA or SMA/anti-F-actin	Positive[2]	1
ANA or SMA/anti-F-actin or anti-LKM or anti-SLA/LP	Strongly positive[3] ≥1:40 Positive	2
IgG	>Upper limit of normal >1.1 × upper limit of normal	1 2
Liver histology (with evidence of hepatitis)	Compatible with AIH Typical AIH	1 2
Absence of viral hepatitis	Yes	2
		≥6: Probable AIH ≥7: Definite AIH

[1]Addition of points achieved (maximum 2 points for autoantibodies).

[2]IFA: ≥1:40 when assessed on tissue sections; ≥1:80 or 1:160 for ANA when assessed on HEp-2 cells, depending on local standards. F-actin or ANA ELISAs with locally established cut-offs.

[3]IFA: ≥1:80 when assessed on tissue sections; ≥1:160 or 1:320 for ANA when assessed on HEp-2 cells. F-actin or ANA ELISAs with cut-offs established locally; Important note: If ELISA-based autoantibody assessment is negative despite clinical suspicion of AIH, IFA should be performed in addition. Definition of compatible or typical findings at the histological level is shown in Supplementary Table 3. However, substitution of the above histological findings with the 2022 IAIHPG criteria [6] (likely for typical and possible for compatible) should be considered, as they may increase the sensitivity of the diagnosis of AIH and ultimately, optimize clinical diagnosis.

IAIHG, international autoimmune hepatitis group; AIH, autoimmune hepatitis; ANA, anti–nuclear autoantibodies; SMA, smooth muscle autoantibodies; anti-LKM, anti–liver kidney microsomal antibodies; anti-SLA/LP, antibodies against soluble liver antigens/liver pancreas autoantigen; IgG immunoglobulin G; IFA, immunofluorescence assay; ELISA, enzyme-linked immunosorbent assay; IAIHPG, international AIH pathology group

Management of AIH

All patients with active disease should receive immunosuppressive treatment (Fig. 4) [1,7,9-11,22,40-42,89]. Indeed, several old studies have shown that untreated patients with moderate to severe AIH have a poor prognosis [125,126]. Decision on the initiation of immunosuppression in patients with mild activity is still controversial, particularly for older patients, as treatment-associated side-effects should be balanced against the risk of disease progression [127,128]. In addition, resolution of AIH may occur spontaneously, resulting in treatment withholding (Fig.4). However, if ALT or IgG levels increase or fluctuate, close long-term follow up (every 3-6 months), including new liver biopsy, is advised in these patients in order not to miss a subclinical relapse.

Before treatment initiation, investigation for HBV and HAV serological markers is recommended, with the appropriate vaccinations for unvaccinated patients or those without previous virus exposure. Yearly vaccination against influenza virus, SARS-CoV-2, and *Streptococcus pneumoniae* according to the local guidelines should also be administered to all patients. As AIH patients suffer from age-dependent deterioration of the cortical bone microarchitecture [129], evaluation of the bone mineral density by dual energy X-ray absorptiometry (DEXA) at baseline and during follow up seems rational to identify patients who are at increased risk of osteoporosis. In this regard, a recent retrospective cross-sectional study revealed that almost 20% of AIH patients older than 50 years have osteoporosis, whereas older age, low body mass index (<23 kg/m^2), corticosteroid use for >90 months, and liver fibrosis (transient elastography values >8 kPa) were independent risk factors for bone loss [130].

Recommendations 28-33

- AIH management should aim to achieve a complete clinical, biochemical and histological response in an attempt to tackle the progression of liver disease **(Evidence 2, Strong recommendation)**
- Treatment should be initiated in all patients with active disease, including those with severe fibrosis and/or cirrhosis **(Evidence 1, Strong recommendation)**
- Treatment may not be required in patients with spontaneous resolution, but close long-term follow up is advised to promptly diagnose possible subclinical disease progression **(Evidence 4, Weak recommendation)**
- Vaccination against HAV and HBV should be given before treatment initiation to all susceptible AIH patients **(Evidence 5, Strong recommendation)**
- Other vaccinations (influenza, SARS-CoV2, *Streptococcus pneumoniae*, etc.) should comply with local recommendations **(Evidence 5, Strong recommendation)**
- DEXA measurement should be considered before treatment initiation and during follow up, according to the osteoporosis risk, in all AIH patients before initiation or during therapy **(Evidence 3, Strong recommendation)**

Primary treatment endpoints

In 2022, the IAIHG conducted a systematic review, including 2-round Delphi processes and external validation in a large cohort of AIH patients, to identify and standardize the definitions of the most important outcome measures of treatment response; the aim was to harmonize and enable comparisons of these parameters among studies (Table 6) [7]. Accordingly, "complete biochemical response" (CBR) was defined as normalization of aminotransferases and IgG no later than 6 months after starting

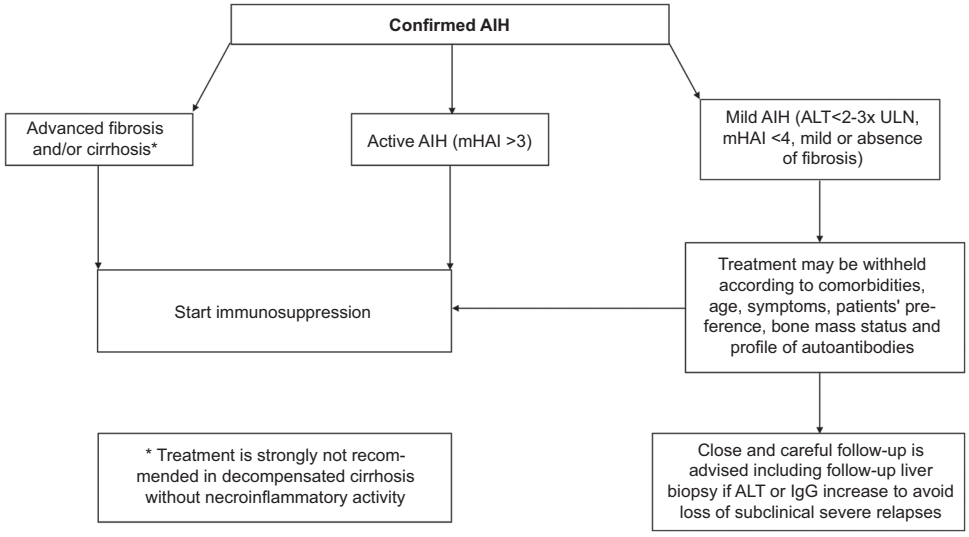

Figure 4 Indications for initiation of treatment in patients with AIH
AIH, autoimmune hepatitis; ULN, upper limit of normal; mHAI, modified hepatic activity index; ALT, alanine aminotransferase; IgG, immunoglobulin G

immunosuppression. "Insufficient response" was defined as a lack of CBR after 6 months of immunosuppressive therapy, and is applicable for both first-line and second-line treatments. It should be emphasized, however, that an "insufficient response" does not necessarily mean that treatment should be changed immediately; nevertheless, it should alert the physician, as it may have some prognostic value. In addition, as the comparison of patients achieving CBR within 6 months with those who responded after 6 months was based on a relatively inadequate sample size, the evaluation of "insufficient response" no later than 12 months could be an alternative option [7]. In a recent retrospective study by the IAIHG, including the largest cohort of AIH patients in the world (n=2559), it was shown that the achievement of CBR within 6 months was an independent prognostic factor for a favorable outcome, even though 17% of patients without CBR at 6 months achieved it at 12 months and this finding also had prognostic significance [40]. Similar findings were reported in a recent retrospective study from South Korea, where patients with CBR within 12 months had the highest chance of favorable outcomes [131]. To define the "insufficient response" in an index patient, appropriate predniso(lo)ne and azathioprine (AZA) or mycophenolate mofetil (MMF) doses should be administered and adherence to treatment must be confirmed.

"Non-response" was defined as a reduction of aminotransferases in <50% from baseline values within 4 weeks after initiation of immunosuppression [7]. However, a recent retrospective cohort study reported that a rapid decrease of aminotransferases (≥80% from baseline within 8 weeks) was associated with normalization of AST/ALT levels at 6 and 12 months and significantly better outcomes compared to slow responders, suggesting that the proposed 4-week timeframe for the definition of "non-response" may be too early [132]. An initial "non-response" should raise serious concerns regarding alternative diagnosis or potential problems with treatment adherence [1,10,11]. The term "remission" was defined at the histological level by the absence of necroinflammatory activity (mHAI <4/18), which can be assessed 12 months after starting immunosuppression or at any time during treatment (Table 6). "Intolerance to treatment" was defined as any adverse event potentially related to the immunosuppressive treatment leading to drug cessation [7].

Table 6 Definitions of response criteria and endpoints in AIH (adapted from [7])

Endpoints	Definitions
Complete biochemical response (CBR)	Normalization of aminotransferases and IgG; it should be achieved in less than 6 months after treatment initiation*
Insufficient response	Lack of CBR; It should be determined no later than 6 months after initiation of immunosuppression*
Non-response	<50% decrease of aminotransferases within 4 weeks after initiation of treatment**
Remission	mHAI <4/18; it could be obtained 12 months after initiation of immunosuppression or at any time point during treatment
Intolerance to treatment	Any adverse event possibly related to treatment, as assessed by the treating physician, leading to discontinuation of the drug

*Assessment of CBR and insufficient response no later than 12 months could also be an alternative option under real-life conditions.

**Four weeks may be too early, and non-response at 8 weeks could also be evaluated

AIH, autoimmune hepatitis; IgG, immunoglobulin G; mHAI, modified hepatic activity index

Statements 26-31

- Definition of CBR: Normalization of aminotransferases and IgG **(Evidence 2, Strong statement)**
- Definition of insufficient response: Lack of CBR **(Evidence 2, Strong statement)**
- Definition of non-response: Aminotransferase decrease less than 50% from baseline after 4 weeks from treatment initiation **(Evidence 2, Strong statement)**
- Definition of remission of the disease: mHAI less than 4 on liver biopsy **(Evidence 2, Strong statement)**
- Definition of intolerance: Any adverse event potentially related to treatment leading to drug withdrawal **(Evidence 2, Strong statement)**
- Rapid decrease of aminotransferases (≥80% from baseline levels) after 8 weeks of treatment is associated with CBR at 6 and 12 months after treatment initiation and significantly better outcomes **(Evidence 3, Strong statement)**

Recommendations 34-37

- CBR and insufficient response should be assessed no later than 6-12 months after initiation of either first-line or second-line treatment **(Evidence 2, Strong recommendation)**
- An "insufficient response" should be defined only if patients have received at least 0.5 mg/kg/day predniso(lo)ne and up to 10 mg/day as maintenance therapy, along with the appropriate dose of MMF or AZA **(Evidence 2, Strong recommendation)**
- An initial non-response after 4 weeks of treatment should alert clinicians to the possibility of an alternative diagnosis or problems with adherence **(Evidence 2, Strong recommendation)**
- Remission of the disease should be assessed by second liver biopsy, ideally 12 months after treatment, or pragmatically at any time during therapy **(Evidence 2, Strong recommendation)**

Induction of treatment response

Traditionally, for more than 40 years, the first-line induction treatment has been predniso(lo)ne in combination

with AZA, as this combination strategy has been proven to bear considerably fewer side-effects than predniso(lo)ne monotherapy [1,10,11,41,42,126]. The dose of predniso(lo)ne ranges between 0.5 and 1 mg/kg/day, preferably in a once daily dose in the morning, followed by progressive tapering under strict monitoring of aminotransferases. Rapid tapering of corticosteroids (e.g., 5-10 mg/1-2 weeks) is desirable, but should be done strictly in accordance with the response. A recent retrospective multicenter study tried to address whether lower predniso(lo)ne doses were sufficient for induction of response in patients with AIH [133]. This retrospective study in 451 adults with AIH showed that the rate of biochemical response at 6 months, defined only by ALT normalization, was not statistically different between those who received high- (≥0.5 mg/kg/day; median initial dose: 50 mg/day) and low-dose predniso(lo)ne (<0.5 mg/kg/day; median initial dose: 20 mg/day). Even though this study pointed out that high-dose corticosteroids might not be necessary to induce a response, it should be emphasized that it was retrospective study extending over 4 decades, while there were no data on IgG or histology [133]. In addition, the 2 comparison groups differed significantly at baseline, in terms of simplified score, ALT, bilirubin and presence of cirrhosis [133].

AZA at an initial dose of 50 mg/day is frequently added after 2 weeks of predniso(lo)ne treatment if bilirubin is <6 mg/dL, to avoid diagnostic uncertainties and clinical challenges between primary non-response and AZA toxicity [1,10,11,43]. AZA is then progressively increased according to response or its toxicity up to 1-2 mg/kg/day [1,10,11,42,43]. AZA should never be used alone as induction therapy [1,9-11,42,43]. AZA should be given cautiously in patients with cytopenias, pregnancy, malignancies or thiopurine methyltransferase (TPMT) deficiency. The primary aim of predniso(lo)ne/AZA combination or predniso(lo)ne monotherapy should be the achievement of a clinical and biochemical response as soon as possible, at the lowest level of corticosteroid use. Ideally, the clinical and biochemical response should persist after complete cessation of corticosteroids.

Systematic reviews have reported suboptimal CBR rates (≤50%) [126,134,135]. It should be stressed that the standard treatments are based on randomized studies conducted during the past 5 decades, with the inevitable inherent problems of no investigation for HCV, using different criteria of response from that recently endorsed by the IAIHG [7], while the last report was published almost 30 years ago [125,136,137].

Budesonide has been recommended by the American Association for the Study of Liver Diseases (AASLD) CPGs, as an alternative first-line treatment option instead of predniso(lo)ne in non-cirrhotic adults without AS-AIH, in an attempt to reduce the corticosteroid-related side-effects [11]. To date, only 1 randomized trial showed that a combination therapy of budesonide (9 mg/day) with AZA resulted in significantly higher biochemical response rates, defined only by normalization of aminotransferases, without the development of the common corticosteroid-related side-effects compared to the control group, while side-effects were fewer [138]. However, many uncertainties and concerns have been raised about this study, as the blinded phase of randomization for a chronic and quite rare disease lasted only 6 months, IgG normalization was not included in the response criteria, and no information was provided on the rapidity of response and outcome in terms of histology remission, cirrhosis progression and liver-related mortality. Moreover, side-effects and response rates in the controls were surprisingly higher and lower, respectively, compared to previous studies, probably as a result of the initial fixed dose and fixed reduction dose schedule of predniso(lo)ne in the control group, compared to the budesonide, which was given at a high dose until achievement of response. Another point is the scanty information we have regarding the best approach to budesonide reduction, as the proposed initial dose is equivalent to 30-40 mg of predniso(lo)ne, which is considered too high for long-term treatment. Notably, the same treatment schedule failed to show any important benefit in children, as the primary endpoint was achieved in only 16% and 15% of AIH patients in the budesonide and predniso(lo)ne group, respectively [139].

To sum up, the abovementioned serious concerns may indicate a therapeutic bias [138]. Therefore, it is reasonable to conclude that we need more robust data before making a positive recommendation for a more expensive agent as first-line therapy in AIH. On the other hand, a very recent multicenter study in 381 AIH patients from Spain showed that budesonide was inferior to standard predniso(lo)ne therapy, as attested by the significantly higher CBR rates at 6 and 12 months, as well as during follow up, in the predniso(lo)ne group, whereas adverse events did not differ between the 2 groups when patients with AIH-related cirrhosis were excluded [140].

In the last 15 years, MMF—the first selective, potent, non-competitive, and reversible inhibitor of isoform type-II of inosine-5'-monophosphate dehydrogenase [141]—in combination with predniso(lo)ne has been efficiently used as first-line induction treatment [38,142-146]. A number of real-world prospective studies, propensity matching trials and meta-analyses indicate MMF at 1.5-2 g/day as a safe and effective first-line treatment option for the induction and maintenance of response [38,142-146]. A proposed schedule for MMF administration is shown in Fig. 5.

A recent, prospective, open-label, randomized, multicenter superiority trial (CAMARO trial; NCT02900443) has recently confirmed the previous studies by indicating the superiority of MMF compared to AZA in treatment-naïve AIH patients [147]. Most importantly, patients in the AZA group experienced severe adverse events significantly more frequently, which subsequently led to higher rates of cessation of treatment compared to the MMF group, suggesting superior tolerability of MMF.

However, female patients of childbearing age with AIH should be informed in detail about the potential risks, as MMF is teratogenic. Thus, effective and strict contraceptive measures are strongly advised during immunosuppression, and up to 12 weeks after drug withdrawal. At screening, all female patients should have a negative pregnancy test, and they should be willing to use, or already using, 2 methods of birth control, such as diaphragm, copper intrauterine device, hormonal contraceptives, condom by the partner, sponge or spermicide.

Recommendations 38-43

- Predniso(lo)ne (0.5-1 mg/kg/day) in combination with MMF (1.5-2 g/day) should be the first-line treatment of AIH **(Evidence 2, Strong recommendation)**
- The combination of predniso(lo)ne with AZA (starting at 50 mg/day whenever bilirubin is <6 mg/dL, and ideally after 2 weeks from corticosteroid initiation to a final dose of 1-2 mg/kg/day) is still a first-line treatment option for AIH, but it seems inferior to the MMF combination, considering the response rates and tolerability **(Evidence 2, Strong recommendation)**
- Counseling of female patients of reproductive age about effective contraceptive measures during immunosuppression with MMF and up to 12 weeks after drug cessation is strongly recommended **(Evidence 2, Strong recommendation)**
- A lower predniso(lo)ne dose (<0.50 mg/kg/day) may also be effective in inducing a response in some patients **(Evidence 3, Weak recommendation)**
- Induction therapy and a tapering schedule of corticosteroids should be individualized strictly according to the response **(Evidence 4, Strong recommendation)**
- Budesonide (9 mg/day) is not recommended as first-line therapy in AIH instead of predniso(lo)ne, as it is inferior to the standard corticosteroids **(Evidence 2, Strong recommendation)**

Maintenance therapy

The standard maintenance treatment is monotherapy with either tailored doses of MMF (1.5-2 g/day) or AZA (2 mg/kg/day) after predniso(lo)ne withdrawal [14,35,38,42,126,134,137,143,145,146]. Patients with mild disease at initial biopsy who demonstrated intolerance to both AZA and MMF and have achieved CBR can continue with predniso(lo)ne monotherapy at the lowest dose to maintain response. The minimum duration of immunosuppression should be 4 years, with at least the last 2 years being in persistent CBR.

In patients who are on maintenance treatment with AZA and have not achieved CBR, measurement of 6-thioguanine (6-TGN), its active metabolite, is warranted to assess whether biochemical activity might be due to underdosing of AZA or non-adherence [1,10,11,148].

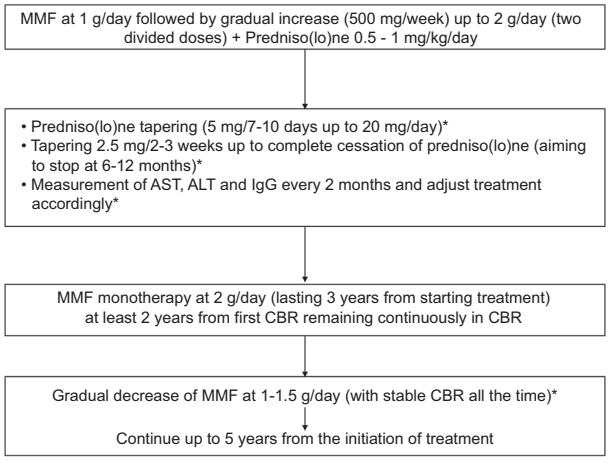

Figure 5 Proposed algorithm for the use of predniso(lo)ne with mycophenolate mofetil (MMF) in treatment-naïve patients with AIH
*In case of flares or relapses, predniso(lo)ne should be increased or restarted, respectively, up to the dose that achieved initial CBR, and then tapered, either by decreasing the predniso(lo)ne tapering dose by half with the same interval time, or by a twofold increase of the interval time
AIH, autoimmune hepatitis; CBR, complete biochemical response; AST, aspartate aminotransferase; ALT, alanine aminotransferase; IgG, immunoglobulin G

Recommendations 44-47

- The optimal maintenance therapy should be monotherapy with MMF or AZA **(Evidence 1, Strong recommendation)**
- Low-dose predniso(lo)ne monotherapy can only be used in patients with mild disease who achieved CBR and are intolerant to both MMF and AZA **(Evidence 3, Weak recommendation)**
- Maintenance therapy should be adjusted to a dosage that maintains persistent CBR **(Evidence 1, Strong recommendation)**
- The minimum total duration of treatment should be 4 years, and at least 2 years after the achievement of CBR **(Evidence 2, Strong recommendation)**

Treatment cessation

One important and critical decision is in whom and when immunosuppression can be safely stopped. The achievement of CBR and histological remission of the disease, followed by sustained off-treatment remission in the long-term, is of paramount importance and is the ideal aim of AIH management in both children and adults [1,10,11,41,42,149,150]. A recent systematic review of published studies between 1972 and 2018 reported a wide range of relapse rates between 25% and 100% [149]. A low probability of relapse after immunosuppression withdrawal has been associated with the presence of DI-ALH or viral-induced AIH, absence of other autoimmune diseases, normal IgG levels at baseline, seronegativity for anti-SLA/LP, a shorter time to achieve continuous and sustained CBR (e.g., <6 months), absence of relapse episodes, longer duration of treatment (≥4 years), and deeply normal aminotransferases (below half the ULN) and IgG levels (<1200 mg/dL) at the time of withdrawal, suggesting that careful selection of patients is essential [95,126,146,149-151].

Ongoing necroinflammatory activity or cirrhosis on second liver biopsy despite CBR is an additional important predictive marker of relapse after treatment withdrawal. In this context, a recent multicenter study showed that CBR alone is a poor marker of histological remission in patients with already established severe fibrosis and/or cirrhosis; therefore, only liver biopsy can reliably assess the activity of AIH in

such patients [152]. In general, liver biopsy before treatment withdrawal is desirable, as a considerable number of patients with CBR still have interface hepatitis on histology or may have progression of liver disease to cirrhosis; thus, they cannot stop immunosuppressive therapy because of the potential harmful effects of a relapse [149,150,153,154]. However, many patients are reluctant to undergo a second liver biopsy. In that case, LSMs by FibroScan can offer a completely safe and probably reliable and effective noninvasive method for monitoring fibrosis progression. Indeed, recent studies have shown that LSMs correlate efficiently with fibrosis stage, indicating quite precisely the cutoff points for severe fibrosis and cirrhosis (9 kPa and 12.5-16 kPa, respectively) [107-112]. Liver fibrosis can be accurately assessed in patients with AIH who have been treated for >6 months [107,110,111,155]. Fig. 6 illustrates a proposed algorithm for the selection and follow up of patients with AIH in whom immunosuppression cessation can be implemented.

Regarding children, several small studies in the past, with short follow up and using strict criteria including liver histology, have shown a relapse-free rate ranging between 45% and 87% after treatment withdrawal [156-159]. In the largest ever published multicenter study with long-term follow up (n=117; median follow up 20 years), it was shown that treatment cessation is feasible even without prior liver biopsy [41]. The authors were able to show that 53% of patients in whom treatment cessation was achieved under medical surveillance, without prior liver biopsy, did not relapse. Continuously deep normal aminotransferase levels, along with a prothrombin ratio ≥70%, were the best prognostic markers of successful withdrawal [41].

A trial of treatment withdrawal needs close cooperation between the patient and clinicians. It should be considered only when there is sustained CBR for ≥24 months. Unfortunately, there are no clear cut CPGs on how to taper the drugs safely and efficiently. Practically, the duration of corticosteroid tapering varies from 6-8 weeks to 3-4 months, while some physicians stop AZA and MMF completely and others withdraw these drugs gradually [1,10,134,146,149,150]. After withdrawal, as many as around three quarters of AIH patients may suffer from myalgias and arthralgias, which may persist in the long term. Following treatment withdrawal, all patients should be monitored closely by determination of aminotransferases and IgG every 3-4 weeks for ≥3 months, and every 3 months thereafter, over the first year, when there is the highest risk of relapse [1,10,11,149,150]. Subsequently, laboratory monitoring should be performed every 6 months for the next 3 years, followed indefinitely by annually assessment [134,160]. In parallel, periodic assessment of fibrosis by LSMs (e.g., annually) may also be helpful to identify those with fibrosis progression. In case of relapse, subsequent attempts should be avoided, as further relapses are very common and are related to worse outcomes [149,150].

After treatment withdrawal, aminotransferases may elevate transiently (usually <2xULN), and therefore, it is advisable to repeat the test in the first instance to check for potential normalization. Other causes, such as viral hepatitis, alcohol-associated liver disease, DILI, hepatic or portal vein thrombosis, MASLD and biliary tract disease should be carefully excluded before a final diagnosis of relapse is established.

Statements 32-33

- Relapse rates after treatment withdrawal vary between 25% and 100%, with the lowest being observed among MMF-treated patients **(Evidence 2, Strong statement)**
- After withdrawal of corticosteroids, about 75% of patients may suffer from myalgias and arthralgias, which may persist for up to 12 months or more **(Evidence 3, Weak statement)**

Recommendations 48-54

- A trial of treatment withdrawal is recommended in carefully selected patients **(Evidence 1, Strong recommendation)**
- Liver biopsy before treatment withdrawal is desirable, but as many patients are reluctant to undergo this procedure, alternative noninvasive assessment of severe fibrosis and/or cirrhosis by transient elastography (FibroScan) should be considered **(Evidence 2, Strong recommendation)**
- In children, treatment withdrawal may be feasible even without prior liver biopsy, especially in those with aminotransferases <0.5 × ULN and prothrombin ratio ≥70% **(Evidence 3, Weak recommendation)**
- Patients who have received adequate induction and maintenance treatment (≥4 years) without achieving CBR or with ongoing necroinflammatory activity (mHAI>3) and/or severe fibrosis/cirrhosis on second liver biopsy or by LSM (FibroScan) should continue immunosuppression indefinitely **(Evidence 1, Strong recommendation)**
- When treatment withdrawal has been decided upon, tapering of corticosteroids may last from 6-8 weeks to 3-4 months, whereas AZA and MMF cessation can be done either instantly or gradually **(Evidence 3, Weak recommendation)**
- Lifelong close monitoring following treatment withdrawal is recommended for all patients, as relapse can occur at any time after treatment cessation **(Evidence 1, Strong recommendation)**
- Subsequent attempts at drug withdrawal after a relapse episode following first withdrawal are not recommended **(Evidence 2, Strong recommendation)**

Relapse and flare of AIH

Relapse can occur in patients after complete discontinuation of treatment, while flares represent an increase of liver biochemical indices during tapering of induction therapy or during maintenance therapy. Even though a strict definition of relapse in AIH is lacking, it should be considered when

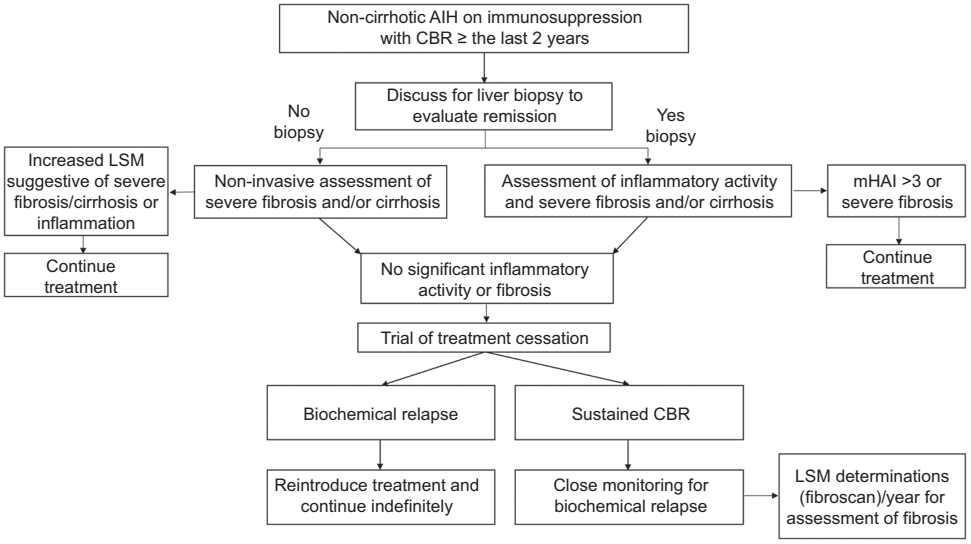

Figure 6 Proposed algorithm for treatment withdrawal in AIH patients
AIH, autoimmune hepatitis; CBR, complete biochemical response; LSM, liver stiffness measurement; mHAI, modified hepatic activity index

clinical and/or laboratory indices reappear (ALT ≥2-3 × ULN and/or elevation of IgG which usually precedes ALT increase) [1,10,11,148]. A new biopsy is not usually needed to confirm relapse or flare.

Relapses and flares are successfully treated quite easily with the initial treatment regimens used in the induction therapy schedule, by increasing the corticosteroid dose slightly and transiently. The net result is the re-achievement of CBR in most patients [149,150]. As in relapse cases, other causes of increased aminotransferases and problems with treatment adherence should be carefully excluded to avoid a misconception of flare episodes [42,161].

Recommendations 55-56

- Re-biopsy is not recommended to confirm relapse or flare if other causes of high aminotransferases have been carefully excluded **(Evidence 2, Strong recommendation)**
- Treatment of relapses or flares should be identical to the starting schedule, and results in re-achievement of CBR in almost all patients **(Evidence 1, Strong recommendation)**

Monitoring during treatment

Considerable attention is warranted in patients with MetS, as extended corticosteroid treatment may exaggerate several of its components. An individualized approach to corticosteroid regimen, modification of treatment for MetS components, and lifestyle adaptations (weight loss, physical exercise) are recommended [10,11,63-65,71].

Patients under AZA should be monitored regularly (on a weekly basis) during the first month with aminotransferases, prothrombin time, fasting glucose and full blood count, as its toxicity occurs most frequently during the first 6 weeks of treatment [1,10,11,162]. In the MMF-treated group, initial investigation of the same parameters can be determined only at 4 weeks to assess non-response [7].

Subsequently, clinical and laboratory monitoring (including IgG determination) should be performed at 2-3-month intervals to assess CBR [7]. If CBR has been achieved, monitoring intervals can be performed every 3-6 months. As in other autoimmune diseases under treatment with corticosteroids, dietary restrictions (low salt diet, avoidance of carbohydrates, etc.) and administration of calcium and vitamin D supplements seems reasonable.

Recommendations 57-59

- In patients with concurrent MASLD or components of the MetS, an individualized approach to corticosteroid regimen, modification of treatment for diabetes mellitus, hypertension and dyslipidemia, as well as lifestyle adaptations are recommended **(Evidence 2, Strong recommendation)**
- Regular clinical and laboratory evaluation should be performed at least at 1, 3, 6 and 12 months after treatment initiation to assess drug toxicity and response to treatment **(Evidence 2, Strong recommendation)**
- Vitamin D supplementation and adequate calcium intake should be considered in patients under long-term corticosteroid treatment **(Evidence 3, Strong recommendation)**

Intolerance to and side-effects of first-line therapies

A fair number of patients develop intolerance to predniso(lo)ne and/or AZA or MMF. Administration of corticosteroids has

been associated with several side-effects, especially in those receiving predniso(lo)ne therapy >15 mg/day for >2 years. In general, corticosteroid cessation due to side-effects is reported in 15% of cases [1,10,11,42]. Physicians should aim at administering high dose of corticosteroids for short periods and adjust MMF or AZA sufficiently promptly to spare steroids. A switch to budesonide in predniso(lo)ne responders who nevertheless develop side-effects, even though MMF or AZA have been increased to the highest dose, is not recommended, as recent data showed that adverse events in non-cirrhotic patients were similar in predniso(lo)ne and budesonide treated patients [140].

Side-effects related to AZA administration can occur in up to 25% of patients; they include arthralgias, fever, gastrointestinal problems, pancreatitis, hepatotoxicity, skin rash, bone marrow suppression, opportunistic infections and malignancy [1,10,11,41,42,146,147,162]. Recently, a large retrospective study reported a 15% discontinuation rate of AZA in the first year [162]. Furthermore, the first prospective data from the European Reference Network (ERN)-Rare-Liver registry showed that the rate of AZA intolerance within the first 6 months was much higher (37%) [135]. In this regard, TPMT activity or genotyping, along with determination of AZA metabolites, could help in guiding AZA treatment [1,10,11,148,163,164]. However, these procedures are time consuming, not widely available, and are not covered by most health insurance services.

MMF has been proven safer and more tolerable [38,42,142-147]. In most cases, MMF is not discontinued because of intolerance, but for other reasons, such as patient's wish for pregnancy or a shortage of drug supplies [42,146]. In addition, recent systematic reviews with meta-analyses [165-167] showed that MMF is an excellent option for second-line treatment in patients intolerant to AZA, or with related side-effects, with response rates ranging from 62-82%. Therefore, apart from first-line treatment, MMF should be considered as the appropriate second-line therapy in AZA intolerant patients [11,165-168].

6-methyl mercaptopurine (6-MP), the first active metabolite of AZA, might be a potential alternative treatment in AIH patients experiencing intolerance, as 50-75% of this group will eventually tolerate 6-MP [148]. Initial recommended doses range from 0.5-1 mg/kg/day, and are subsequently titrated according to 6-TGN levels. However, this choice is not widely acceptable by many authorities [11], as data on 6-MP come from small retrospective studies with low rates of CBR (approximately 36%) compared to MMF, whereas its use stipulates monitoring of 6-TGN, which is not widely available [11,168,169].

Tacrolimus (TAC), a calcineurin inhibitor, has also been investigated as second-line treatment in the setting of AZA intolerance. One large multicenter study reported normalization of aminotransferases in 94.1% of AZA intolerant patients, with the respective rate of MMF administration being 92% [170]. Based on these results, AASLD recommended both MMF- and TAC-based therapies as appropriate second-line treatments [11]. However, HASL, EASL, the IAIHG and the ERN on Hepatological Diseases [1,10,148] do not endorse TAC as a potential second-line option, since the abovementioned study [170] was retrospective, included a very heterogeneous group of patients who were treated with different treatment schedules, and had irregular follow-up data. Recently, many other similar studies with more systematic data showed that, even though TAC is a very potent drug, it requires close monitoring because of a quite small therapeutic window, while toxicity remains a major issue [171-173]. A recent study confirmed the limited effectiveness and the risks of this therapy in intolerant patients [174]. Therefore, for the time being, it seems reasonable for MMF to be given first to all patients who are intolerant to thiopurines, and TAC should be kept as third-line treatment for cases with ongoing insufficient response (Fig. 7) [168].

Statements 34-35

- Determination of TPMT activity and AZA metabolites can help in guiding AZA treatment, but they are time-consuming and not widely available **(Evidence 3, Weak statement)**
- The discontinuation rate of AZA because of intolerance in the first year of treatment is high (15-37%) **(Evidence 2, Strong statement)**

Recommendations 60-63

- MMF should be the second-line treatment of choice in patients with intolerance or side-effects related to thiopurines **(Evidence 2, Strong recommendation)**
- 6-MP can be an alternative option in AZA-related intolerant patients **(Evidence 4, Weak recommendation)**
- Switching to budesonide in predniso(lo)ne responders because of steroid side-effects is not usually recommended, as adverse events are similar in both groups and the efficacy of budesonide is inferior **(Evidence 3, Strong recommendation)**
- TAC should not be used as second-line treatment for AZA intolerant patients **(Evidence 2, Strong recommendation)**

Insufficient response to first-line therapies

In AIH patients who show an insufficient response under combination treatment with predniso(lo)ne and AZA, 6-TGN levels should be determined first [148,163]. Patients with 6-TGN levels less than 220 pmol/8 × 10^8 red blood cells should be assessed for non-adherence. After non-adherence is ruled out, optimization of 6-TGN levels, either by increasing the dose of AZA up to 2 mg/kg/day or by adding allopurinol, which blocks the 6-methylmercaptopurine pathway, and reducing the dose of AZA to about 25% of the previous dose, should be tried [148,175]. In patients with

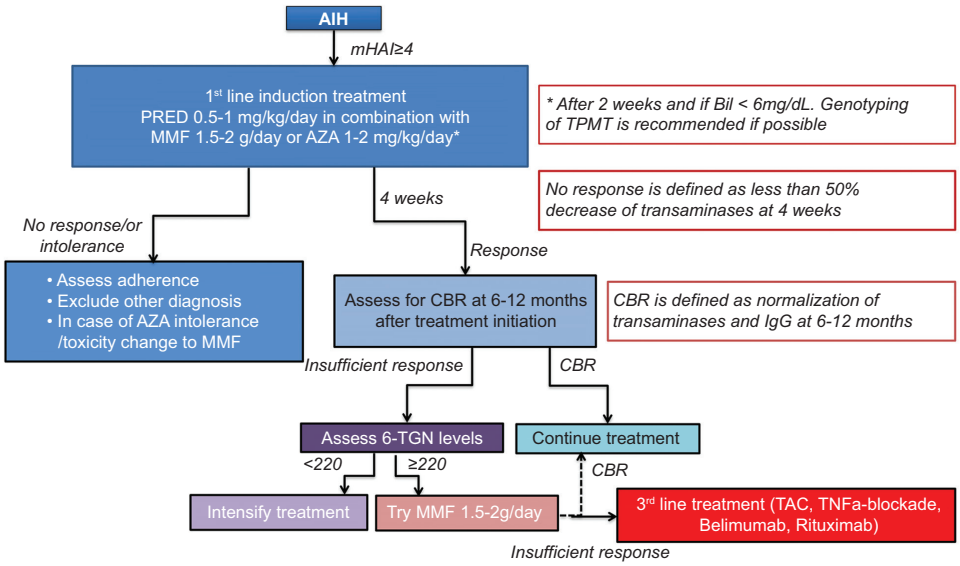

Figure 7 Proposed treatment algorithm for patients with AIH
AIH, autoimmune hepatitis; mHAI, modified hepatic activity index; PRED, predniso(lo)ne; MMF, mycophenolate mofetil; AZA, azathioprine; Bil, bilirubin; TPMT, thiopurine methyltransferase; CBR, complete biochemical response; IgG, immunoglobulin G; 6-TGN, 6-thioguanine; TAC, tacrolimus; TNFα, tumor necrosis factor alpha

insufficient response and 6-TGN levels above 220 pmol/8 × 10^8 red blood cells, it is prudent to first exclude an alternative or concurrent diagnosis [1,10,11,148]. Viral infections by Epstein-Barr virus and cytomegalovirus, MASLD and/or MASH because of corticosteroid use, and DILI because of supplements and/or herbals, should be appropriately excluded before an index patient is defined as an insufficient responder [42,148].

The suggested cutoff for 6-TGN levels has been chosen from previous experience in transplantation and IBD, as well as from 2 retrospective studies in AIH patients [176,177], even though another recent retrospective study from the UK showed that lower cutoff levels could also be of clinical significance [163]. Repeated relapses during maintenance therapy should also be considered as insufficient response. MMF can be used after unsuccessful intensification of AZA related first-line therapies, as recent systematic reviews and real-world studies have shown response rates ranging from 32-57% in insufficient responders, resulting in a considerable reduction in the number of patients who are candidates for third-line therapies [145,146,165-167]. In addition, in case of insufficient response to MMF first-line therapy, switching to thiopurine-related therapies should be attempted before third-line therapies are initiated [145,146].

There are no robust data on the use of TAC as a potential second-line treatment in insufficient responders. An ongoing phase IIIB, multicenter, open-label, parallel-group, randomized controlled trial (TAILOR study) will probably address this issue, as it will investigate the effectiveness and safety of TAC versus MMF in these patients [178].

Patients experiencing an insufficient response to first-and/or second-line regiments are expected to exhibit lower response rates to third-line therapies, compared to those with drug intolerance, and often need double and/or triple immunosuppression to achieve CBR [148]. Several agents have been used, though existing data to date rely only on uncontrolled small case series, where individual agents were used according to local expertise: TAC, cyclosporin, methotrexate, cyclophosphamide, mTOR inhibitors and biologic regimens, including tumor necrosis factor-α (TNF-α) blockade agents, anti-CD20 (rituximab), B cell activating factor (BAFF) inhibitors (belimumab and ianalumab) or ustekinumab (Fig. 7) [168,170,174,176,179-186]. The use of these drugs required the exclusion of latent infections that could emerge in the context of profound immunosuppression [187,188]. Therefore, they should only be given in reference centers. Additionally, among TNF-α blockade agents, infliximab should be considered with caution, as it may result in unforeseen complications with opposite outcomes, such as induction of an immune-mediated liver disease resembling AIH, or even true AIH [17,168,186].

Recommendations 64-68

- In patients with insufficient response to AZA-based therapies, measurement of 6-TGN levels is recommended first in order to assess whether biochemical activity is due to underdosing of AZA or non-adherence **(Evidence 2, Strong recommendation)**
- After non-adherence is ruled out, intensification of treatment, either by increasing the dose of AZA up to 2 mg/kg/day or by adding allopurinol (contraindicated in pregnancy), is recommended **(Evidence 3, Strong recommendation)**
- MMF should be used before starting third-line therapies after unsuccessful intensification of AZA-related first-line therapies **(Evidence 2, Strong recommendation)**
- In patients with insufficient response after adequate

first- and second-line treatments, third-line therapies with cyclosporin or TAC, methotrexate, cyclophosphamide, mTOR inhibitors, rituximab, TNF-α blockade agents, BAFF inhibitors or ustekinumab may be initiated in expertise centers **(Evidence 4, Weak recommendation)**
- Patients undergoing these therapies should be assessed for the risk of opportunistic infections and receive appropriate prophylaxis or vaccination **(Evidence 3, Strong recommendation)**

Adherence to treatment

Adherence to treatment is a prerequisite for a successful outcome in AIH [1,10,11,42]. Non-adherence to treatment should always be considered in cases who fail to meet the criteria of treatment response, and even more in those presenting with flares and relapses [159,189,190].

As stated previously, depending on availability, measurement of 6-TGN may be a useful tool to evaluate non-adherence to AZA-based first-line treatment. Accumulating data suggest that AIH patients, and especially children and adolescents, have an impaired quality of life, mainly related to increased anxiety and depression, and further stress their impact on treatment non-adherence [30-32,189,191]. As several factors related to patients, physicians and the disease *per se* have been recognized to influence quality of life in AIH, it is evident that physicians face great challenges in treating these patients, and they should rely on a multidisciplinary approach [159,189,191].

Pre-treatment guidance and discussion of treatment risks and benefits is essential, and might actively engage patients and ensure treatment compliance. Specialty units with integrated psychologists, psychiatrists, social and youth workers, committed specialist nurses, as well as dedicated transition clinics, will aid in bridging the gap between pediatric and adult care and improve patients' outcomes [192].

Recommendations 69-71

- Adherence to treatment is a prerequisite for a favorable outcome in all patients **(Evidence 2, Strong recommendation)**
- Transition from childhood to adulthood should be handled by a dedicated multidisciplinary team **(Evidence 3, Strong recommendation)**
- A multidisciplinary approach should be offered to patients with anxiety or depression to ensure compliance and prevent physicians from erroneously characterizing patients as non-responders **(Evidence 4, Strong recommendation)**

Management of specific forms of AIH

Adults and children with AS-AIH

The treatment of patients with AS-AIH or AS-AIH with ALF, including AIH cases with acute-on-chronic liver failure (ACLF), has been a matter of contention during the last decades. Untreated AS-AIH patients have a dismal prognosis, with progression to ALF in 50-60% of patients, death rates up to 20%, and a need for liver transplantation in 20% [1,11,193-195]. Existing data originate mostly from real-life studies, while early studies relied on small numbers of patients without a uniform definition of AS-AIH [35,37,193,196-200]. Overall treatment response ranged between 36-100%. Extrapolating data from these studies has yielded evidence to suggest that stratifying patients with AS-AIH according to individual characteristics is essential, as they carry different prognoses and should be managed accordingly. Patients who have AS-AIH with ALF or ACLF carry the worst prognosis, with response rates to corticosteroid treatment of 8-41%, and should be referred for liver transplantation as soon as possible [35,37,196-200].

Recent studies have assisted in delineating the role and timing of corticosteroids as modifiable factors of outcome in AS-AIH, even though the optimal dose and route of administration remain to be determined [35,37,196,199,200]. Early administration of corticosteroids in patients with genuine AS-AIH (icteric with INR ≥1.5 but without encephalopathy and chronic lesions on histology) seems to be highly effective, with significantly increased 90-day transplant-free survival. The success of treatment relies closely on the correct selection of patients, and accumulating data strongly justify a trial of oral or preferentially intravenous corticosteroids early during disease presentation [35,37,42,43,196,199,200]. In a Greek cohort of AS-AIH patients, such an approach resulted in 95.2% long-term survival without liver transplantation (median follow up: 5.3 years) [35].

Studies evaluating treatment of AS-AIH, with or without ALF/ACLF, in childhood and adolescence are scarce and do not allow firm conclusions [83]. Only 2 small studies in 9 and 13 children with ALF due to AIH reported recovery with corticosteroids in 44.4% and 76.9%, respectively [201,202].

To sum up, even though established guidelines do not exist, available data, although of low quality, suggest that all AIH patients with AS-AIH without encephalopathy should be considered for a trial of corticosteroid administration with sufficiently high doses (≥1 mg/kg/day), and probably best intravenously, as soon as possible (the sooner the better) [1,10,35,42,199,203]. Subsequently, evaluation of liver function—INR, bilirubin, and model for end-stage liver disease (MELD) score—both at treatment initiation and early during follow up (treatment day 3-7) is imperative to recognize those with a low probability of response who might benefit from early referral for liver transplantation [37,42,196,203]. This approach will also minimize possible infectious complications from longstanding immunosuppression. There is no evidence to support the prophylactic use of antibiotics and/or antifungals in this setting. Rather, as the role of corticosteroids in patients with

AS-AIH and ACLF or ALF is very limited, this group of patients should be immediately listed for liver transplantation [194,195].

Statement 36

- Data on the role of corticosteroids in patients with AS-AIH with ALF or ACLF are very limited **(Evidence 4, Strong statement)**

Recommendations 72-74

- Patients with AS-AIH should receive a treatment trial with corticosteroids (preferably intravenously) as early as possible, whereas patients with AS-AIH and ALF or ACLF should be evaluated directly for liver transplantation **(Evidence 3, Strong recommendation)**
- If corticosteroids are given to patients with AS-AIH and ALF or ACLF, strict surveillance for the development of infections and close monitoring of the efficacy of corticosteroids should be performed **(Evidence 2, Strong recommendation)**
- Patients with AS-AIH without ALF or ACLF who do not improve within 3-7 days of corticosteroid initiation should be immediately evaluated for liver transplantation **(Evidence 3, Strong recommendation)**

AIH in pregnant women

The management of AIH in a pregnant woman with already established AIH, or new-onset AIH, is identical to the non-pregnant state, apart from the use of MMF [1,10,11,49]. Immunosuppression (corticosteroids with or without thiopurines) is safe, and should be continued during pregnancy and breastfeeding to prevent exacerbation of the disease [49,50,53]. Data on budesonide use in non-cirrhotic pregnant women with AIH are extremely limited [204]. Counseling for the achievement of CBR at least 1 year prior to conception is an important issue, as it is associated with favorable outcomes for both mothers and babies [49,205,206].

A minimal adjustment of immunosuppressive therapy (e.g., 5-10 mg/day predniso(lo)ne ±50-75 mg/day AZA) in pregnant women with previously established AIH in CBR appears possible, as the disease usually has lower activity throughout pregnancy [1,10,11,49,205,206]. However, higher doses after delivery to minimize the risk of relapse in the postpartum period should be considered. In cases with AIH-PBC or AIH-PSC variants, UDCA can be continued along with immunosuppression throughout pregnancy to theoretically mitigate pruritus and improve cholestatic markers, even though a recent large retrospective study on PSC pregnant patients including 46 with AIH-PSC variant did not show a protective effect of UDCA [49,207].

Statement 37

- Women of childbearing age with previously known AIH, and particularly those with CBR for at least 1 year before conception, should not be excluded from pregnancy and breastfeeding **(Evidence 2, Strong statement)**

Recommendations 75-77

- Pregnant women with either previously known or new-onset AIH should be managed as in the non-pregnant state, except for MMF use, which is contraindicated **(Evidence 2, Strong statement)**
- Treatment with predniso(lo)ne, with or without thiopurines, should be continued in preexisting AIH, and should be administered in new-onset AIH **(Evidence 2, Strong recommendation)**
- Lowering of immunosuppressive therapy should be considered during pregnancy, followed by an increase after delivery **(Evidence 3, Strong recommendation)**

Patients with DI-ALH

Evidence-based data on the management of DI-ALH are limited [1,10,11,62,67,208,209]. Initially, in any suspected case of DI-ALH the implicated agent should be stopped immediately (Fig. 3). The subsequent decision on a short course of corticosteroids should be individualized in patients with symptoms, and particularly when liver biochemistry does not improve or even worsens after withdrawal of the suspected agent [42,62,67,210]. However, the exact period of waiting for improvement is largely unknown, even though an international collaborative study showed that corticosteroids should be initiated, at least in those who have accelerating disease, within 30 days of stopping the offending drug [211]. When corticosteroids are being considered, a liver biopsy is very useful for confirmation of AIH-like lesions and exclusion of other diagnoses (Fig. 3) [42,62,67,208,209].

The rapidity of response is significantly faster in DI-ALH patients compared to those with AIH [212,213], but data on the corticosteroid dose that should be used are very limited, with a recent study suggesting prednisolone at 30-40 mg/day for jaundiced patients [62,67,210,214]. The outcome of DI-ALH after the achievement of CBR and a fast tapering of corticosteroids is generally good, with practically very low risk of relapse (Fig. 3).

Recommendations 78-80

- In patients with DI-ALH, the implicated agent should be stopped immediately **(Evidence 1, Strong statement)**
- A short course of corticosteroids (2-3 months) should be considered in all patients with no improvement or

worsening of liver tests after withdrawal of the suspected agent, but data on their dosage are limited **(Evidence 2, Strong recommendation)**
- Liver biopsy should be considered to confirm AIH-like lesions and exclude other diagnoses **(Evidence 2, Strong recommendation)**

Patients with HIV and AIH

AIH has been reported in patients with HIV [215,216]. Although this association was thought to be initially very rare, a recent cross-sectional study from the USA showed a prevalence of 52.8/100,000 HIV infected patients [217]. The underlying pathogenesis is quite enigmatic, but the development of an immune reconstitution-related AIH after antiretroviral therapy should be considered [218]. Treatment of AIH in this setting should be individualized, although significant complications (e.g., opportunistic infections) are rare (Table 2).

Elderly patients with AIH

Treatment schedules in elderly patients with AIH are similar to those used in other adults. Elderly patients are characterized by a more frequent response to treatment and a higher prevalence of concomitant autoimmune diseases compared to younger patients, but the liver-related mortality is identical (Table 2) [14,21,28].

In elderly patients with no symptoms and mild disease on liver biopsy, the initiation of treatment could be withheld if other established comorbidities with considerable severity are present (e.g., uncontrolled diabetes, severe osteoporosis, current or past history of psychosis and refractory arterial hypertension). In elderly patients with mild disease, but without severe comorbidities, initiation of treatment with low predniso(lo)ne dose (e.g., ≤0.5 mg/kg/day), followed by a rapid steroid de-escalation in combination with MMF or AZA could be considered [14,72,127,128].

Immunosuppressive therapy is recommended in all elderly patients with AIH who have at least moderate activity, but the dose and tapering schedules should be considered carefully according to concurrent comorbidities.

Recommendations 81-84

- In patients with HIV and concurrent AIH, immunosuppression should be administered on an individualized basis **(Evidence 4, Strong recommendation)**
- In elderly patients with at least moderate necroinflammatory activity immunosuppressive therapy is recommended **(Evidence 3, Strong recommendation)**
- In the case of comorbidities, the dose and tapering schedules should be considered carefully, irrespectively of age **(Evidence 3, Strong recommendation)**
- In elderly asymptomatic patients with mild necroinflammatory activity and concurrent comorbidities a watch-and-wait strategy is recommended **(Evidence 4, Strong recommendation)**

Variants of AIH

There are no randomized controlled trials assessing the best treatment options for patients with AIH variants [1,10,11,73,74,79,80]. These cases can be treated according to the predominant pattern of histological injury. As a result, the addition of immunosuppression to UDCA in patients with well-established PBC, if there is at least moderate necroinflammatory activity on liver histopathology, is recommended [73,219]. Patients with PBC-AIH variant seem to need lower doses of immunosuppression and maintain CBR after stopping treatment at higher rates compared to patients with AIH. A recent systematic review and meta-analysis revealed similar favorable results of combination therapy, with higher transplant-free survival, when studies with long-term follow up (>90 months) were included [220]. It is not certain whether patients with AIH who develop features of PBC will benefit from the addition of UDCA, but this management appears reasonable, as combination therapy may theoretically protect them from the long-term complications of PBC.

Similarly, the treatment of patients with AIH-PSC variant is largely empiric [1,10,11,79,80,84]. In clinical practice, immunosuppressive treatment with or without UDCA may be considered in these patients if biochemical, serological, and histological activity are present [74,79,80,84]. Response criteria have recently been suggested for the pediatric population [83]. In this context, a simplified score >5 and an mHAI >3 could prompt physicians to initiate immunosuppression in patients with PSC [74,80,221]. Small retrospective studies showed that AZA administration may increase survival without increasing the risk of cholangiocarcinoma in PSC patients [84,222].

Recommendations 85-87

- UDCA plus immunosuppression is recommended in patients with PBC-AIH variant and mHAI>3 **(Evidence 2, Strong recommendation)**
- If AIH is the predominant component, immunosuppression can be started first, and UDCA could be added if CBR is not achieved **(Evidence 4, Weak recommendation)**
- In patients with AIH-PSC (or PSC-AIH) variant, immunosuppression with or without UDCA can be considered under close follow up **(Evidence 3, Weak recommendation)**

Patients with AIH and liver-related comorbidities

AIH can coexist with other hepatic diseases, such as rarely with chronic HBV or HCV infection (depending on their prevalence in an index area), alcohol-associated liver disease, and more frequently with MASLD and/or MASH (Table 2) [44,45,63-65,223-226]. In these cases, the concurrent diagnosis of AIH is very difficult and may be missed, resulting in a poorer prognosis [44,45]. HBV patients with concurrent features of AIH at baseline should be treated first for HBV, and AIH management should be reassessed after a successful suppression of the virus. Immunosuppression for AIH should be started, along with antiviral prophylaxis, according to the EASL and the Hellenic Center for Disease Control and Prevention (HCDCP) CPGs in those with hepatitis B surface antigen positivity, but without detectable HBV DNA, or without indications for HBV therapy [227,228]. Likewise, in patients with concurrent HCV, direct acting antivirals should be used first, and immunosuppressive therapy can be initiated after the eradication of HCV if biochemical activity and mHAI are still high (mHAI >3).

The management of AIH patients with concurrent alcohol-associated liver disease or MASLD is also difficult, as the coexistence of MASLD or even components of the MetS, or alcohol-associated liver disease, affect the prognosis. Therefore, a closer and stricter surveillance and follow up seems reasonable [45,63-65]. In this setting, concurrent diseases should be managed intensively in parallel with AIH, according to the respective CPGs [63-65,71,226,229]. A proposed algorithm for the management of AIH with concurrent alcohol-associated liver disease or MASLD is illustrated in Fig. 8A,B.

Recommendations 88-91

- In patients with AIH and coexistence of chronic HBV or HCV, antiviral treatment should start first, and AIH management should be reassessed after HBV suppression or HCV eradication, respectively **(Evidence 4, Strong recommendation)**
- Patients with chronic HBV infection but without typical indications for HBV treatment should be assessed for the need of HBV prophylaxis, depending on the immunosuppressive therapy for AIH **(Evidence 4, Strong recommendation)**
- In patients with AIH who are infected with HBV or HCV during follow up, antiviral treatment is recommended without stopping immunosuppressive therapy **(Evidence 4, Strong recommendation)**
- In patients with AIH and coexistence of alcohol-associated liver disease, MASLD or MASH, a closer and stricter follow up is recommended, managing both concurrent diseases and aiming at the lowest effective dose of corticosteroid **(Evidence 3, Strong recommendation)**

Patients with AIH and decompensated cirrhosis

Management of patients with decompensated cirrhosis at AIH diagnosis can be challenging, because of the risk of treatment-related complications and the lack of data. Very few small and heterogeneous studies have addressed the safety and efficacy of immunosuppressive treatment in patients with AIH who present with decompensated cirrhosis [230,231]. Recently, a large retrospective multicenter study from the IAIHG in 214 patients showed that the absence of overt hepatic encephalopathy and MELD-Na ≤28 at diagnosis were benign signs, while a decline of MELD-Na ≥11 after 4-weeks of immunosuppression had 100% negative predictive value for death or liver transplantation. Almost half of the patients who received immunosuppression recompensated, suggesting that treatment is beneficial in carefully selected patients with AIH-related decompensated cirrhosis and active disease [232].

Recommendation 92

- Immunosuppression should be considered in carefully selected AIH patients with decompensated cirrhosis at diagnosis (absence of overt hepatic encephalopathy, and MELD-Na ≤28) **(Evidence 3, Strong recommendation)**

Management of AIH after liver transplantation

In the setting of liver transplantation, 2 entities related to AIH have been considered: namely, plasma cell rich–rejection hepatitis (known also as *de-novo* AIH) in patients who have been transplanted for other than AIH causes (about 5%), and recurrence of AIH (20-25% of patients) [233,234]. Both conditions are usually managed with the standard predniso(lo)ne schedules combined with MMF or AZA [1,10,11,46,234]. Early recognition of plasma cell rich–rejection hepatitis is important, as it can avoid re-transplantation and improve the patients' long-term survival [1,10,11,46,233,234].

Recommendation 93

- AIH after liver transplantation, either as plasma cell rich–rejection hepatitis in patients transplanted for another reason, or recurrent AIH, should be treated according to the basic principles of AIH management **(Evidence 2, Strong recommendation)**

Concluding remarks

AIH diagnosis is based on a combination of laboratory (increase of IgG), serological (autoantibodies), and

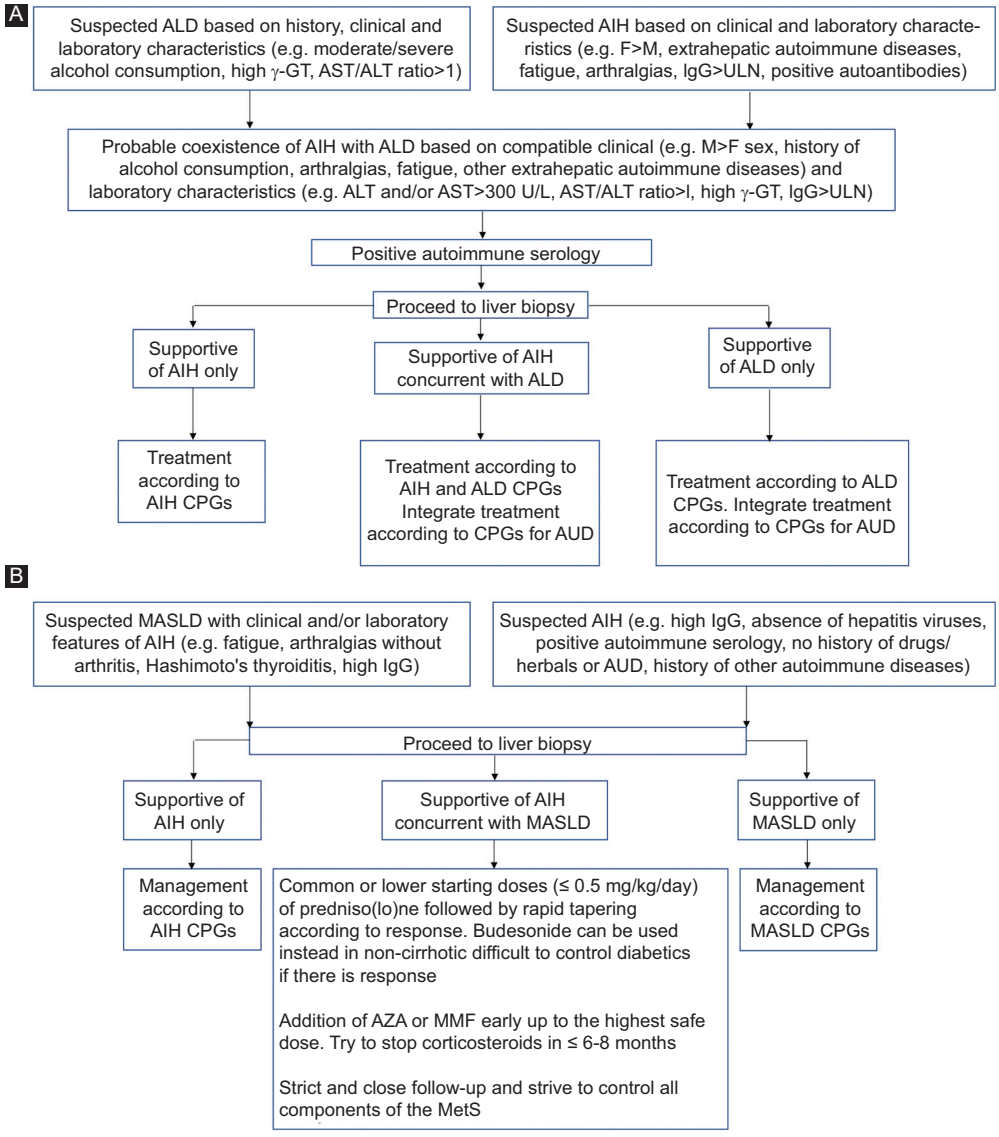

Figure 8 Proposed algorithm for the management of patients with suspected AIH and concurrent alcohol-associated liver disease (A, adapted from ref. 45) or MASLD (B, adapted from ref. 63)
ALD, alcohol-associated liver disease; γ-GT, gamma-glutamyl transpeptidase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; AIH, autoimmune hepatitis; F, female; M, male; IgG, immunoglobulin G; ULN, upper limit of normal; AUD, alcohol use disorder; CPGs, clinical practice guidelines; MASLD, metabolic dysfunction-associated steatotic liver disease; AZA, azathioprine; MMF, mycophenolate mofetil; MetS, metabolic syndrome

histological findings (portal and/or lobular hepatitis with or without interface hepatitis), usually in the absence of other liver diseases. As there is no specific diagnostic marker, the disease is largely underestimated or unrecognized. The reliable detection and interpretation of autoantibodies and histological findings are the cornerstones for a prompt diagnosis. Most patients respond very efficiently to immunosuppression, with almost normal life expectancy and a quite good quality of life. However, many still experience considerable morbidity because of delayed or missed diagnosis, drug intolerance and side-effects, insufficient response, relapses or flares, and poor adherence.

The establishment of the ERN on Hepatological Diseases, consisting of major European expertise centers in the diagnosis and management of AIH, will be a decisive factor in improving the holistic management of patients. In addition, research on the etiopathogenetic mechanisms and diagnostics of AIH will improve our understanding and timely diagnosis of this potentially catastrophic liver disease. In this regard, pIgG and metabolomics, along with the need for standardization of immunoassays for autoantibody detection, have recently gained attention, as all may soon improve the diagnostic workup of patients with suspected AIH [102,105,235]. In particular, the results from metabolomics suggest different metabolic processes in AIH compared to other liver diseases, but it is currently unknown whether certain of these metabolites could theoretically affect the immune responses and the development of AIH [105].

Moreover, the development of noninvasive imaging testing, such as LSMs by FibroScan and multiparametric magnetic resonance imaging, is expected to further assist our effective follow up of patients without the need for repeated liver biopsies [236-238].

Up to the present, most AIH patients need long-term immunosuppression, but patients would prefer cure and management of both hepatic and non-hepatic symptoms, not only disease remission. A hopeful sign is that, during recent years, several Phase II/III trials have been under way to investigate the effectiveness of novel treatments (NCT03217422, phase II/III randomized placebo-control trial investigating ianalumab, a BAFF receptor blocker, in patients with an insufficient response or intolerance to standard of care; NCT04371718, phase II trial investigating JKB-122, a TLR4 antagonist that has resulted in attenuation of liver inflammation in animal models of AIH; NCT05569759, phase IIa study investigating zetomipzomib, a selective inhibitor of immunoproteasome, in patients with insufficient response to first-line treatment). Considering the above data, it seems that the future of AIH is rather promising, but more efforts and new ideas in the field are still warranted. The recent data on MMF efficacy could further enhance these encouraging efforts by minimizing the percentage of patients with an insufficient response. Furthermore, the identification of immunophenotypic alterations in AIH patients taking MMF, along with genotyping analysis on specific polymorphisms of the involved genes of MMF metabolic pathways, could help us elucidate the differences between AIH patients' responses and move towards an optimized and more personalized management.

References

1. Dalekos GN, Koskinas J, Papatheodoridis GV. Hellenic Association for the Study of the Liver (HASL) Clinical Practice Guidelines: Autoimmune Hepatitis. *Ann Gastroenterol* 2019;**32**:1-23.
2. Zachou K, Arvaniti P, Lyberopoulou A, Dalekos GN. Impact of genetic and environmental factors on autoimmune hepatitis. *J Transl Autoimmun* 2021;**4**:100125.
3. Terziroli Beretta-Piccoli B, Mieli-Vergani G, Vergani D. HLA, gut microbiome and hepatic autoimmunity. *Front Immunol* 2022;**13**:980768.
4. Zachou K, Arvaniti P, Lyberopoulou A, et al. Altered DNA methylation pattern characterizes the peripheral immune cells of patients with autoimmune hepatitis. *Liver Int* 2022;**42**:1355-1368.
5. Galaski J, Weiler-Normann C, Schakat M, et al. Update of the simplified criteria for autoimmune hepatitis: evaluation of the methodology for immunoserological testing. *J Hepatol* 2021;**74**:312-320.
6. Lohse AW, Sebode M, Bhathal PS, et al. Consensus recommendations for histological criteria of autoimmune hepatitis from the International AIH Pathology Group: Results of a workshop on AIH histology hosted by the European Reference Network on Hepatological Diseases and the European Society of Pathology. *Liver Int* 2022;**42**:1058-1069.
7. Pape S, Snijders RJALM, Gevers TJG, et al; International Autoimmune Hepatitis Group (IAIHG) collaborators(‡). Systematic review of response criteria and endpoints in autoimmune hepatitis by the International Autoimmune Hepatitis Group. *J Hepatol* 2022;**76**:841-849.
8. Whiting PF, Rutjes AW, Westwood ME, et al; QUADAS-2 Group. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med* 2011;**155**:529-536.
9. Shiffman ML. Autoimmune hepatitis: epidemiology, subtypes, and presentation. *Clin Liver Dis* 2024;**28**:1-14.
10. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Autoimmune hepatitis. *J Hepatol* 2015;**63**:971-1004.
11. Mack CL, Adams D, Assis DN, et al. 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. *Hepatology* 2020;**72**:671-722.
12. Lv T, Li M, Zeng N, et al. Systematic review and meta-analysis on the incidence and prevalence of autoimmune hepatitis in Asian, European, and American population. *J Gastroenterol Hepatol* 2019;**34**:1676-1684.
13. Czaja AJ. Global disparities and their implications in the occurrence and outcome of autoimmune hepatitis. *Dig Dis Sci* 2017; **62**:2277-2292.
14. Dalekos GN, Azariadis K, Lygoura V, Arvaniti P, Gampeta S, Gatselis NK. Autoimmune hepatitis in patients aged 70 years or older: disease characteristics, treatment response and outcome. *Liver Int* 2021;**41**:1592-1599.
15. Hahn JW, Yang HR, Moon JS, et al. Global incidence and prevalence of autoimmune hepatitis, 1970-2022: a systematic review and meta-analysis. *EClinicalMedicine* 2023;**65**:102280.
16. Lamba M, Ngu JH, Stedman CAM. Trends in incidence of autoimmune liver diseases and increasing incidence of autoimmune hepatitis. *Clin Gastroenterol Hepatol* 2021;**19**:573-579.
17. Valgeirsson KB, Hreinsson JP, Björnsson ES. Increased incidence of autoimmune hepatitis is associated with wider use of biological drugs. *Liver Int* 2019;**39**:2341-2349.
18. Grønbaek L, Otete H, Ban L, et al. Incidence, prevalence and mortality of autoimmune hepatitis in England 1997-2015. A population-based cohort study. *Liver Int* 2020;**40**:1634-1644.
19. de Boer YS, Gerussi A, van den Brand FF, et al; Dutch Autoimmune Hepatitis Study Group. Association between black race and presentation and liver-related outcomes of patients with autoimmune hepatitis. *Clin Gastroenterol Hepatol* 2019;**17**:1616-1624.
20. Lee DU, Kwon J, Koo C, et al. Clinical implications of gender and race in patients admitted with autoimmune hepatitis: updated analysis of US hospitals. *Frontline Gastroenterol* 2023;**14**:111-123.
21. Grønbaek L, Vilstrup H, Pedersen L, Jepsen P. Extrahepatic autoimmune diseases in patients with autoimmune hepatitis and their relatives: a Danish nationwide cohort study. *Liver Int* 2019;**39**:205-214.
22. Ferronato M, Lalanne C, Quarneti C, et al. The evolving phenotype of autoimmune hepatitis across the millennium: the 40-year experience of a referral centre in Italy. *Liver Int* 2024;**44**:791-798.
23. Grønbæk L, Vilstrup H, Pedersen L, Christensen K, Jepsen P. Family occurrence of autoimmune hepatitis: A Danish nationwide registry-based cohort study. *J Hepatol* 2018;**69**:873-877.
24. Floreani A, De Martin S, Secchi MF, Cazzagon N. Extrahepatic autoimmunity in autoimmune liver disease. *Eur J Intern Med* 2019;**59**:1-7.
25. Tanaka A, Mori M, Matsumoto K, Ohira H, Tazuma S, Takikawa H. Increase trend in the prevalence and male-to-female ratio of primary biliary cholangitis, autoimmune hepatitis, and primary sclerosing cholangitis in Japan. *Hepatol Res* 2019;**49**:881-889.

26. Grønbæk L, Vilstrup H, Jepsen P. Autoimmune hepatitis in Denmark: incidence, prevalence, prognosis, and causes of death. A nationwide registry-based cohort study. *J Hepatol* 2014;**60**:612-617.
27. Schwinge D, Schramm C. Sex-related factors in autoimmune liver diseases. *Semin Immunopathol* 2019;**41**:165-175.
28. Birn-Rydder R, Jensen MD, Jepsen P, Grønbaek L. Extrahepatic autoimmune diseases in autoimmune hepatitis: Effect on mortality. *Liver Int* 2022;**42**:2466-2472.
29. Haggård L, Glimberg I, Lebwohl B, et al. High prevalence of celiac disease in autoimmune hepatitis: Systematic review and meta-analysis. *Liver Int* 2021;**41**:2693-2702.
30. Michel M, Spinelli F, Grambihler A, et al. Health-related quality of life in patients with autoimmune hepatitis. *Qual Life Res* 2021;**30**:2853-2861.
31. Snijders RJ, Milkiewicz P, Schramm C, Gevers TJ. Health-related quality of life in autoimmune hepatitis. *World J Hepatol* 2021;**13**:1642-1652.
32. Schramm C, Wahl I, Weiler-Normann C, et al. Health-related quality of life, depression, and anxiety in patients with autoimmune hepatitis. *J Hepatol* 2014;**60**:618-624.
33. Stravitz RT, Lefkowitch JH, Fontana RJ, et al; Acute Liver Failure Study Group. Autoimmune acute liver failure: proposed clinical and histological criteria. *Hepatology* 2011;**53**:517-526.
34. Muratori P, Carbone M, Stangos G, et al. Clinical and prognostic implications of acute onset of autoimmune hepatitis: an Italian multicentre study. *Dig Liver Dis* 2018;**50**:698-702.
35. Zachou K, Arvaniti P, Azariadis K, et al. Prompt initiation of high-dose i.v. corticosteroids seems to prevent progression to liver failure in patients with original acute severe autoimmune hepatitis. *Hepatol Res* 2019;**49**:96-104.
36. Karkhanis J, Verna EC, Chang MS, et al; Acute Liver Failure Study Group. Steroid use in acute liver failure. *Hepatology* 2014;**59**:612-621.
37. Rahim MN, Liberal R, Miquel R, Heaton ND, Heneghan MA. Acute severe autoimmune hepatitis: Corticosteroids or liver transplantation? *Liver Transpl* 2019;**25**:946-959.
38. Zachou K, Gatselis N, Papadamou G, Rigopoulou EI, Dalekos GN. Mycophenolate for the treatment of autoimmune hepatitis: prospective assessment of its efficacy and safety for induction and maintenance of remission in a large cohort of treatment-naïve patients. *J Hepatol* 2011;**55**:636-646.
39. Gatselis N, Triantos C, Papatheodoridis G, et al. Autoimmune hepatitis (AIH) in Greece: first results from the Hellenic Autoimmune Liver Diseases Study Group of the Hellenic Association for the Study of the Liver (HASL). *J Hepatol* 2023;**78**(S1):S400-S401.
40. Slooter CD, van den Brand FF, Lleo A, et al; Dutch AIH Study Group and International Autoimmune Hepatitis Group. Lack of complete biochemical response in autoimmune hepatitis leads to adverse outcome first report of the IAIHG Retrospective Registry. *Hepatology* 2024;**79**:538-550.
41. Maggiore G, Bernard O, Mosca A, Ballot E, Johanet C, Jacquemin E. Long-term outcomes of patients with type 1 or 2 autoimmune hepatitis presenting in childhood. *J Hepatol* 2023;**78**:979-988.
42. Dalekos GN, Samakidou A, Lyberopoulou A, Banakou E, Gatselis NK. Recent advances in the diagnosis and management of autoimmune hepatitis. *Pol Arch Intern Med* 2022;**132**:16334.
43. Dalekos GN, Gatselis NK. Autoimmune serology testing in clinical practice: An updated roadmap for the diagnosis of autoimmune hepatitis. *Eur J Intern Med* 2023;**108**:9-17.
44. Rigopoulou EI, Zachou K, Gatselis N, Koukoulis GK, Dalekos GN. Autoimmune hepatitis in patients with chronic HBV and HCV infections: patterns of clinical characteristics, disease progression and outcome. *Ann Hepatol* 2013;**13**:127-135.
45. Rigopoulou EI, Gatselis N, Arvaniti P, Koukoulis GK, Dalekos GN. Alcoholic liver disease and autoimmune hepatitis: Sometimes a closer look under the surface is needed. *Eur J Intern Med* 2021;**85**:86-91.
46. Kerkar N, Yanni G. 'De novo' and 'recurrent' autoimmune hepatitis after liver transplantation: A comprehensive review. *J Autoimmun* 2016;**66**:17-24.
47. Demetris AJ, Bellamy C, Hübscher SG, et al. 2016 Comprehensive update of the Banff Working Group on liver allograft pathology: introduction of antibody-mediated rejection. *Am J Transplant* 2016;**16**:2816-2835.
48. Zachou K, Weiler-Normann C, Muratori L, Muratori P, Lohse AW, Dalekos GN. Permanent immunosuppression in SLA/LP-positive autoimmune hepatitis is required although overall response and survival are similar. *Liver Int* 2020;**40**:368-376.
49. European Association for the Study of the Liver. EASL Clinical Practice Guidelines on the management of liver diseases in pregnancy. *J Hepatol* 2023;**79**:768-828.
50. Wang CW, Grab J, Tana MM, Irani RA, Sarkar M. Outcomes of pregnancy in autoimmune hepatitis: a population-based study. *Hepatology* 2022;**75**:5-12.
51. Sharma R, Simon TG, Stephansson O, et al. Pregnancy outcomes in women with autoimmune hepatitis - a nationwide population-based cohort study with histopathology. *Clin Gastroenterol Hepatol* 2023;**21**:103-114.
52. Grønbaek L, Vilstrup H, Jepsen P. Pregnancy and birth outcomes in a Danish nationwide cohort of women with autoimmune hepatitis and matched population controls. *Aliment Pharmacol Ther* 2018;**48**:655-663.
53. Danielsson Borssén, Wallerstedt S, Nyhlin N, et al. Pregnancy and childbirth in women with autoimmune hepatitis is safe, even in compensated cirrhosis. *Scand J Gastroenterol* 2016;**51**:479-485.
54. Gatselis NK, Dalekos GN. Molecular diagnostic testing for primary biliary cholangitis. *Expert Rev Mol Diagn* 2016;**16**:1001-1010.
55. Dalekos GN, Gatselis NK. Variant and specific forms of autoimmune cholestatic liver diseases. *Arch Immunol Ther Exp (Warsz)* 2019;**67**:197-211.
56. Gatselis NK, Zachou K, Loza AJM, et al; International Autoimmune Hepatitis Group. Prevalence and significance of antimitochondrial antibodies in autoimmune hepatitis (AIH): Results from a large multicentre study of the International AIH Group. *Eur J Intern Med* 2023;**116**:43-50.
57. Zellos A, Spoulou V, Roma-Giannikou E, Karentzou O, Dalekos GN, Theodoridou M. Autoimmune hepatitis type-2 and Epstein-Barr virus infection in a toddler: art of facts or an artifact? *Ann Hepatol* 2013;**12**:147-151.
58. Dalekos GN, Wedemeyer H, Obermayer-Straub P, et al. Epitope mapping of cytochrome P4502D6 autoantigen in patients with chronic hepatitis C during alpha-interferon treatment. *J Hepatol* 1999;**30**:366-375.
59. Vento S, Cainelli F, Renzini C, Concia E. Autoimmune hepatitis type 2 induced by HCV and persisting after viral clearance. *Lancet* 1997;**350**:1298-1299.
60. Sgamato C, Rocco A, Compare D, et al. Autoimmune liver diseases and SARS-CoV-2. *World J Gastroenterol* 2023;**29**:1838-1851.
61. Hartl J, Miquel R, Zachou K, et al. Features and outcome of AIH patients without elevation of IgG. *JHEP Rep* 2020;**2**:100094.
62. Andrade RJ, Aithal GP, de Boer YS, et al; IAIHG and EASL DHILI Consortium. Nomenclature, diagnosis and management of drug-induced autoimmune-like hepatitis (DI-ALH): An expert opinion meeting report. *J Hepatol* 2023;**79**:853-866.
63. Dalekos GN, Gatselis NK, Zachou K, Koukoulis GK. NAFLD and autoimmune hepatitis: Do not judge a book by its cover. *Eur J Intern Med* 2020;**75**:1-9.

64. Takahashi A, Arinaga-Hino T, Ohira H, et al; Japan AIH Study Group (JAIHSG). Non-alcoholic fatty liver disease in patients with autoimmune hepatitis. *JGH Open* 2018;**2**:54-58.
65. Zachou K, Azariadis K, Lytvyak E, et al; International Autoimmune Hepatitis Group (IAIHG). Treatment responses and outcomes in patients with autoimmune hepatitis and concomitant features of non-alcoholic fatty liver disease. *JHEP Rep* 2023;**5**:100778.
66. Rinella ME, Lazarus JV, Ratziu V, et al; NAFLD Nomenclature consensus group. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. *Hepatology* 2023;**78**:1966-1986.
67. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Drug-induced liver injury. *J Hepatol* 2019;**70**:1222-1261.
68. Efe C, Kulkarni AV, Terziroli Beretta-Piccoli B, et al. Liver injury after SARS-CoV-2 vaccination: features of immune-mediated hepatitis, role of corticosteroid therapy and outcome. *Hepatology* 2022;**76**:1576-1586.
69. Björnsson ES, Medina-Caliz I, Andrade RJ, Lucena MI. Setting up criteria for drug-induced autoimmune-like hepatitis through a systematic analysis of published reports. *Hepatol Commun* 2022;**6**:1895-1909.
70. Hennes EM, Zeniya M, Czaja AJ, et al; International Autoimmune Hepatitis Group. Simplified criteria for the diagnosis of autoimmune hepatitis. *Hepatology* 2008;**48**:169-176.
71. Rinella ME, Neuschwander-Tetri BA, Siddiqui MS, et al. AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease. *Hepatology* 2023;**77**:1797-1835.
72. Chen J, Eslick GD, Weltman M. Systematic review with meta-analysis: clinical manifestations and management of autoimmune hepatitis in the elderly. *Aliment Pharmacol Ther* 2014;**39**:117-124.
73. Lindor KD, Bowlus CL, Boyer J, Levy C, Mayo M. Primary Biliary Cholangitis: 2018 Practice Guidance from the American Association for the Study of Liver Diseases. *Hepatology* 2019;**69**:394-419.
74. European Association for the Study of the Liver. EASL Clinical Practice Guidelines on sclerosing cholangitis. *J Hepatol* 2022;**77**:761-806.
75. Chazouillères O, Wendum D, Serfaty L, Montembault S, Rosmorduc O, Poupon R. Primary biliary cirrhosis-autoimmune hepatitis overlap syndrome: clinical features and response to therapy. *Hepatology* 1998;**28**:296-301.
76. Zhang W, De D, Mohammed KA, et al. New scoring classification for primary biliary cholangitis-autoimmune hepatitis overlap syndrome. *Hepatol Commun* 2018;**2**:245-253.
77. Yang F, Wang Q, Wang Z, et al. The natural history and prognosis of primary biliary cirrhosis with clinical features of autoimmune hepatitis. *Clin Rev Allergy Immunol* 2016;**50**:114-123.
78. Rojas CP, Bodicharla R, Campuzano-Zuluaga G, Hernandez L, Rodriguez MM. Autoimmune hepatitis and primary sclerosing cholangitis in children and adolescents. *Fetal Pediatr Pathol* 2014;**33**:202-209.
79. Milkiewicz P, Krawczyk M, Wunsch E, Ponsioen C, Hirschfield GM, Hubscher SG. Primary sclerosing cholangitis with features of autoimmune hepatitis: exploring the global variation in management. *Hepatol Commun* 2020;**4**:399-408.
80. Dalekos GN, Gatselis NK. Primary sclerosing cholangitis – autoimmune hepatitis overlap. In: M. Eric Gershwin, John M. Vierling, Atsushi Tanaka, and Michael P. Manns (Eds). Liver Immunology: Principles and Practice, Springer International Publishing, Cham, 2020, pp. 359-373.
81. Weismuller TJ, Trivedi PJ, Bergquist A, et al. Patient age, sex, and inflammatory bowel disease phenotype associate with course of primary sclerosing cholangitis. *Gastroenterology* 2017;**152**:1975-1984.
82. Tiniakos DG, Brain JG, Bury YA. Role of histopathology in autoimmune hepatitis. *Dig Dis* 2015;**33 Suppl** 2:53-64.
83. Mieli-Vergani G, Vergani D, Baumann U, et al. Diagnosis and management of pediatric autoimmune liver disease: ESPGHAN Hepatology Committee Position Statement. *J Pediatr Gastroenterol Nutr* 2018;**66**:345-360.
84. Zenouzi R, Lohse AW. Long-term outcome in PSC/AIH "overlap syndrome": does immunosuppression also treat the PSC component? *J Hepatol* 2014;**61**:1189-1191.
85. Lewin M, Vilgrain V, Ozenne V, et al. Prevalence of sclerosing cholangitis in adults with autoimmune hepatitis: a prospective magnetic resonance imaging and histological study. *Hepatology* 2009;**50**:528-537.
86. Rigopoulou EI, Dalekos GN. Current trends and characteristics of hepatocellular carcinoma in patients with autoimmune liver diseases. *Cancers (Basel)* 2021;**13**:1023.
87. Jensen MD, Jepsen P, Vilstrup H, Grønbæk L. Increased cancer risk in autoimmune hepatitis: a Danish nationwide cohort study. *Am J Gastroenterol* 2022;**117**:129-137.
88. Tansel A, Katz LH, El-Serag HB, et al. Incidence and determinants of hepatocellular carcinoma in autoimmune hepatitis: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2017;**15**:1207-1217.
89. Colapietro F, Maisonneuve P, Lytvyak E, et al; International Autoimmune Hepatitis Group. Incidence and predictors of hepatocellular carcinoma in patients with autoimmune hepatitis. *J Hepatol* 2024;**80**:53-61.
90. Singal AG, Llovet JM, Yarchoan M, et al. AASLD practice guidance on prevention, diagnosis, and treatment of hepatocellular carcinoma. *Hepatology* 2023;**78**:1922-1965.
91. Sebode M, Weiler-Normann C, Liwinski T, Schramm C. Autoantibodies in autoimmune liver disease-clinical and diagnostic relevance. *Front Immunol* 2018;**9**:609.
92. Bonroy C, Vercammen M, Fierz W, et al; European Federation of Laboratory Medicine (EFLM) Working Group "Autoimmunity Testing," the European Autoimmune Standardization Initiative (EASI) and International Consensus on Antinuclear Antibody Patterns (ICAP). Detection of antinuclear antibodies: recommendations from EFLM, EASI and ICAP. *Clin Chem Lab Med* 2023;**61**:1167-1198.
93. Zhang WC, Zhao FR, Chen J, Chen WX. Meta-analysis: diagnostic accuracy of antinuclear antibodies, smooth muscle antibodies and antibodies to a soluble liver antigen/liver pancreas in autoimmune hepatitis. *PLoS One* 2014;**9**:e92267.
94. Zachou K, Gampeta S, Gatselis NK, et al. Anti-SLA/LP alone or in combination with anti-Ro52 and fine specificity of anti-Ro52 antibodies in patients with autoimmune hepatitis. *Liver Int* 2015;**35**:660-672.
95. Kirstein MM, Metzler F, Geiger E, et al. Prediction of short- and long-term outcome in patients with autoimmune hepatitis. *Hepatology* 2015;**62**:1524-1535.
96. Montano-Loza AJ, Shums Z, Norman GL, Czaja AJ. Prognostic implications of antibodies to Ro/SSA and soluble liver antigen in type 1 autoimmune hepatitis. *Liver Int* 2012;**32**:85-92.
97. Oikonomou KG, Zachou K, Dalekos GN. Alpha-actinin: a multidisciplinary protein with important role in B-cell driven autoimmunity. *Autoimmun Rev* 2011;**10**:389-396.
98. Zachou K, Oikonomou K, Renaudineau Y, et al. Anti-α actinin antibodies as new predictors of response to treatment in autoimmune hepatitis type 1. *Aliment Pharmacol Ther* 2012;**35**:116-125.
99. Muratori P, Granito A, Pappas G, et al. The serological profile of the autoimmune hepatitis/primary biliary cirrhosis overlap syndrome. *Am J Gastroenterol* 2009;**104**:1420-1425.
100. Pisetsky DS, Lipsky PE. New insights into the role of antinuclear

antibodies in systemic lupus erythematosus. *Nat Rev Rheumatol* 2020;**16**:565-579.
101. Granito A, Muratori L, Tovoli F, Muratori P. Diagnostic role of anti-dsDNA antibodies: do not forget autoimmune hepatitis. *Nat Rev Rheumatol* 2021;**17**:244.
102. Taubert R, Engel B, Diestelhorst J, et al; UK-AIH Consortium. Quantification of polyreactive immunoglobulin G facilitates the diagnosis of autoimmune hepatitis. *Hepatology* 2022;**75**:13-27.
103. Engel B, Diestelhorst J, Hupa-Breier KL, et al. Detection of polyreactive immunoglobulin G facilitates diagnosis in children with autoimmune hepatitis. *Hepatol Int* 2024;**18**:1214-1226.
104. Bengtsson AA, Trygg J, Wuttge DM, et al. Metabolic profiling of systemic lupus erythematosus and comparison with primary Sjögren's syndrome and systemic sclerosis. *PLoS One* 2016;**11**:e0159384.
105. Dimou A, Zachou K, Kostara C, et al. NMR-based metabolomic signature: an important tool for the diagnosis and study of pathogenesis of autoimmune hepatitis. *Hepatology* 2024;**80**:266-277.
106. Harrington C, Krishnan S, Mack CL, Cravedi P, Assis DN, Levitsky J. Noninvasive biomarkers for the diagnosis and management of autoimmune hepatitis. *Hepatology* 2022;**76**:1862-1879.
107. Hartl J, Denzer U, Ehlken H, et al. Transient elastography in autoimmune hepatitis: timing determines the impact of inflammation and fibrosis. *J Hepatol* 2016;**65**:769-775.
108. Guo L, Zheng L, Hu L, Zhou H, Yu L, Liang W. Transient elastography (FibroScan) performs better than non-invasive markers in assessing liver fibrosis and cirrhosis in autoimmune hepatitis patients. *Med Sci Monit* 2017;**23**:5106-5112.
109. Xu Q, Sheng L, Bao H, et al. Evaluation of transient elastography in assessing liver fibrosis in patients with autoimmune hepatitis. *J Gastroenterol Hepatol* 2017;**32**:639-644.
110. Hartl J, Ehlken H, Sebode M, et al. Usefulness of biochemical remission and transient elastography in monitoring disease course in autoimmune hepatitis. *J Hepatol* 2018;**68**:754-763.
111. Zachou K, Lygoura V, Arvaniti P, et al. FibroMeter scores for the assessment of liver fibrosis in patients with autoimmune liver diseases. *Ann Hepatol* 2021;**22**:100285.
112. Janik MK, Kruk B, Szczepankiewicz B, et al. Measurement of liver and spleen stiffness as complementary methods for assessment of liver fibrosis in autoimmune hepatitis. *Liver Int* 2021;**41**:348-356.
113. Zhang X, Jain D. The many faces and pathologic diagnostic challenges of autoimmune hepatitis. *Hum Pathol* 2023;**132**:114-125.
114. Colapietro F, Masetti C, Pugliese N, Lleo A. Recommendations for histological criteria of autoimmune hepatitis from the international AIH pathology: Validation on a monocentric cohort. *Liver Int* 2022;**42**:2583-2584.
115. Ishak K, Baptista A, Bianchi L, et al. Histological grading and staging of chronic hepatitis. *J Hepatol* 1995;**22**:696-699.
116. Zen Y, Notsumata K, Tanaka N, Nakanuma Y. Hepatic centrilobular zonal necrosis with positive antinuclear antibody: a unique subtype or early disease of autoimmune hepatitis? *Hum Pathol* 2007;**38**:1669-1675.
117. Dienes HP, Erberich H, Dries V, Schirmacher P, Lohse A. Autoimmune hepatitis and overlap syndromes. *Clin Liver Dis* 2002;**6**:349-362, vi.
118. Czaja AJ, Muratori P, Muratori L, Carpenter HA, Bianchi FB. Diagnostic and therapeutic implications of bile duct injury in autoimmune hepatitis. *Liver Int* 2004;**24**:322-329.
119. de Boer YS, van Nieuwkerk CM, Witte BI, Mulder CJ, Bouma G, Bloemena E. Assessment of the histopathological key features in autoimmune hepatitis. *Histopathology* 2015;**66**:351-362.
120. Beisel C, Weiler-Norman C, Teufel A, Lohse AW. Association of autoimmune hepatitis and systemic lupus erythematodes: a case series and review of the literature. *World J Gastronterol* 2014;**20**:12662-12667.
121. Tani C, Elefante E, Arnaud L, et al. Rare clinical manifestations in systemic lupus erythematosus: a review on frequency and clinical presentation. *Clin Exp Rheumatol* 2022;**40 Suppl** 134:93-102.
122. Sood V, Lal BB, Rawat D, et al. Spectrum of pediatric autoimmune liver disease and validation of its diagnostic scores in Indian children. *J Pediatr Gastroenterol Nutr* 2018;**67**:e65-e72.
123. Imanieh M, Farzaneh NA, Dehghani SM, Shahrebabak MG, Hosseinabadi SH. Evaluation of validity and efficiency of diagnostic criteria in autoimmune hepatitis in children. *Turk J Gastroenterol* 2021;**32**:526-531.
124. Rigopoulou EI, Davies ET, Pares A, et al. Prevalence and clinical significance of isotype specific antinuclear antibodies in primary biliary cirrhosis. *Gut* 2005;**54**:528-532.
125. Kirk AP, Jain S, Pocock S, Thomas HC, Sherlock S. Late results of the Royal Free Hospital prospective controlled trial of prednisolone therapy in hepatitis B surface antigen negative chronic active hepatitis. *Gut* 1980;**21**:78-83.
126. Lamers MM, van Oijen MG, Pronk M, Drenth JP. Treatment options for autoimmune hepatitis: a systematic review of randomized controlled trials. *J Hepatol* 2010;**53**:191-198.
127. Feld JJ, Dinh H, Arenovich T, Marcus VA, Wanless IR, Heathcote EJ. Autoimmune hepatitis: effect of symptoms and cirrhosis on natural history and outcome. *Hepatology* 2005;**42**:53-62.
128. Czaja AJ. Features and consequences of untreated type 1 autoimmune hepatitis. *Liver Int* 2009;**29**:816-823.
129. Schmidt C, Stürznickel J, Strahl A, et al. Bone microarchitecture in patients with autoimmune hepatitis. *J Bone Miner Res* 2021;**36**:1316-1325.
130. Schmidt T, Schmidt C, Strahl A, et al. A system to determine risk of osteoporosis in patients with autoimmune hepatitis. *Clin Gastroenterol Hepatol* 2020;**18**:226-233.
131. Choi J, Choi GH, Lee D, et al. Long-term clinical outcomes in patients with autoimmune hepatitis according to treatment response in Asian country. *Liver Int* 2019;**39**:985-994.
132. Pape S, Gevers TJG, Vrolijk JM, et al. Rapid response to treatment of autoimmune hepatitis associated with remission at 6 and 12 months. *Clin Gastroenterol Hepatol* 2020;**18**:1609-1617.
133. Pape S, Gevers TJG, Belias M, et al. Predniso(lo)ne dosage and chance of remission in patients with autoimmune hepatitis. *Clin Gastroenterol Hepatol* 2019;**17**:2068-2075.
134. van Gerven NM, Verwer BJ, Witte BI, et al; Dutch Autoimmune Hepatitis Working Group. Relapse is almost universal after withdrawal of immunosuppressive medication in patients with autoimmune hepatitis in remission. *J Hepatol* 2013;**58**:141-147.
135. Schregel I, Papp M, Sipeki N, et al; European Reference Network (ERN) RARE-LIVER. Unmet needs in autoimmune hepatitis: results of the prospective multicentre European Reference Network Registry (R-LIVER). *Liver Int* 2024. doi: 10.1111/liv.16035
136. Summerskill WH, Korman MG, Ammon HV, Baggenstoss AH. Prednisone for chronic active liver disease: dose titration, standard dose, and combination with azathioprine compared. *Gut* 1975;**16**:876-883.
137. Johnson PJ, McFarlane IG, Williams R. Azathioprine for long-term maintenance of remission in autoimmune hepatitis. *N Engl J Med* 1995;**333**:958-963.
138. Manns MP, Woynarowski M, Kreisel W, et al; European AIH-BUC-Study Group. Budesonide induces remission more effectively than prednisone in a controlled trial of patients with autoimmune hepatitis. *Gastroenterology* 2010;**139**:1198-1206.
139. Woynarowski M, Nemeth A, Baruch Y, et al; European Autoimmune Hepatitis-Budesonide Study Group. Budesonide versus prednisone with azathioprine for the treatment of

autoimmune hepatitis in children and adolescents. *J Pediatr* 2013;**163**:1347-1353.e1.
140. Díaz-González Á, Hernández-Guerra M, Pérez-Medrano I, et al; ColHai Registry. Budesonide as first-line treatment in patients with autoimmune hepatitis seems inferior to standard predniso(lo)ne administration. *Hepatology* 2023;**77**:1095-1105.
141. Naffouje R, Grover P, Yu H, et al. Anti-tumor potential of IMP dehydrogenase inhibitors: a century-long story. *Cancers (Basel)* 2019;**11**:1346.
142. Hlivko JT, Shiffman ML, Stravitz RT, et al. A single center review of the use of mycophenolate mofetil in the treatment of autoimmune hepatitis. *Clin Gastroenterol Hepatol* 2008;**6**:1036-1040.
143. Zachou K, Gatselis NK, Arvaniti P, et al. A real-world study focused on the long-term efficacy of mycophenolate mofetil as first-line treatment of autoimmune hepatitis. *Aliment Pharmacol Ther* 2016;**43**:1035-1047.
144. Yu ZJ, Zhang LL, Huang TT, Zhu JS, He ZB. Comparison of mycophenolate mofetil with standard treatment for autoimmune hepatitis: a meta-analysis. *Eur J Gastroenterol Hepatol* 2019;**31**:873-877.
145. Dalekos GN, Arvaniti P, Gatselis NK, et al. First results from a propensity matching trial of mycophenolate mofetil vs. azathioprine in treatment-naive AIH patients. *Front Immunol* 2022;**12**:798602.
146. Dalekos GN, Arvaniti P, Gatselis NK, et al. Long-term results of mycophenolate mofetil vs. azathioprine use in individuals with autoimmune hepatitis. *JHEP Rep* 2022;**4**:100601.
147. Snijders RJALM, Stoelinga AEC, Gevers TJG, et al; Dutch Autoimmune Hepatitis Working Group. An open-label randomised-controlled trial of azathioprine vs. mycophenolate mofetil for the induction of remission in treatment-naive autoimmune hepatitis. *J Hepatol* 2024;**80**:576-585.
148. Lohse AW, Sebode M, Jørgensen MH, et al. Second-line and third-line therapy for autoimmune hepatitis: a position statement from the European Reference Network on Hepatological Diseases and the International Autoimmune Hepatitis Group. *J Hepatol* 2020;**73**:1496-1506.
149. Harrison L, Gleeson D. Stopping immunosuppressive treatment in autoimmune hepatitis (AIH): is it justified (and in whom and when)? *Liver Int* 2019;**39**:610-620.
150. Moon AM, Spiritos Z, King LY, Barritt AS IV. Immunosuppression in autoimmune hepatitis: Is there an end game? *Am J Gastroenterol* 2020;**115**:498-501.
151. Hartl J, Ehlken H, Weiler-Normann C, et al. Patient selection based on treatment duration and liver biochemistry increases success rates after treatment withdrawal in autoimmune hepatitis. *J Hepatol* 2015;**62**:642-646.
152. Laschtowitz A, Zachou K, Lygoura V, et al. Histological activity despite normal ALT and IgG serum levels in patients with autoimmune hepatitis and cirrhosis. *JHEP Rep* 2021;**3**:100321.
153. Lüth S, Herkel J, Kanzler S, et al. Serologic markers compared with liver biopsy for monitoring disease activity in autoimmune hepatitis. *J Clin Gastroenterol* 2008;**42**:926-930.
154. Dhaliwal HK, Hoeroldt BS, Dube AK, et al. Long-term prognostic significance of persisting histological activity despite biochemical remission in autoimmune hepatitis. *Am J Gastroenterol* 2015;**110**:993-999.
155. Olivas I, Arvaniti P, Gabeta S, et al. Liver stiffness after 6 months of treatment predicts clinical outcomes in autoimmune hepatitis. *JHEP Rep* 2024 (in press) DOI: https://doi.org/10.1016/j.jhepr.2024.101213.
156. Deneau M, Book LS, Guthery SL, Jensen MK. Outcome after discontinuation of immunosuppression in children with autoimmune hepatitis: a population-based study. *J Pediatr* 2014;**164**:714-719.
157. Rodrigues AT, Liu PM, Fagundes ED, et al. Clinical characteristics and prognosis in children and adolescents with autoimmune hepatitis and overlap syndrome. *J Pediatr Gastroenterol Nutr* 2016;**63**:76-81.
158. Sheiko MA, Sundaram SS, Capocelli KE, Pan Z, McCoy AM, Mack CL. Outcomes in pediatric autoimmune hepatitis and significance of azathioprine metabolites. *J Pediatr Gastroenterol Nutr* 2017;**65**:80-85.
159. Di Giorgio A, Hadzic N, Dhawan A, et al. Seamless management of juvenile autoimmune liver disease: long-term medical and social outcome. *J Pediatr* 2020;**218**:121-129.
160. Czaja AJ. Late relapse of type 1 autoimmune hepatitis after corticosteroid withdrawal. *Dig Dis Sci* 2010;**55**:1761-1769.
161. Zachou K, Azariadis K, Sofia M, et al. Acute non-A, non-B, non-C hepatitis differences and similarities between hepatitis E virus infection and autoimmune hepatitis, with phylogenetic analysis of hepatitis E virus in humans and wild boars. *Ann Gastroenterol* 2022;**35**:532-540.
162. Pape S, Gevers TJG, Vrolijk JM, et al. High discontinuation rate of azathioprine in autoimmune hepatitis, independent of time of treatment initiation. *Liver Int* 2020;**40**:2164-2171.
163. Candels LS, Rahim MN, Shah S, Heneghan MA. Towards personalised medicine in autoimmune hepatitis: Measurement of thiopurine metabolites results in higher biochemical response rates. *J Hepatol* 2021;**75**:324-332.
164. Czaja AJ. Review article: opportunities to improve and expand thiopurine therapy for autoimmune hepatitis. *Aliment Pharmacol Ther* 2020;**51**:1286-1304.
165. Santiago P, Schwartz I, Tamariz L, Levy C. Systematic review with meta-analysis: mycophenolate mofetil as a second-line therapy for autoimmune hepatitis. *Aliment Pharmacol Ther* 2019;**49**:830-839.
166. Nicoll AJ, Roberts SK, Lim R, et al; ALA Clinical Research Network, Gastroenterological Society of Australia. Beneficial response to mycophenolate mofetil by patients with autoimmune hepatitis who have failed standard therapy, is predicted by older age and lower immunoglobulin G and INR levels. *Aliment Pharmacol Ther* 2019;**49**:1314-1322.
167. Kolev M, Diem S, Diem L, et al. Mycophenolate mofetil as second line treatment in autoimmune hepatitis - A retrospective single center analysis. *J Transl Autoimmun* 2022;**5**:100172.
168. Arvaniti P, Olivas I, Rodriguez-Tajes S, Dalekos GN, Londoño MC. Second- and third-line treatment agents in autoimmune hepatitis (AIH): where do we stand? *Explor Dig Dis* 2024;**3**:92-106.
169. Hübener S, Oo YH, Than NN, et al. Efficacy of 6-mercaptopurine as second-line treatment for patients with autoimmune hepatitis and azathioprine intolerance. *Clin Gastroenterol Hepatol* 2016;**14**:445-453.
170. Efe C, Hagström H, Ytting H, et al. Efficacy and safety of mycophenolate mofetil and tacrolimus as second-line therapy for patients with autoimmune hepatitis. *Clin Gastroenterol Hepatol* 2017;**15**:1950-1956.
171. De Lemos-Bonotto M, Valle-Tovo C, Costabeber AM, Mattos AA, Azeredo-da-Silva ALF. A systematic review and meta-analysis of second-line immunosuppressants for autoimmune hepatitis treatment. *Eur J Gastroenterol Hepatol* 2018;**30**:212-216.
172. Zizzo AN, Valentino PL, Shah PS, Kamath BM. Second-line agents in pediatric patients with autoimmune hepatitis: a systematic review and meta-analysis. *J Pediatr Gastroenterol Nutr* 2017;**65**:6-15.
173. Terziroli Beretta-Piccoli B, Mieli-Vergani G, Vergani D. Autoimmune hepatitis: standard treatment and systematic review of alternative treatments. *World J Gastroenterol* 2017;**23**:6030-6048.
174. Pape S, Nevens F, Verslype C, Mertens C, Drenth JPH, Tjwa ETTL.

Profiling the patient with autoimmune hepatitis on calcineurin inhibitors: a real-world-experience. *Eur J Gastroenterol Hepatol* 2020;**32**:727-732.
175. de Boer YS, van Gerven NM, de Boer NK, Mulder CJ, Bouma G, van Nieuwkerk CM. Allopurinol safely and effectively optimises thiopurine metabolites in patients with autoimmune hepatitis. *Aliment Pharmacol Ther* 2013;**37**:640-646.
176. Dhaliwal HK, Anderson R, Thornhill EL, et al. Clinical significance of azathioprine metabolites for the maintenance of remission in autoimmune hepatitis. Hepatology 2012;56:1401-1408.
177. Weltzsch JP, Bartel CF, Waldmann M, et al. Optimizing thiopurine therapy in autoimmune hepatitis: A multi-center study on monitoring metabolite profiles and co-therapy with allopurinol. *Hepatology* 2024 (in press) doi: *10.1097/HEP.0000000000000940*.
178. Stoelinga AEC, Tushuizen ME, van den Hout WB, et al; Dutch Autoimmune Hepatitis Group. Tacrolimus versus mycophenolate for AutoImmune hepatitis patients with incompLete response on first-line therapy (TAILOR study): a study protocol for a phase III, open-label, multicentre, randomised controlled trial. *Trials* 2024;**25**:61.
179. Haridy J, Nicoll A, Sood S. Methotrexate therapy for autoimmune hepatitis. *Clin Gastroenterol Hepatol* 2018;**16**:288-289.
180. Weiler-Normann C, Schramm C, Quaas A, et al. Infliximab as a rescue treatment in difficult-to-treat autoimmune hepatitis. *J Hepatol* 2013;**58**:529-534.
181. Roberts SK, Strasser SI, Nicoll AJ, et al; ALA Clinical Research Network. Efficacy and safety profile of calcineurin inhibitor salvage therapy in autoimmune hepatitis. *Scand J Gastroenterol* 2020;**55**:1309-1317.
182. Than NN, Hodson J, Schmidt-Martin D, et al. Efficacy of rituximab in difficult-to-manage autoimmune hepatitis: results from the International Autoimmune Hepatitis Group. *JHEP Rep* 2019;**1**:437-445.
183. Arvaniti P, Giannoulis G, Gabeta S, Zachou K, Koukoulis GK, Dalekos GN. Belimumab is a promising third-line treatment option for refractory autoimmune hepatitis. *JHEP Rep* 2020;**2**:100123.
184. Kolev M, Sarbu AC, Möller B, Maurer B, Kollert F, Semmo N. Belimumab treatment in autoimmune hepatitis and primary biliary cholangitis - a case series. *J Transl Autoimmun* 2023;**6**:100189.
185. Terziroli Beretta-Piccoli B, Buescher G, Dalekos G, et al. Hepatic safety and efficacy of immunomodulatory drugs used in patients with autoimmune hepatitis. *J Autoimmun* 2023;**140**:103113.
186. Vollmer O, Felten R, Mertz P, Lebrun-Vignes B, Salem JE, Arnaud L. Characterization of auto-immune hepatitis associated with the use of anti-TNFα agents: An analysis of 389 cases in VigiBase. *Autoimmun Rev* 2020;**19**:102460.
187. Fragoulis GE, Nikiphorou E, Dey M, et al. 2022 EULAR recommendations for screening and prophylaxis of chronic and opportunistic infections in adults with autoimmune inflammatory rheumatic diseases. *Ann Rheum Dis* 2023;**82**:742-753.
188. Kucharzik T, Ellul P, Greuter T, et al. ECCO Guidelines on the prevention, diagnosis, and management of infections in inflammatory bowel disease. *J Crohns Colitis* 2021;**15**:879-913.
189. Sockalingam S, Blank D, Abdelhamid N, Abbey SE, Hirschfield GM. Identifying opportunities to improve management of autoimmune hepatitis: evaluation of drug adherence and psychosocial factors. *J Hepatol* 2012;**57**:1299-1304.
190. Manteuffel M, Williams S, Chen W, Verbrugge RR, Pittman DG, Steinkellner A. Influence of patient sex and gender on medication use, adherence, and prescribing alignment with guidelines. *J Womens Health (Larchmt)* 2014;**23**:112-119.
191. Janik MK, Wunsch E, Raszeja-Wyszomirska J, et al. Autoimmune hepatitis exerts a profound, negative effect on health-related quality of life: A prospective, single-centre study. *Liver Int* 2019;**39**:215-221.
192. Kelly D. Theory to reality: the role of the transition nurse coordinator. *Br J Nurs* 2014;**23**:888, 890, 892-894.
193. Sonthalia N, Rathi PM, Jain SS, et al. Natural history and treatment outcomes of severe autoimmune hepatitis. *J Clin Gastroenterol* 2017;**51**:548-556.
194. European Association for the Study of the Liver. EASL Clinical Practical Guidelines on the management of acute (fulminant) liver failure. *J Hepatol* 2017;**66**:1047-1081.
195. European Association for the Study of the Liver. EASL Clinical Practice Guidelines on acute-on-chronic liver failure. *J Hepatol* 2023;**79**:461-491.
196. Rahim MN, Miquel R, Heneghan MA. Approach to the patient with acute severe autoimmune hepatitis. *JHEP Rep* 2020;**2**:100149.
197. Anand L, Choudhury A, Bihari C, et al; APASL ACLF (APASL ACLF Research Consortium) Working Party. Flare of autoimmune hepatitis causing acute on chronic liver failure: diagnosis and response to corticosteroid therapy. *Hepatology* 2019;**70**:587-596.
198. Sharma S, Agarwal S, Gopi S, et al. Determinants of outcomes in autoimmune hepatitis presenting as acute on chronic liver failure without extrahepatic organ dysfunction upon treatment with steroids. *J Clin Exp Hepatol* 2021;**11**:171-180.
199. De Martin E, Coilly A, Chazouillères O, et al; FILFOIE consortium – France. Early liver transplantation for corticosteroid non-responders with acute severe autoimmune hepatitis: the SURFASA score. *J Hepatol* 2021;**74**:1325-1334.
200. Téllez L, Sánchez Rodríguez E, Rodríguez de Santiago E, et al. Early predictors of corticosteroid response in acute severe autoimmune hepatitis: a nationwide multicenter study. *Aliment Pharmacol Ther* 2022;**56**:131-143.
201. Di Giorgio A, Bravi M, Bonanomi E, et al. Fulminant hepatic failure of autoimmune aetiology in children. *J Pediatr Gastroenterol Nutr* 2015;**60**:159-164.
202. Ramachandran J, Sajith KG, Pal S, Rasak JV, Prakash JA, Ramakrishna B. Clinicopathological profile and management of severe autoimmune hepatitis. *Trop Gastroenterol* 2014;**35**:25-31.
203. Weiler-Normann C, Lohse AW. Acute autoimmune hepatitis: many open questions. *J Hepatol* 2014;**61**:727-729.
204. Rahim MN, Ran S, Shah S, Hughes S, Heneghan MA. Safety and efficacy of budesonide during pregnancy in women with autoimmune hepatitis. *Hepatology* 2021;**73**:2601-2606.
205. Chung YY, Heneghan MA. Autoimmune hepatitis in pregnancy: pearls and pitfalls. *Hepatology* 2022;**76**:502-517.
206. Si T, Huang Z, Hegarty R, Ma Y, Heneghan MA. Systematic review with meta-analysis: outcomes of pregnancy in patients with autoimmune hepatitis. *Aliment Pharmacol Ther* 2022;**55**:1368-1378.
207. Nayagam JS, Weismüller TJ, Milkiewicz P, et al; International PSC Study Group (IPSCSG). Maternal liver-related symptoms during pregnancy in primary sclerosing cholangitis. *JHEP Rep* 2024;**6**:100951.
208. Chalasani NP, Maddur H, Russo MW, Wong RJ, Reddy KR; Practice Parameters Committee of the American College of Gastroenterology. ACG Clinical Guideline: diagnosis and management of idiosyncratic drug-induced liver injury. *Am J Gastroenterol* 2021;**116**:878-898.
209. Fontana RJ, Liou I, Reuben A, et al. AASLD practice guidance on drug, herbal, and dietary supplement-induced liver injury. *Hepatology* 2023;**77**:1036-1065.
210. Björnsson ES, Vucic V, Stirnimann G, Robles-Díaz M. Role of corticosteroids in drug-induced liver injury. A systematic review. *Front Pharmacol* 2022;**13**:820724.
211. Niu H, Ma J, Medina-Caliz I, et al. Potential benefit and lack of

serious risk from corticosteroids in drug-induced liver injury: an international, multicentre, propensity score-matched analysis. *Aliment Pharmacol Ther* 2023;**57**:886-896.
212. Martínez-Casas OY, Díaz-Ramírez GS, Marín-Zuluaga JI, et al. Differential characteristics in drug-induced autoimmune hepatitis. *JGH Open* 2018;**2**:97-104.
213. Weber S, Benesic A, Rotter I, Gerbes AL. Early ALT response to corticosteroid treatment distinguishes idiosyncratic drug-induced liver injury from autoimmune hepatitis. *Liver Int* 2019;**39**:1906-1917.
214. Björnsson HK, Gudbjornsson B, Björnsson ES. Infliximab-induced liver injury: clinical phenotypes, autoimmunity and the role of corticosteroid treatment. *J Hepatol* 2022;**76**:86-92.
215. Ofori E, Ramai D, Ona MA, Reddy M. Autoimmune hepatitis in the setting of human immunodeficiency virus infection: A case series. *World J Hepatol* 2017;**9**:1367-1371.
216. Mubder M, Azab M, Jayaraj M, et al. Autoimmune hepatitis in patients with human immunodeficiency virus infection: A systematic review of the published literature. *Medicine (Baltimore)* 2019;**98**:e17094.
217. Saleem S, Inayat F, Khan AA, et al. The demographics of autoimmune hepatitis in human immunodeficiency virus-infected patients: a United States cross-sectional study. *Prz Gastronterol* 2023;**18**:93-99.
218. Murunga E, Andersson M, van Rensburg C. Autoimmune hepatitis: a manifestation of immune reconstitution inflammatory syndrome in HIV infected patients? *Scand J Gastroenterol* 2016;**51**:814-818.
219. Ozaslan E, Efe C, Heurgué-Berlot A, et al. Factors associated with response to therapy and outcome of patients with primary biliary cirrhosis with features of autoimmune hepatitis. *Clin Gastroenterol Hepatol* 2014;**12**:863-869.
220. Freedman BL, Danford CJ, Patwardhan V, Bonder A. Treatment of overlap syndromes in autoimmune liver disease: a systematic review and meta-analysis. *J Clin Med* 2020;**9**:1449.
221. Schulze K, Weismüller TJ, Bubenheim M, et al; German PSC Study Group. Criteria used in clinical practice to guide immunosuppressive treatment in patients with primary sclerosing cholangitis. *PLoS One* 2015;**10**:e0140525.
222. Zenouzi R, Weismüller TJ, Jørgensen KK, et al. No evidence that azathioprine increases risk of cholangiocarcinoma in patients with primary sclerosing cholangitis. *Clin Gastroenterol Hepatol* 2016;**14**:1806-1812.
223. Georgiadou SP, Zachou K, Liaskos C, Gabeta S, Rigopoulou EI, Dalekos GN. Occult hepatitis B virus infection in patients with autoimmune liver diseases. *Liver Int* 2009;**29**:434-442.
224. Simoes CC, Saldarriaga OA, Utay NS, et al. Direct-acting antiviral treatment of patients with hepatitis C resolves serologic and histopathologic features of autoimmune hepatitis. *Hepatol Commun* 2019;**3**:1113-1123.
225. Rosen D, Chu J, Morotti R, et al. Hepatitis C virus-autoimmune hepatitis overlap syndrome in an adolescent. *J Pediatr Gastroenterol Nutr* 2015;**61**:e7-e9.
226. Dalekos GN, Gatselis NK, Koukoulis GK. Non-alcoholic steatohepatitis or autoimmune hepatitis? Sometimes a closer look under the surface is needed. *BMJ Case Rep* 2020;**13**:e238400.
227. European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. *J Hepatol* 2017;**67**:370-398.
228. Dalekos GN, Goulis I, Manolakopoulos S, Papaevangelou V, Papatheodoridis G. Clinical Practice Guidelines for the Management of Hepatitis B Virus Infection. Hellenic Center for Disease Control and Prevention, Hellenic Ministry of Health, Athens, December 2017 (online edition, www.keelpno.gr).
229. Crabb DW, Im GY, Szabo G, Mellinger JL, Lucey MR. Diagnosis and treatment of alcohol-associated liver diseases: 2019 practice guidance from the American Association for the Study of Liver Diseases. *Hepatology* 2020;**71**:306-333.
230. Wang Z, Sheng L, Yang Y, et al. The management of autoimmune hepatitis patients with decompensated cirrhosis: real-world experience and a comprehensive review. *Clin Rev Allergy Immunol* 2017;**52**:424-435.
231. Sharma S, Agarwal S, Kaushal K, et al. Presence and type of decompensation affects outcomes in autoimmune hepatitis upon treatment with corticosteroids. *JGH Open* 2021;**5**:81-90.
232. Arvaniti P, Rodriguez-Tajes S, Padilla M, et al. Predictive models of treatment benefit in patients with autoimmune hepatitis and decompensated cirrhosis at diagnosis. *J Hepatol* 2023;**78**(S1):S392.
233. Montano-Loza AJ, Vargas-Vorackova F, Ma M, et al. Incidence and risk factors associated with de novo autoimmune hepatitis after liver transplantation. *Liver Int* 2012;**32**:1426-1433.
234. Kwon JH, Hanouneh IA, Allende D, et al. De novo autoimmune hepatitis following liver transplantation. *Transplant Proc* 2018;**50**:1451-1456.
235. Damoiseaux J. The perspective on standardisation and harmonisation: the viewpoint of the EASI president. *Auto Immun Highlights* 2020;**11**:4.
236. Janowski K, Shumbayawonda E, Dennis A, et al. Multiparametric MRI as a noninvasive monitoring tool for children with autoimmune hepatitis. *J Pediatr Gastroenterol Nutr* 2021;**72**:108-114.
237. Arndtz K, Shumbayawonda E, Hodson J, et al. Multiparametric magnetic resonance imaging, autoimmune hepatitis, and prediction of disease activity. *Hepatol Commun* 2021;**5**:1009-1020.
238. Bajre M, Moawad M, Shumbayawonda E, et al. Liver MultiScan as an alternative to liver biopsy to monitor autoimmune hepatitis in the National Health Service in England: an economic evaluation. *BMJ Open* 2022;**12**:e058999.

Supplementary material

Supplementary Table 1 Diagnostic criteria for AIH-PBC variant (adapted from [75])

PBC criteria*
ALP > 2×ULN or γ-GT > 5×ULN
AMA ≥ 1:40
Liver biopsy showing florid bile duct lesions
AIH criteria*
ALT > 5×ULN
IgG > 2×ULN or a positive test for SMA
Liver biopsy showing moderate or severe periportal or periseptal lymphocytic piecemeal necrosis

*At least 2 of the 3 criteria should be satisfied for each disease
PBC, primary biliary cholangitis; AIH, autoimmune hepatitis; ALP, alkaline phosphatase; ULN, upper limit of normal; AMA, antimitochondrial antibodies; ALT, alanine aminotransferase; IgG, immunoglobulin G; SMA, smooth muscle antibodies

Supplementary Table 2 New diagnostic score for AIH-PBC variant diagnosis (adapted from [76])

Component	Result	Score
Biochemical category		
AST or ALT above ULN	>2	+3
	1.5-2	+2
	1-1.5	+1
	<1	0
ALP above ULN	>1	+2
	0.75-1	+1
	<0.75	0
Serum globulin above ULN	>1.5	+2
	1-1.5	+1
	<1	0
Immunologic category		
ANA, SMA, or LKM1	>1:80	+3
	1:80	+2
	1:40	+1
	<1:40	0
Or		
anti-SLA/LP, pANCA	Positive	+2
AMA	Positive	+3
Histologic category		
	Interface hepatitis	+3
	Lymphoplasmacytic	
	Hepatic rosettes	+1
	Granulomas	+3
	Florid ductal lesion	+1
	Ductular proliferation	+1
	Bile duct loss	+1
Others category		
Viral markers	Positive	-3
	Negative	+3
Drugs	Yes	-4
	No	+1
Alcohol	<25 g/day	+2
	>60 g/day	-2
Interpretation of score	Definitive	≥21
	Probable	19 or 20
	Rejected	<19

AIH, autoimmune hepatitis; PBC, primary biliary cholangitis; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; ULN, upper limit of normal; ANA, antinuclear antibodies; SMA, smooth muscle antibodies; anti-LKM1, live kidney microsomal type 1 antibodies; anti-SLA/LP, antibodies against soluble liver antigens/liver pancreas; pANCA, perinuclear anti-neutrophil cytoplasmic antibodies; AMA, antimitochondrial antibodies

Supplementary Table 3 Simplified criteria for the diagnosis of autoimmune hepatitis (adapted from [70])

Parameter	Finding	Points
ANA or SMA positive	≥ 1:40	+1
ANA or SMA positive or anti-LKM positive or anti-SLA/LP positive	≥ 1:80 ≥ 1:40 Positive	+2*
Liver histology (presence of hepatitis is necessary)	Typical AIH** Compatible with AIH** Atypical**	+2 +1 0
Serum IgG levels	> ULN > 1.1 x ULN	+1 +2
Absence of viral hepatitis***	Yes No	+2 0
Sum		≥ 6: Probable AIH ≥ 7: Definite AIH

*Addition of points achieved for all autoantibodies (maximum, 2 points).

**Definition of typical lesions as in ref. 74; Compatible liver histology: chronic hepatitis with lymphocytic infiltration without all the features considered typical; Atypical: histological lesions supporting another diagnosis.

***In chronic cases absence of hepatitis B and C viral markers; in acute cases absence of serological markers of acute hepatitis A, B, C, D and E is needed. ANA or SMA detection refers to the use of immunofluorescence assay on rodent tissues, not ELISA

ANA, antinuclear antibodies; SMA, smooth muscle antibodies; anti-LKM1, live kidney microsomal type 1 antibodies; anti-SLA/LP, antibodies against soluble liver antigens/liver pancreas; AIH, autoimmune hepatitis; IgG, immunoglobulin G; ULN, upper limit of normal; ELISA, enzyme-linked immunosorbent assay

Supplementary Table 4 Proposed scoring criteria for the diagnosis of AIH and AIH-PSC variant in the pediatric population (adapted from [83])

Characteristic	Cutoff	AIH points	AIH-PSC points
ANA and/or SMA*	≥1:20**	1	1
	≥1:80	2	2
Anti-LKM1* or	≥1:10**	1	1
	≥1:80	2	1
Anti-LC1	Positive**	2	1
Anti-SLA/LP	Positive**	2	2
pANNA	Positive	1	2
IgG	>ULN	1	1
	>1.2 ULN	2	2
Liver histology	Compatible	1	1
	Typical	2	2
Absence of viral hepatitis (A, B, E, EBV), MASH, Wilson, and drug exposure	Yes	2	2
Extrahepatic autoimmunity	Yes	1	1
Family history of autoimmune disease	Yes	1	1
Cholangiography	Normal	2	-2
	Abnormal	-2	2

Score ≥7 = Probable AIH; ≥8: Definite AIH. Score ≥7: Probable AIH-PSC; ≥8: Definite AIH-PSC.

*Antibodies measured by immunofluorescence assay on a composite rodent substrate (kidney, liver, stomach).

**Addition of points achieved for ANA, SMA, anti-LKM-1, anti-LC-1, and anti-SLA/LP autoantibodies cannot exceed a maximum of 2 points

AIH, autoimmune hepatitis; AIH-PSC, autoimmune hepatitis – primary sclerosing cholangitis; ANA, antinuclear antibody; SMA, smooth muscle antibodies; anti-LKM-1, anti-liver kidney microsomal antibody type 1; anti-LC-1, anti-liver cytosol type 1; anti-SLA/LP, anti-soluble liver antigen/liver pancreas; pANNA, peripheral antinuclear neutrophil antibodies; IgG, immunoglobulin G; ULN, upper limit of normal, EBV, Epstein–Barr virus; MASH, metabolic-dysfunction associated steatohepatitis