Clinical Practice Guidelines

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EASL Clinical Practice Guidelines on the management of autoimmune hepatitis☆

European Association for the Study of the Liver*

Summary

Autoimmune hepatitis (AIH) is a chronic liver disease of unknown aetiology which may affect any patient irrespective of age, sex, and ethnicity. At baseline, the clinical spectrum of the disease varies largely from asymptomatic cases to acute liver failure with massive hepatocyte necrosis. The aim of these EASL guidelines is to provide updated guidance on the diagnosis and management of AIH both in adults and children. Updated guidance on the management of patients with variants and specific forms of AIH is also provided, as is detailed guidance on the management of AIH-associated cirrhosis, including surveillance for portal hypertension and hepatocellular carcinoma, as well as liver transplantation in decompensated cirrhosis.

Introduction

Autoimmune hepatitis (AIH) is a chronic progressive immune-mediated inflammatory disease of the liver that is associated with a high mortality rate if left untreated (6-fold higher in the first year after diagnosis and 2-fold higher after 1 year).[1] This is even more pronounced in the paediatric population, with an 8-fold higher mortality risk.[2] AIH affects females and males of all ages and all ethnicities.[3–9] While AIH is traditionally considered a rare disease, recent population-based studies indicate a rising trend in both incidence and prevalence.[10,11] In a recent systematic review and meta-analysis encompassing 37 studies with a total sample size of 239,345,726 participants and 55,839 patients across 18 countries on five continents, the global pooled incidence of AIH was 1.28 cases/100,000 inhabitant-years, whereas the global pooled prevalence was 15.65 cases/100,000 inhabitants.[12] In adults and children, the respective incidence and prevalence varies from 0.67-2.2/100,000 and 0.23-0.4/100,000 per year and from 4 to 42.7/100,000 and 2.4 to 9.9/100,000 population, respectively.[7,11–13] Notably, both incidence and prevalence increased substantially, with 3.1-fold and 2.8-fold rises, respectively, compared to rates observed before the 2000s.[2,12] Rates of AIH incidence and prevalence were higher in populations characterised by a high human development index, females, adults aged over 65 years, North American populations (compared to Europe, Asia, and Oceania), and locations at high latitudes (>45°).[12] A previous systematic review had also described the higher prevalence of AIH in European and American populations in comparison to Asian populations.[13]

Several studies have highlighted variations in disease presentation and outcomes among different ethnic groups with Sub-Saharan African (children), Indian (both children and adults) and Brazilian (only adult) patients being younger with more severe hepatitis compared to patients from Western countries.[14–21] In addition, a population-based analysis reported that black patients with AIH face a greater risk of hospitalisation and death during hospitalisation compared to their white counterparts.[17] Likewise, recent US studies, utilising inpatient databases for AIH and comparing outcomes between black and Hispanic patients and their matched white counterparts, found that the former experienced more adverse hospital outcomes, including elevated rates of disease complications and associated costs.[18,22] A retrospective multicentre study further highlighted that patients with AIH of black background tend to present at an earlier age. This subgroup also experienced a more severe disease course, with an increased likelihood of liver transplantation (LT) or death due to liver failure.[16] While these differences may be influenced by genetic factors,[23,24] socioeconomic factors and limited access to healthcare facilities could also contribute to ethnic health disparities.[25]

AIH incidence peaks in children, teenagers, and adults between the fourth and sixth decade of life.[1,7,10–13,26,27] However, it has become clear during the last years that there is an increasing prevalence of elderly-onset AIH.[7,10,28–33] This increase may reflect the general aging of the population and increased medical awareness of this entity not only among specialists but also among general practitioners. The disease is

* Corresponding author. Address: European Association for the Study of the Liver. The EASL Building – Home of Hepatology, 7 rue Daubin, CH 1203 Geneva, Switzerland. Tel.: +41 (0) 22 807 03 60. *E-mail address:* easloffice@easloffice.eu

Clinical Practice Guideline Panel: Chair: George N. Dalekos; Secretary to the Chair: Nikolaos Gatselis; Panel members: Joost PH Drenth, Michael Heneghan, Marianne H. Jørgensen, Ansgar W. Lohse, Maria-Carlota Londoño, Luigi Muratori, Maria Papp, Marianne Samyn, Dina Tiniakos; EASL Governing Board representative: Ana Lleo.

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predominant among females (F/M ratio 3-4:1) but, the male-to-female ratio seems to have changed over time, indicating a relative increase in male patients with AIH.[7,34] Recent studies revealed that male patients experience worse hospital outcomes, higher rates of disease complications, and higher hospital costs compared to their female counterparts.[18,22] A nationwide cohort study from Denmark further supports this notion, indicating a higher rate of AIH-related deaths in males[1] a tendency also seen in a paediatric cohort.[2] These differences may be attributed to gender-related comorbidities, sex-related dissimilarities in immunogenetics, hypothalamic-pituitary-gonadal system, and sex hormones that potentially influence disease activity and progression, as well as differences in medical adherence.[35–37]

Patients with AIH and their first-degree relatives are at increased risk of developing extrahepatic autoimmune diseases.[7,26,38–45] Indeed, a large nationwide study from Denmark in 2,479 patients with AIH, revealed that approximately 20% of patients had extrahepatic autoimmune diseases at diagnosis with an additional 13% developing new or further extrahepatic autoimmunity within the first 5 years after diagnosis.[44] The most reported associations include thyroid disorders (8%-18%), skin conditions (8%), and inflammatory bowel disease (IBD, 4%-22%)[39,44,45] (Box 1). Coeliac disease is another condition that has been linked to AIH, with a significantly higher prevalence rate than that in the general population (4% *vs.* 0.4%).[41,46] In children, the prevalence of coeliac disease is even higher, ranging from 11% to 46%.[47]

Of note, in the large Danish study, the presence of extrahepatic autoimmune diseases appears to affect all-cause mortality, being higher amongst those with more than one extrahepatic autoimmune disease.[44]

In 2015, the European Association for the Study of the Liver (EASL) released guidelines for the management of patients with AIH.[3] Recognising significant developments and the large number of relevant publications, the EASL Governing Board mandated a panel of experts to provide updated clinical practice guidelines (CPGs) for AIH. These guidelines aim to provide, in a practical manner, a thorough overview of various aspects of AIH, establishing a framework to assist clinicians involved in the management of patients with AIH, including hepatologists, gastroenterologists, internists, specialists in training, and general practitioners, covering both the adult and paediatric populations. The objective was to provide statements and recommendations based on the most reliable evidence on the management of AIH.

Box 1. Common extrahepatic autoimmune diseases in patients with autoimmune hepatitis.

- Hashimoto thyroiditis
- Rheumatoid arthritis; systemic lupus erythematosus; Sjögren's syndrome
- Coeliac disease; inflammatory bowel disease
- Grave's disease; vitiligo; alopecia
- Diabetes mellitus type-1; psoriasis
- Panniculitis, mononeuritis, urticaria pigmentosa, Sweet´s syndrome, idiopathic thrombocytopenic purpura, polymyositis, haemolytic anaemia, uveitis
- Autoimmune polyendocrinopathy-candidiasis ectodermal dystrophy syndrome also known as autoimmune polyendocrinopathy syndrome-type 1

Methodology

The current CPGs were developed in accordance with the new format recently recommended by EASL.[48] The panel initially identified four main topics for consideration: i) clinical spectrum and natural history of AIH, in order to provide insight into its diverse presentation and disease progression, ii) diagnosis and differential diagnosis to elucidate robust methodologies for accurate and prompt identification of the disease, iii) treatment and monitoring (including specific forms and variants of AIH and paediatric AIH), and iv) quality of life and support to emphasise the holistic wellbeing of patients beyond medical intervention. Together, these topics form a comprehensive approach to enhance the understanding, diagnosis, treatment, and overall care of individuals affected by AIH. Utilising the PICO format [P - Patient, Population, or Problem; I - Intervention, Prognostic Factor, or Exposure; C – Comparison or Intervention (if appropriate); O – Outcome], the panel formulated 28 key questions.

PICO questions were submitted to the Delphi panel, consisting of a diverse group of 40 international experts, including two patient representatives. An online platform facilitated the evaluation process, requiring each question to achieve at least 75% agreement for approval, which was attained for all PICO questions. Subsequently, an extensive literature search was conducted using PubMed, Embase, Google Scholar and Scopus. To develop these guidelines for AIH, we employed a dual approach to ensure comprehensive evidence collection. First, we utilised artificial intelligence (AI) tools (Gemini Liver AI and ChatGPT version 3.0) to assist in systematic literature searching to identify and classify relevant sources from a wide range of databases, accelerating the initial phase of literature collection. In addition, manual literature searches were conducted by our expert panel team to supplement and validate the AI findings, ensuring no key evidence was overlooked. This dual process allowed us to maintain a high standard of accuracy and comprehensiveness in gathering evidence for each recommendation. The platform of Clinical Guideline Services (https://www.guideline-services.com) was used to facilitate this process. The quality of evidence was assessed according to the Oxford Centre for Evidence-based Medicine (OCEBM) criteria[49] (Table 1).

Each expert assumed responsibility for formulating proposals for statements related to specific guideline topics, by contributing tables of evidence and text to the entire panel. The strength of recommendations was assessed using the OCEBM criteria, resulting in two categories: strong or weak/open (Table 2).

All recommendations and statements, including the level of evidence (LoE) and grade, underwent thorough discussion and approval by the entire CPG panel. Subsequently, the draft statements and recommendations of the CPG panel were submitted to the Delphi panel for review and voting. The voting results guided the process as follows: <50% approval necessitated rewrite of the recommendation/statement and resubmission to the Delphi panel; 50%-75% approval indicated a need for improvement of the recommendation/statement

Table 1. Level of evidence based on the Oxford Centre for Evidence-based Medicine.

Level	Criteria	Simple model for high, intermediate and low evidence
1	Systematic reviews (SR) (with homogeneity) of randomised-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-randomised, retrospective)	
3	Non-randomised-controlled cohort/follow-up study/control arm of randomised trial (SR is generally better than an individual study)	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 is generally better than an individual study)	
5	Expert opinion (mechanism-based reasoning)	Any estimate of effect is uncertain

Table 2. Grades of recommendation.

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

without resubmission; 75-90% approval indicated consensus; and ≥90% approval indicated strong consensus. Neutral votes were not counted when calculating the consensus. The suggested modifications were integrated into a revised version, which was further reviewed by the EASL Governing Board and external reviewers. The Delphi panel agreement on each of the recommendations and statements is provided in the Appendix.

Clinical spectrum and natural history of AIH

How does AIH present in adults, children, and early adulthood?

Statement

- The clinical manifestations of AIH vary from asymptomatic to acute liver failure and they present at any liver fibrosis stage regardless of age, sex, and ethnicity **(LoE 2, strong consensus).**

The presentation of AIH does vary from asymptomatic mild AIH or chronic AIH with established advanced fibrosis at

Table 3. Presentation of AIH in adults, children, and early adulthood.

	Adult		Paediatric	
	Definition	**Prevalence**	**Definition**	**Prevalence**
Asymptomatic AIH	Absence of symptoms, only elevated liver biochemistry[7,72]	6-23%[52,55,58,59,72]	Absence of symptoms, only elevated liver biochemistry	12-18%[55]
Chronic AIH	>6 months from onset of elevated liver biochemistry or symptoms[# 7,72]	48-68%[58,65]	>6 months from onset of elevated liver biochemistry or symptoms	33-52%[61,62]
Acute AIH	<30 days from onset of symptoms[* 67,72]	10-26%[51,55,58]		19-58%[55,57,61]
Acute exacerbation of chronic AIH	Acute injury developing in patients with underlying (often unrecognised) chronic disease	About one-third of patients with AIH have cirrhosis at diagnosis[7,50,57,71,72]		
Acute severe AIH	Acute presentation with jaundice and coagulation disturbance (INR ≥1.5 and <2), but without encephalopathy[66,67]			
ACLF	Acute injury developing in patients with (often unrecognised) cirrhosis and extrahepatic organ failure[68]		Acute injury developing in patients with (often unrecognised) cirrhosis with extrahepatic organ failure[68]	26%[61]
ALF	Hepatic necrosis with encephalopathy within 8 weeks from onset[53,69]		Elevated ALT and INR >1.5 and encephalopathy or elevated ALT and INR >2 regardless the presence of encephalopathy[70]	3.6-12.5%[56,61–63] with 3-fold higher risk in LKM1-related AIH[57]

No definition of presentation:[51,55].

ACLF, acute-on-chronic liver failure; AIH, autoimmune hepatitis; ALF, acute liver failure; ALT, alanine aminotransferase; INR, international normalised ratio; LKM1, liver kidney microsomal type 1 antibodies.

*Jaundice, fatigue, drowsiness, fever.

#Manifestation of advanced fibrosis or cirrhosis, symptoms related to chronic liver disease, *e.g.* pruritus, malaise, jaundice, fatigue, arthralgias and abdominal pain/discomfort.

baseline to fulminant life-threatening acute liver failure (ALF) with massive hepatocyte necrosis.[3,5,7,50,51] The classification of subtypes and presentation prevalence are listed in Table 3. In adults, the diverse subtypes are associated with differing survival rates, with an excellent prognosis in mild AIH (10-year survival rate of 98%),[52] while AIH presenting with ALF is associated with a 21-day transplant-free survival rate of only 14.5-20%, with 18-23.8% of patients dying before LT.[53,54]

AIH can occur in all age groups, from infants to elderly patients.[31,55–58] The presentation of AIH is influenced by age, with a tendency for milder disease, a higher frequency of asymptomatic cases, a higher frequency of cirrhosis and more extrahepatic autoimmune manifestations in elderly patients.[31,55,59] In contrast, children and adolescents more often have an AIH-primary sclerosing cholangitis (PSC) variant, and the youngest children more frequently have liver kidney microsomal type 1 (LKM1) and/or liver cytosol type 1 (LC1)-related AIH compared to adults.[56,57,60–64]

The pattern of presentation seems similar for adult and paediatric populations, except for the higher prevalence of ALF in LKM1/LC1-related AIH in younger children. However, data are based on small single-centre studies, and large population-based studies are lacking.[51,65–69] The difference in diagnostic criteria for ALF should be taken into consideration for those presenting acutely (Table 3). Notably, owing to the risk of rapid deterioration, paediatric ALF can be diagnosed independently of encephalopathy if the international normalised ratio (INR) is higher than 2.[70]

At the time of diagnosis, about 20-33% of both adult and paediatric patients have evidence of advanced liver disease.[7,50,57,71,72] Changes over recent decades have been studied, showing that adult patients are now older at presentation, more frequently have an acute presentation, and are less likely to have cirrhosis than in the past.[73] Of note, adult male patients present at a younger age and are more likely to have cirrhosis at the time of diagnosis compared to females, while female patients show a higher prevalence of extrahepatic autoimmune diseases.[43]

Is it still useful and clinically motivating to subclassify AIH into subtypes according to serological markers/autoimmune serology?

Recommendation

- Subclassifying adult patients with AIH into different subtypes according to autoantibody profile cannot be recommended **(LoE 3, weak recommendation, consensus).**

AIH is characterised by the presence of serum autoantibodies in the vast majority of patients.[74–77] Historically, three subtypes of AIH have been proposed according to the pattern of autoantibodies detected. Initially, two major types, the most common type 1 AIH (AIH-1) and the less common type 2 AIH (AIH-2), were proposed with antinuclear (ANA) and smooth muscle antibodies (SMA) being typical of AIH-1 and anti-LKM1 and anti-LC1 antibodies typical of AIH-2.[74–78] Later, the discovery of antibodies against soluble liver antigen/liver pancreas (anti-SLA/LP) led to the proposal of a third subtype (AIH-3).[79]

AIH-2 usually affects younger patients, including infants.[74,77,80] In addition, two retrospective studies postulated a more severe disease and worse prognosis,[81] as well as the need for lifelong immunosuppression in most patients with AIH-3,[82] even though the overall response and survival were not affected in the latter study. However, the prognostic implications ascribed to anti-SLA/LP antibody may reflect its almost universal coexistence with antibodies to Ro52 autoantigen in almost all patients with AIH and anti-SLA/LP reactivity, as these antibodies have independently been associated with poor prognosis in AIH.[83,84]

The validity of the aforementioned sub-classifications is questionable and subject to ongoing debate. Indeed, a recent and the largest ever long-term observational study on children with AIH showed that AIH severity in childhood and response to treatment was independent of autoantibody status, with anti-LKM1-positive patients showing the same spectrum of disease activity, response rates and long-term prognosis as patients with AIH-1.[85,86] On the other hand, previous and recent large cohort studies have shown that patients with ANA and/or SMA and those with anti-SLA/LP share most clinical, biochemical, histological and prognostic features.[82,84,87,88] In sum, distinction of AIH into subtypes according to the serological markers of autoimmune serology does not seem to be clinically helpful, at least in adults, and is thus not recommended.

When and how should a clinical suspicion of the diagnosis of AIH/primary biliary cholangitis (PBC), AIH/PSC or autoimmune sclerosing cholangitis (ASC) variants be established?

Recommendations

- The diagnosis of a variant syndrome of AIH and one of the cholestatic immune-mediated diseases PSC or PBC should be considered whenever there are concomitant cholestatic features **(LoE 2, strong recommendation, strong consensus).**
- The possibility of underlying or associated sclerosing cholangitis should be considered in every case of childhood AIH **(LoE 2, strong recommendation, strong consensus).**
- Magnetic resonance cholangiography is recommended for the initial work-up of all childhood AIH cases independently of elevated cholestatic enzymes, as well as of young adults with cholestasis or those not achieving a complete biochemical response (CBR) and should be repeated when there is remaining disease activity or cholestatic features upon follow-up **(LoE 3, strong recommendation, strong consensus).**
- Investigation for PBC-specific autoantibodies is recommended, before any other test, in all adults with AIH and biochemical features of cholestasis **(LoE 2, strong recommendation, strong consensus).**
- Magnetic resonance cholangiography is recommended in adults with cholestatic features, either at diagnosis or during follow-up when testing for PBC-specific autoantibodies is negative **(LoE 3, strong recommendation, strong consensus).**

Amongst the wide spectrum of presentation of immune-mediated liver disease, there can be considerable overlap of clinical, serological and histological features of AIH with one of the two cholestatic liver diseases, PSC and PBC.[89–91] In fact, PSC in childhood may often manifest with an acute inflammatory disease showing all features of AIH but later evolving into a typical PSC. This entity was initially termed autoimmune sclerosing cholangitis (ASC) and a relative diagnostic score has been proposed for the paediatric population by the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) Hepatology Committee (Table 4).[62,80] ASC probably just represents the most inflammatory form of PSC and should more likely be regarded as part of the spectrum of PSC variant syndromes.[92] In clinical practice, the terminology has been heterogeneous. For clinical purposes it has become customary to first name the dominant disease and then the less dominant disease. Thus, in this context of an AIH guideline, we use the terms AIH/PSC and AIH/PBC,[3,5] while PSC/AIH or PSC variant syndrome with features of AIH is the standard terminology in the PSC literature,[93] and similarly PBC/AIH or PBC variant syndrome the terminology in the PBC literature.[94] The International Autoimmune Hepatitis Group (IAIHG) has in fact put forward that PSC and PBC are the underlying disease processes in the vast majority of cases, with a few exceptions of truly concomitant disease, and should thus guide diagnostic and therapeutic guidelines. It is for this reason that in this guideline we just address diagnosis and the key aspects of therapy (see below), and otherwise refer readers to the PBC and PSC guidelines.[93,94]

Particularly in children, PSC may manifest with a clinical and histological picture indiscernible from AIH.[62,95] In some of these children, there may already be bile duct irregularities on cholangiography, but often these irregularities due to sclerosing cholangitis may only develop later in the disease course or be so minimal that they cannot be reliably detected by present-day imaging. Therefore, not only is cholangiography recommended in all children with AIH, repeat cholangiography may be required regularly along the disease path. Cholangiography in children under the age of 6 years is not needed if gamma-glutamyltransferase (GGT) is normal. However, as patients with AIH/PSC usually do not achieve a CBR following immunosuppressive induction therapy, it is important to consider this diagnosis whenever CBR cannot be achieved. Other features suggestive of underlying PSC may be prominent splenomegaly, marked portal hypertension, and evidence of concomitant IBD.[64,96] PSC variant syndrome with a strong inflammatory component typical of AIH may also occur in young adults, and the threshold for cholangiography should be low in young adults with AIH with cholestatic laboratory features or not achieving CBR upon immunosuppressive therapy.

PBC/AIH and AIH/PBC is more commonly seen in middle-aged women and is usually associated with typical cholestatic laboratory features. Screening for PBC-specific autoantibodies – namely anti-mitochondrial antibodies (AMA) with specificity for the M2 antigens, and PBC-specific ANA, such as antibodies against gp210 and sp100 (by ELISA, immunoblot or indirect immunofluorescence testing [IFT] on HEp2 cells giving a rim like membranous or multiple nuclear dots pattern, respectively) should be undertaken in all such cases if history of potential drug-induced liver injury (DILI) and ultrasound investigation are not helpful, and it can be argued that it should be part of the work-up of all newly diagnosed patients with AIH.[97–99] However, the specificity and sensitivity of these antibodies in the context of AIH is not well studied, and low levels of these autoantibodies may be detectable in pure AIH, especially if there is marked hypergammaglobulinaemia. Similarly, histological demonstration of non-suppurative destructive cholangitis, the typical hallmark of PBC, can occasionally also be observed in very active AIH without the presence of PBC.[100] Thus, it may be advisable to revisit the serology during follow-up, and a repeat biopsy may be indicated in cases of diagnostic uncertainty. Alternatively, in uncertain cases, a therapeutic trial of adding ursodeoxycholic acid (UDCA) to standard immunosuppressive therapy could be justified. In this context, the old

Table 4. Proposed scoring system for the diagnosis of AIH and the AIH/PSC variant in the paediatric age group.[80]

Characteristic	Cut-off	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
	>1.2x 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.

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

*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.

***Substitution of the histological component with the 2022 IAHPG criteria is expected to increase the sensitivity of AIH diagnosis also in children, as the new criteria are applicable in atypical cases with acute onset and predominantly lobular pattern of inflammation.[9]

"Paris criteria" may help to attain a firm diagnosis, but they are quite strict and have been described mainly to homogenise groups of patients with an assured AIH/PBC diagnosis (Table S1).[101] Recently, a group from the US proposed a quite complex new score (Table S2) with high sensitivity (98.5%) and specificity (92.8%), but external validation is still pending.[102] Irrespective of the score used, a liver biopsy to confirm the presence of moderate and/or severe hepatitis is mandatory.

While PBC variant syndrome (PBC/AIH and/or AIH/PBC) may manifest coincidentally, the two disease features may also develop sequentially.[3,93,94,98,102,103] More common is the primary manifestation of AIH and subsequent development of PBC features, but also acute flares with an acute AIH-like picture can occur in patients with long-standing PBC. Therefore, diagnostic work-up for these variant conditions may not only be indicated at initial diagnosis but also during follow-up. Several expert centres repeat screening for the key autoantibodies as well as immunoglobulin class G (IgG) and immunoglobulin class M levels in addition to the measurement of aminotransferases and cholestatic enzyme levels at regular intervals, such as yearly or every other year. Due to a lack of reliable data on the usefulness of this approach, clear guidance cannot be given.

What are the long-term complications of AIH and how should they be identified?

Statement

- Long-term complications of AIH are related to disease progression and cancer risk as in any other aetiology of liver disease **(LoE 2, strong consensus).**

Recommendations

- Surveillance and early recognition of disease complications are recommended in all patients with AIH **(LoE 5, strong recommendation, strong consensus).**
- Monitoring for complications, including portal hypertension and hepatocellular carcinoma (HCC), is recommended in patients with AIH-related cirrhosis as per dedicated guidelines **(LoE 3, strong recommendation, strong consensus).**

Long-term complications of AIH can be a consequence of both disease progression and immunosuppressive treatment. In this section, we describe liver-related complications while treatment-related complications will be discussed later. Liver-related complications are, in principle, the same as for any other cause of acute or chronic liver disease. ALF is the predominant complication in acute, acute-on-chronic liver failure (ACLF), or fulminant presentations of the disease; it can be precipitated by arbitrary cessation or tapering of immunosuppressant therapy, and because of various secondary insults affecting the liver (*e.g.* infectious events, drugs or toxic agents).[104] In chronic disease, especially in undiagnosed or insufficiently treated patients, cirrhosis, decompensation, and HCC can occur.[1,105]

HCC occurs significantly less frequently in patients with AIH even after cirrhosis development compared to liver diseases of other aetiology (1-9% of patients with AIH-related cirrhosis, with an annual incidence of 1.1-1.9%).[106–109] A recent large, observational, multicentric retrospective study in 1,428 patients with AIH from the IAIHG registry, with a median follow-up of 11.1 years, confirmed previous studies demonstrating that its incidence and prevalence are quite low (1.44 cases/1,000 patient-years and 1.7%, respectively) compared to other liver diseases.[110] However, a significantly increasing incidence after cirrhosis development was observed (cumulative HCC incidence: 2.6%, 4.6%, 5.6% and 6.6% at 5, 10, 15, and 20 years after cirrhosis, respectively).[110] Obesity (hazard ratio [HR] 2.94, $p = 0.04$)], advanced age (≥50 years; HR 2.94, $p = 0.04$), alcohol consumption (≥25 g/day; HR 4.12, $p = 0.06$), and AIH/PSC variant syndrome at baseline (HR 5.18, $p = 0.007$) were additional independent risk factors for HCC development in addition to the presence of cirrhosis (HR 3.17, $p = 0.01$).[110] However, this was a retrospective study in which adherence to the HCC surveillance programme could not be determined, and HCC diagnoses were not centrally reviewed.

Diagnosis and differential diagnosis

How should AIH be diagnosed? What are the diagnostic scoring criteria to establish a firm AIH diagnosis in adults and children?

Recommendations

- The diagnosis of AIH should be based on a distinct IgG elevation, the presence of autoantibodies, and a likely or possible liver histology **(LoE 2, strong recommendation, strong consensus).**
- A careful exclusion of all known causes of acute and chronic liver diseases is recommended for AIH diagnosis, although coexistence with metabolic dysfunction-associated steatotic liver disease (MASLD), alcohol-related liver disease (ALD) or viral hepatitis is possible **(LoE 3, strong recommendation, strong consensus).**
- The simplified diagnostic criteria are recommended in clinical practice to help in the diagnosis of AIH if rodent tissue sections are used for ANA and SMA detection **(LoE 3, strong recommendation, strong consensus).**
- The updated simplified diagnostic criteria can be applied if HEp-2 cells or ELISAs are used for ANA and SMA detection **(LoE 3, weak recommendation, consensus).**
- The International AIH Pathology Group (IAHPG) consensus histological criteria can be applied when using the simplified scoring system, as they may increase the sensitivity of AIH diagnosis **(LoE 3, weak recommendation, strong consensus).**
- In paediatric patients, the revised 2018 ESPGHAN scoring system can be used **(LoE 3, weak recommendation, strong consensus).**
- In cases involving acute forms of AIH, AIH variants, concurrent liver disease, and drug-induced autoimmune-like hepatitis (DI-ALH), the diagnostic scores should be applied with caution **(LoE 3, strong recommendation, strong consensus).**

AIH should be considered in the differential diagnosis of any patient with liver enzyme alterations or cirrhosis of an unknown origin. In general, the diagnosis of AIH requires the presence of increased aminotransferase and IgG levels, a specific set of autoantibodies, and likely or possible liver histology,[9,111–113] in most cases after the exclusion of other known causes of liver disease (Table 5). However, none of these features, if detected in isolation, is sufficient and specific to confidently diagnose the disease. In other words, AIH is a clinicopathological diagnosis. Nevertheless, the high prevalence of MASLD and alcohol consumption in at least the general adult population makes the coexistence of AIH with these diseases quite common.[114,115] In addition, in countries with a high prevalence of viral hepatitis (especially hepatitis B and D), their association with AIH can be observed.[116,117]

In 1993, the IAIHG set the first diagnostic criteria and proposed a scoring system that was revised in 1999.[111,112] This first attempt required the evaluation of numerous and detailed items and was rather complex for practical daily use; therefore, in 2008, a simplified scoring system was proposed as an easy-to-use clinical tool, assessing just four simple variables: autoantibodies, IgG levels, liver histology and exclusion of viral hepatitis.[113] The simplified diagnostic criteria give 1 or 2 points to the presence of positive autoantibodies, IgG levels, histological features, and the absence of viral hepatitis, making a probable or definite diagnosis if an individual reaches ≥6 and ≥7 points, respectively (Table 6). These criteria have been validated in different ethnic backgrounds, with a sensitivity and specificity of >90% and higher accuracy than the revised criteria.[118–124] However, there are several situations in which the simplified criteria have limited accuracy owing to the definition of the typical and compatible histological features of AIH. These include acute forms of AIH,[125] DI-ALH, variant forms, and the presence of concomitant liver disease (MASLD, viral hepatitis, ALD, Wilson's disease and especially for small children, metabolic diseases), for which the diagnosis should include a profound evaluation of the clinical and histological characteristics by expert pathologists and hepatologists.[114,126]

Another point is the suggested substitution of the histology component of the simplified scoring system with the 2022 IAHPG criteria (see below),[9] which can increase the sensitivity of diagnosing adult AIH according to recent retrospective studies[127,128] and, ultimately, optimise clinical diagnosis.[129]

In the paediatric setting, the simplified 2008 criteria have been widely evaluated and several limitations emerged in terms of sensitivity and specificity,[119,130,131] particularly in children with hyperacute and fulminant presentation of the disease.

In 2018, the ESPGHAN Hepatology Committee proposed a scoring system for the diagnosis of autoimmune liver diseases in the paediatric age group[80] (Table 4). At variance with the 2008 simplified score, in children, the required autoantibodies titre is lower, while the presence of bile duct involvement, associated extrahepatic autoimmune disorders and a history of family autoimmune diseases are also assessed and scored. A score of 7 suggests the diagnosis of probable AIH, a score of 8 or higher points to the diagnosis of definite AIH. A single monocentric validation study on 152 patients with hepatic diseases demonstrated that both the simplified score and the 2018 ESPGHAN scoring system had good accuracy in terms of AIH diagnosis, even though the new score displayed slightly higher sensitivity and specificity (79.5% *vs.* 83.1% and 85.5% *vs.* 88.4%, respectively).[132] Another study reported similar findings.[133] Substitution of the histological component with the 2022 IAHPG criteria is also expected to increase the sensitivity of AIH diagnosis in children, as the new criteria are applicable in atypical cases with acute onset and a predominantly lobular pattern of inflammation.[9]

Autoantibodies are detected in the vast majority of patients with AIH if tested according to guidelines on rodent substrates. However, these recommendations are rarely followed by laboratories in everyday practice, as ELISAs and IFT on HEp2 cells are very often used instead, even though the simplified score does not account for ANA and SMA detection using these methods. Therefore, a recent large multicentre study by the IAIHG in 341 patients was designed to assess the diagnostic validity of ELISAs and IFT in HEp2 cells.[134] The results showed that: 1) ANA ELISAs and F-actin ELISA are potential alternatives to IFT, but the ANA ELISA kits should also include HEp-2 nuclear extracts of unrecognised autoantigens, 2) IFT on HEp-2 cells is a valid alternative when the cut-off titres are increased (minimum of 1:80), and c) ELISA cut-offs need to be validated locally.[134] Therefore, in summary, this study recommends the adaptation of the simplified score to be used for AIH diagnosis in everyday clinical practice by different laboratories, but external validation is still lacking (Table 6).[134]

Which biochemical tests suggest a potential diagnosis of AIH?

Recommendations

- AIH should be suspected in all patients with elevated aminotransferases of unknown aetiology, irrespective of the level of increase, especially in the presence of elevated IgG levels and circulating autoantibodies **(LoE 2, strong recommendation, strong consensus).**
- AIH should also be suspected in all patients with cirrhosis of unknown aetiology, even in the absence of aminotransferase elevations **(LoE 3, strong recommendation, strong consensus).**
- Normal IgG levels should not exclude the diagnosis of AIH **(LoE 3, strong recommendation, strong consensus).**

AIH is characterised by predominantly elevated aminotransferase levels. Alanine aminotransferase (ALT) levels are higher than aspartate aminotransferase (AST) levels in most cases of acute or chronic hepatitis. The extent of aminotransferase elevation is highly variable and encompasses a range from a very slight increase in AST and ALT levels to more than 50 times the upper limit of normal (ULN).[135,136] As acute presentations are becoming more frequently observed,[32,73,137] very high aminotransferase and bilirubin levels are common at diagnosis.[138] The degree of ALT elevation does not correlate with histological activity. In AIH-related cirrhosis, aminotransferases may be moderately elevated or even normal. Less than 20% of patients present with mild elevations in alkaline phosphatase (ALP; <2x ULN) and GGT <5x ULN, but significant elevations in ALP and GGT levels warrant the exclusion of cholestatic variant forms of AIH.[139] However, GGT elevation with normal or near-normal ALP is commonly observed in male patients with AIH and should not be considered as a specific indication of a concomitant cholangiopathy.[139]

Table 5. Differential diagnosis of AIH.

Causes of liver injury	Acute hepatic injury	Chronic hepatic injury	AST and ALT elevation	Laboratory diagnosis and scoring systems
Extrahepatic				
EBV	X		>3x ULN IU/ml	VCA-IgM antibody, EA-D antibody, EBNA antibody, EBV quantitative PCR
CMV	X		>3x ULN IU/ml	CMV IgM antibody CMV quantitative PCR
HSV 1, 2, 6	X		>1,000 IU/ml	HSV 1 and 2 IgM antibodies, HSV qualitative PCR
HIV	X		Mild elevations	HIV-1/-2 antibodies, quantitative PCR
Influenza A, influenza B, respiratory syncytial virus	X		Mild elevations	Positive PCR in respiratory samples
Parvovirus B19	X		>3-5x ULN IU/ml	Parvovirus B19 IgM, qualitative PCR
SARS-CoV-2	X		Mild elevations	Positive PCR or rapid antigen tests in respiratory samples
VZV	X		>1,000 IU/ml	VZV IgM antibodies, qualitative PCR
Coeliac disease	X	x	Mild elevations	Coeliac antibodies
Intrahepatic				
Alcohol-related liver disease	X	x	50-400 IU/ml, AST/ALT ratio >1.5	Heavy alcohol consumption (>50 g/day) for a minimum of 6 months and positive NIAA criteria. Probable (liver biopsy unavailable), definite (liver biopsy available). Patients with chronic alcohol abuse are identified by increased GGT and MCV
Autoimmune-like hepatitis after vaccination against SARS-CoV-2	X		Varies	
DILI/HILI	X	x	Varies	RUCAM score and liver biopsy
MASLD		x	Mild elevations	Steatosis identified in imaging and/or CAP on TE. Raised ALT, AST, GGT with a preserved ALT:AST ratio of 1.5 in the setting of features of metabolic syndrome
Wilson's disease	X	x	Mild elevations	Leipzig's criteria
Haemochromatosis		x		Iron overload (high transferrin saturation and ferritin), HFE C282Y presence
Hepatitis A	X		>400 IU/ml	Anti-HAV IgM
Hepatitis B virus infection or reactivation	X	x	Varies	Elevated HBV DNA, HBsAg, anti-HBc IgM
Hepatitis B virus/hepatitis delta virus (co-infection or supe-infection)	X	x	>400 IU/ml	Anti-HDV IgM and IgG, HDV RNA
Hepatitis C	X	x	Varies	HCV RNA (acute infection); anti-HCV IgG and HCV RNA (chronic infection)
Hepatitis E	X		>400 IU/ml	Anti-HEV IgM and quantitative PCR (HEV RNA)
Ischaemic hepatitis	X		Disproportional peak of AST (usually >1,000 IU/ml) to ALT	Severe coagulopathy (marked prolongation of prothrombin time) that improves rapidly (cardiac event, right and/or left ventricular dysfunction, shock)

AIH, autoimmune hepatitis; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CAP, controlled attenuation parameter; CMV, cytomegalovirus; DILI, drug-induced liver injury; EBNA, Epstein-Barr nuclear antigen; EBV, Epstein-Barr virus; EA-D, early antigen D; GGT, gamma-glutamyltransferase; HAV, hepatitis A virus; HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HDV, hepatitis D virus; HIV, human immunodeficiency virus; HSV, herpes simplex virus; IgG, immunoglobulin class G; IgM, immunoglobulin class M; MASLD, metabolic dysfunction-associated steatotic liver disease; MCV, mean corpuscular volume; NIAA, National Institute on Alcohol Abuse and Alcoholism; RUCAM, Roussel Uclaf Causality Assessment Method; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ULN, upper limit of normal; VCA, viral capsid antigen; TE, transient elastography; VZV, varicella zoster virus.

Table 6. Current and updated simplified criteria for the diagnosis of AIH in adults.[113,134]

	Current criteria*			Updated criteria		
Variable	**0**	**1**	**2**	**0**	**1**	**2**
ANA or SMA	Negative	≥1:40	≥1:80 or anti-LKM ≥1:40 or anti-SLA/LP positive	Negative	Positive**	Strongly positive*** or anti-LKM ≥1:40 or anti-SLA/LP positive
IgG	Normal	>ULN	>1.1x ULN	Normal	>ULN	>1.1x ULN
Liver biopsy	Normal	Compatible#	Typical#	Normal	Compatible#	Typical#
Absence of viral hepatitis	No	—	Yes	No	—	Yes

Score ≥6 = Probable AIH; ≥7: Definite AIH.

Maximum 2 points achieved for autoantibodies. If ELISA-based autoantibody evaluation is negative despite clinical suspicion of AIH, IFT should be performed additionally.

AIH, autoimmune hepatitis; ANA, anti–nuclear antibodies; anti-LKM, anti-liver kidney microsomal antibodies; anti-SLA/LP, antibodies against soluble liver antigens/liver pancreas autoantigen; IAHPG, International AIH Pathology Group; IFT, immunofluorescence testing; IgG, immunoglobulin G; SMA, smooth muscle antibodies; ULN, upper limit of normal.

*Corresponds only to IFT on tissue sections.

**IFT: ≥1:40 when assessed on tissue sections and ≥1:80 or 1:160 for ANA when assessed on HEp-2cells. ELISA with locally established cut-offs.

***IFT: ≥1:80 when assessed on tissue sections and ≥1:160 or 1:320 for ANA when assessed on HEp-2cells. ELISA with cut-offs established locally.

#Definition of compatible or typical findings at the histological level as in ref.[113] However, substitution of the above histological findings with the 2022 IAHPG criteria[9] (likely for typical and possible for compatible) should be considered, as they may increase the sensitivity of AIH diagnosis and, ultimately, optimise clinical diagnosis.

Most patients diagnosed with AIH (85%-95%) exhibit elevated gamma-globulins and IgG levels, even in the absence of cirrhosis. As a result, these parameters have been incorporated as a primary diagnostic criterion for diagnostic scores. However, the prevalence of IgG elevation is lower in patients with an acute presentation and ranges between 25% and 39%.[136,140] The reason for the lack of IgG elevation in certain patients remains unclear, but it may be attributed to shorter exposure to the immunological trigger of the disease, such as in patients with acute AIH,[138,141] or to the presence of genetic variants associated with low IgG levels. Traditionally, elevated IgG levels have been associated with more severe histological activity and a lower probability of achieving a treatment response. However, a recent multicentre study found no significant differences in clinical and histological characteristics between patients with normal or elevated IgG levels at the time of diagnosis, or the probability of achieving a CBR.[141] Nevertheless, patients with normal IgG levels at the time of diagnosis are more likely to remain in remission after immunosuppressive withdrawal.[141]

In addition to elevated IgG levels, patients with active AIH also exhibit elevated IgA levels within or only slightly above the ULN. This could be the result of a link between intestinal permeability, gut dysbiosis, and AIH.[141]

What are the most appropriate methods of investigation for the detection of autoantibodies in children and adults, and how should these be interpreted?

Recommendations

- First screening for ANA, SMA, anti-LKM1 and anti-LC1 should be performed by IFT on triple rodent tissue sections in parallel with anti-SLA/LP testing by solid phase assays **(LoE 2, strong recommendation, strong consensus).**
- In case of a negative IFT result, serum should be re-tested at a lower dilution (1:40 in adults, 1:10 in children) **(LoE 2, strong recommendation, strong consensus).**
- Clinical laboratories should comply with AIH guidelines both regarding the cut-offs of reporting and the techniques they use **(LoE 3, strong recommendation, strong consensus).**

The non-organ-specific autoantibodies ANA and SMA, and organ-specific autoantibodies, such as anti-SLA/LP, anti-LKM1 and anti-LC1 are considered the serological markers of AIH.[76] Even though the detection of these autoantibodies remains a hallmark for AIH diagnosis, they cannot support a definite diagnosis on their own.[74,75,77]

The original method to detect ANA, SMA, anti-LKM1 and anti-LC1 was IFT on snap fresh-frozen sections of rat liver, kidney and stomach.[74,75,77] As of today, IFT is still in use as the screening method of investigation and is performed on in-house or commercially available sections of the three rat substrates and on commercially available HEp-2 cell lines. The recommended starting serum dilution for the IFT is 1:40-1:80 in adults (higher when HEp2 cell lines are used; Table 6), but the starting dilution should be as low as 1:10-1:20 in children (Table 4) because before the age of 10 years the IgG levels are known to be lower than in adults.[142] In patients with extremely elevated IgG levels, the pro-zone effect could be responsible for a falsely negative IFT result, and the sample should be re-tested at higher serial dilutions.[143]

As anti-SLA/LP is not detectable by IFT, it can be assessed only with commercially available solid phase assays using the recombinant SLA/LP autoantigen.[74,75,77,144,145] Investigation for anti-SLA/LP should be performed in parallel with IFT screening and ideally before treatment initiation (Fig. 1).[3,74,75,77,82]

One or more of these autoantibodies are detected in nearly all patients with the disease. The most common associations observed are ANA with SMA and anti-LKM1 with anti-LC1.[73,146] Under the appropriate clinical background, these reactivities support proceeding to a liver biopsy, as AIH is highly likely (Fig. 1). Negative results despite clinical suspicion justify retesting at lower dilutions and potential additional specific investigation for non-standard autoantibodies preferentially in a reference lab, because the autoantibody titres may vary during the course of the disease.[75,77,99]

Second-line, confirmatory tests with recombinant target antigens are available for anti-LKM1 and anti-LC1 reactivities. SMA of VG (stain of vessels and renal glomeruli) or VGT patterns (stain of vessels, glomeruli, and renal tubules) by IFT are quite specific for the diagnosis of AIH.[62,74,75,77] To confirm the specificity of SMA reactivity, additional second-line tests are available for the detection of anti-filamentous actin antibodies and anti-microfilament antibodies, both by IFT on different cellular substrates as well as by solid phase assays.[74,75,77] ANA

and SMA are by far the most represented serological markers, accounting for 60% to 70% of patients, isolated or combined.[147] Anti-SLA/LP is present in 10-20% of patients, irrespective of age at onset.[84,146,148] Anti-LKM1 and anti-LC1, isolated or in association, are mainly detected in paediatric patients, accounting for nearly 40-50% of patients in several paediatric cohorts.[62,78,85]

The diagnostic accuracy of ANA, SMA and anti-SLA/LP in AIH has been assessed in a meta-analysis which showed that ANA has moderate sensitivity and specificity, SMA moderate sensitivity and high specificity, and anti-SLA/LP low sensitivity but high specificity.[149] The diagnostic accuracy seems to increase further with two or more detectable autoantibodies.[150] However, it should be emphasised that autoantibodies are only useful for AIH diagnosis, as they cannot predict the prognosis and outcome of patients. Therefore, monitoring of autoantibody titres is not recommended in adults but might be of clinical importance in children and adolescents.[80] Laboratories should follow the Good Practice Guide by reporting both the assays and the cut-offs they use, as this information may assist physicians in interpretating the results.

A perinuclear staining of anti-neutrophil nuclear antibodies (pANNA) – also known as "atypical" perinuclear anti-neutrophil cytoplasmic antibodies – can frequently be detected by IFT in patients with AIH.[74,75,77,80,99,146] In clinical practice, however, exceptionally few patients with AIH have isolated pANNA reactivity and therefore, this testing is not recommended at the initial screening but only when patients tested negative for ANA, SMA, and anti-SLA/LP (Fig. 1). Furthermore, antibodies to double-stranded DNA (anti-dsDNA) have been detected by ELISA in about 30% of patients with AIH and in up to 60% of patients with AIH/PBC variant.[77,151–153] Therefore, seropositivity for both ANA and anti-dsDNA should not always result in a "superficial diagnosis" of systemic lupus erythematosus (SLE) if other criteria for its diagnosis are lacking. In case of uncertainty, the use of IFT on *Crithidia luciliae*, which includes high dsDNA quantities, could solve the problem as this assay appears to detect anti-dsDNA antibodies with higher specificity than the ELISAs.

Additional AIH-specific autoantigens have been identified using protein microarray technology,[154–156] but their diagnostic and prognostic implications await further confirmatory studies on larger series. In this regard, a recent large multicentre study identified a polyreactive IgG (pIgG), which showed similar sensitivities but higher specificities for AIH diagnosis compared to SMA and ANA.[157] Of note, similar findings were observed in a preliminary evaluation of paediatric patients with AIH.[158] Continuing along the line of identifying potential new biomarkers from autoantibodies, a recent study showed that a nuclear magnetic resonance-based metabolomic signature had

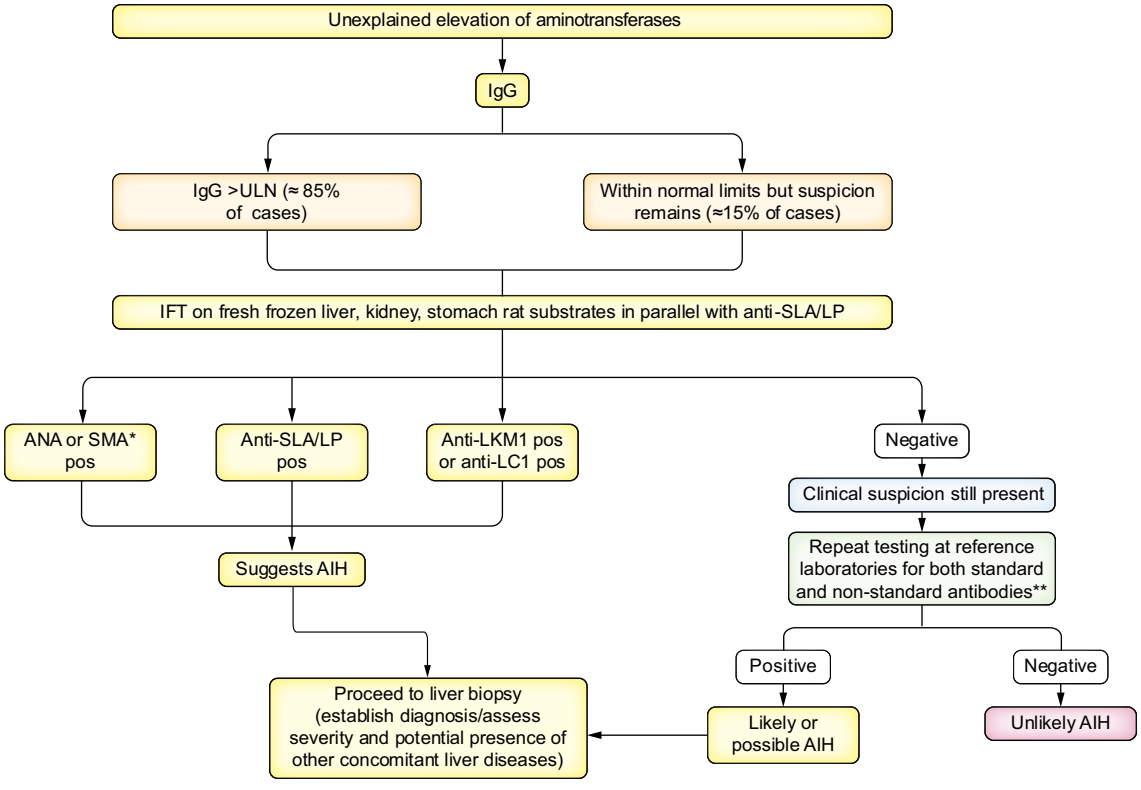

Fig. 1. Proposed autoimmune serology algorithm for patients with suspected AIH. Antibodies are detected in >95% of patients if testing strictly adheres to the guidelines. All laboratories should adhere to the guidelines in terms of assays and cut-offs they use. *ANA and SMA can also be evaluated by IFT on HEp2 cells or ELISAs (for details and rules see text and Table 6).[134] **pANNA, anti-dsDNA, anti-SLA/LP, anti-LKM1, anti-LKM3, anti-LC1, anti-F-actin, anti-Ro52, anti-α-actinin with common and specific assays. If this expert testing is also negative but clinical suspicion is still present a liver biopsy is justified for the rare possibility of autoantibody-negative AIH. AIH, autoimmune hepatitis; ANA, antinuclear antibodies; anti-dsDNA, antibodies against double-stranded DNA; anti-F-actin, antibodies against filamentous actin; anti-LC1, anti-liver cytosol type-1 antibodies; anti-LKM1, anti-liver kidney microsomal type-1 antibodies; anti-LKM3, anti-liver kidney microsomal type-3 antibodies; anti-Ro52, antibodies against Ro52 autoantigen; anti-SLA/LP, antibodies against soluble liver antigens/liver pancreas; IFT, immunofluorescence testing; IgG, immunoglobulin G; pANNA, perinuclear anti-neutrophil nuclear antibodies; SMA, smooth muscle antibodies; ULN, upper limit of normal.

high sensitivity and specificity for AIH diagnosis (95% and 92%, respectively).[159] In sum, these results indicate that pIgG and metabolomics are promising biomarkers that could improve the diagnostic work-up of patients with suspected AIH, even though further international validation studies are needed.

What is the role of liver biopsy in the diagnosis of AIH?

Recommendations

- Liver biopsy is required to establish the diagnosis of AIH **(LoE 1, strong recommendation, strong consensus).**
- The histology report should include grading of necroinflammatory activity, staging of fibrosis and classification of the findings as likely, possible or unlikely AIH **(LoE 2, strong recommendation, strong consensus).**

The liver biopsy as a procedure to obtain liver tissue remains a prerequisite in the management of AIH. Despite the emergence of non-invasive diagnostic tools, histological examination of liver tissue continues to be the diagnostic tool of choice for proper grading and staging of AIH.[160] Establishing the diagnosis of AIH without histology should be an exception because the label AIH comes with the consequence of long-term immunosuppressive treatment.

To maximise the diagnostic properties of a liver biopsy, it should meet specific standards. A liver biopsy specimen should contain at least eight portal tracts. This requirement is best met if the specimen is obtained with a needle of at least 18G, and preferably 16G or wider, and the minimum length of the biopsy cylinder is 1.5 cm.[160] Longer biopsies (over 2.5 cm) may allow for more accurate grading of inflammatory activity and staging of fibrosis severity. However, the diameter of a liver biopsy, which influences the number of complete portal tracts, is often more relevant than its length. Given the irregular distribution of AIH lesions in the liver, obtaining longer biopsies or biopsies from multiple liver segments reduces the risk of sampling error.[9] In children, needle size and length should be determined according to age and weighed against the safety and the disadvantages of an inconclusive liver biopsy.[161]

The pathology report should provide a systematic evaluation of all histological landmarks such as portal tracts, parenchyma, sinusoids, terminal hepatic veins and include comments on the presence, maturity and extent of fibrosis.[9] Histological grading should be performed according to Ishak's modified hepatic activity index (mHAI).[162] Histological staging is required and either the 7-tiered Ishak staging system[162] or a 5-tiered staging system may be applied depending on the experience and the protocols in each centre.

Histological evaluation of a liver biopsy for AIH should start with establishing the dominant pattern of inflammation, *i.e.* portal or lobular. Ideally, the liver biopsy should be evaluated by a specialised liver immunopathologist and not a general pathologist, while the report should include a weighed assessment and classify the findings according to the 2022 IAHPG criteria as likely, possible or unlikely AIH.[9]

- *Likely AIH*
  - Presence of a predominantly portal lymphoplasmacytic infiltrate with more than mild interface hepatitis and/or more than mild lobular hepatitis in the absence of histological features suggestive of another liver disease, or
  - Presence of more than mild lobular hepatitis with portal lymphoplasmacytic infiltrates and/or interface hepatitis and/or portal-based fibrosis in the absence of histological features suggestive of another liver disease
- *Possible AIH*
  - A predominantly portal lymphoplasmacytic infiltrate without more than mild lobular or interface hepatitis in the absence of histological features of another liver disease, or
  - Any lobular hepatitis without any of the three likely features above in the absence of histological features of another liver disease, or
  - A predominantly portal lymphoplasmacytic infiltrate with one or both of the likely features or a predominantly lobular hepatitis with any of the three likely features above in the presence of histological features of another liver disease
- *Unlikely AIH*
  - Presence of portal or lobular hepatitis without the likely features in the presence of histological features of another liver disease

Emperipolesis and hepatocyte rosettes are no longer considered as typical lesions of AIH as they are not specific.[9] However, if they are detected, they may be reported as surrogate markers of disease severity.[9]

A liver biopsy may be used to monitor the response to treatment and may inform the clinical decision to intensify or stop therapy. A systematic review of response criteria has defined remission in AIH histologically as a mHAI <4/18 in an adequate liver biopsy specimen.[163] In clinical practice, the need to establish histological evidence of remission is limited, unless there is a desire to stop therapy. A recent small cohort study in 12 patients with AIH with a CBR for >2 years and evidence of histological remission (mHAI ≤3) established that 67% of them remained in a treatment-free remission during a median follow-up of 62 months.[164] Repeat liver biopsies may also be performed to monitor histological disease activity, particularly in cases with relapse or insufficient response, and if biochemical signs of cholestasis are escalating and the development of a variant disorder (AIH/PBC or AIH/PSC) is suspected.

What other conditions should be considered in the differential diagnosis of AIH?

Recommendation

- Differential diagnosis of AIH should include various causes of liver diseases depending on the presentation (acute hepatitis, chronic hepatitis or cirrhosis) as well as extrahepatic entities, such as coeliac disease and SLE **(LoE 1, strong recommendation, strong consensus).**

All causes of liver injury with an acute or chronic increase of aminotransferase levels or cirrhosis should be considered.

Transaminase elevation can occur without underlying liver disease as well. A comprehensive list of known hepatic and extrahepatic causes of liver injury and their diagnostic criteria are summarised in Tables 4-6.

Acute onset of AIH can present as acute viral hepatitis-like illness and it is thus mandatory to first exclude hepatotropic and non-hepatotropic viruses in cases with acute aminotransferase elevation.[3–5] Of the hepatotropic viruses, hepatitis A virus (HAV) and hepatitis E virus (HEV), as well as a potential acute exacerbation of chronic hepatitis B (HBV), should be excluded. In the case of non-hepatotropic viruses, the characteristic extrahepatic symptoms (*e.g.* upper or lower respiratory symptoms, lymph node enlargement, etc.) may indicate the possibility of a particular viral infection (Table 5). Since 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been added to the list of viruses causing potential acute liver injury.[165] An additional differential diagnostic problem in the case of an acute presentation of AIH is idiosyncratic DILI or herbal-induced liver disease with various clinico/pathological phenotypes. A special form, which is addressed later in the text, is DI-ALH.[166] Other aetiologies in the differential diagnosis of acute AIH cases include the acute Wilsonian crisis, acute alcohol-associated hepatitis, ischaemic hepatitis and liver involvement in systemic autoimmune diseases that have distinctive clinical and laboratory features to establish the diagnosis (Table 5). Coeliac disease was also reported to be associated with a 5-fold higher risk of acute hepatitis.[41,46,47,167] The differential diagnosis of acute AIH is complicated by the fact that autoantibodies and hypergammaglobulinemia may be absent in a significant proportion (15-39% according to old studies) of cases, while false positivity may also occur in cases with significant liver necrosis.

For patients who have persistently abnormal aminotransferase values (≥6 months) or cirrhosis at the time of diagnosis, chronic HBV and chronic hepatitis C virus (HCV) infection should be excluded first based on serology results. If steatosis is present (on abdominal ultrasonography and/or increased controlled attenuation parameter by transient elastography [TE]) the following pathologies are possible from a differential diagnostic point of view: MASLD with or without steatohepatitis (MASH), ALD, DILI or Wilson's disease. In general, the levels of aminotransferases in steatotic liver disease are lower than in AIH and all have characteristic aminotransferase patterns, including AST/ALT ratio values, cholestatic liver enzyme values and other biochemical and serological characteristics[168] (Table 5). However, the differential diagnosis of chronic AIH is sometimes difficult, as low titres of autoantibodies can appear in approximately 20% of patients with MASLD or chronic viral hepatitis, while cirrhosis is characterised by increased IgG regardless of disease aetiology. Besides serologic overlap, MASLD/MASH can co-exist with AIH and may bear some similarities at the histological level, such as lobular inflammation and hepatocyte ballooning, even though lobular inflammation seems to be less intense compared to pure AIH cases.[114] In chronic hepatitis cases, the possibility of coeliac disease should also be considered as in the acute hepatitis cases.[41,46,47]

Another challenge in the differential diagnosis of chronic cases is the discrimination between SLE and AIH. As most patients with AIH suffer from polyarthralgia, it is logical for physicians to consider the diagnosis of SLE instead of AIH in a patient with ANA and anti-dsDNA seropositivity. However, it should be emphasised that the involvement of the liver is not a common systemic manifestation of SLE. Concurrent MASLD because of corticosteroid use, viral hepatitis, and DILI as a result of SLE-related therapies are the most frequent causes of abnormal liver biochemistry in patients with SLE. However, the presence of anti-dsDNA antibodies is not always synonymous with a diagnosis of SLE.[6,77,169,170]

How can we distinguish between drug induced-autoimmune-like hepatitis (DI-ALH) and AIH to optimise patient management and treatment decisions?

Recommendations

- DILI associated with an autoimmune phenotype, *i.e.* the presence of autoantibodies, high IgG levels and/or histological evidence of autoimmunity in the liver, should be considered as possible DI-ALH **(LoE 2, strong recommendation, strong consensus).**
- Differential diagnosis between DI-ALH and AIH should be established by treatment response and disease course. Resolution after withdrawal of the implicated agent with or without a short course of corticosteroids and no relapse in the long term may indicate DI-ALH instead of classic AIH **(LoE 3, strong recommendation, strong consensus).**

Recently, the EASL CPGs on DILI along with an expert opinion meeting report, chose the term DI-ALH instead of drug-induced AIH as the preferred term to describe a variety of acute and chronic liver injuries ascribed to drugs, herbals, and dietary supplements in susceptible individuals.[166,171] This quite problematic and enigmatic entity is characterised in more instances by the presence of clinical, serological and/or histological markers of classical AIH making its differential diagnosis difficult. According to the recently published expert opinion meeting report, more than 40 different substances including vaccines against SARS-CoV-2 have been implicated to cause DI-ALH so far.[166,172–177] The process of identifying/determining such links, however, is dynamic. Minocycline, nitrofurantoin, hydralazine, methyldopa, interferon, imatinib, adalimumab, infliximab, statins and dietary supplements (*e.g.* Khat and Tinospora cordifolia) are amongst the drugs associated with "highly probable" DI-ALH.[172–177] Therefore, the onset of liver damage based on abnormal liver biochemistry associated with an autoimmune phenotype (serum autoantibodies and high IgG levels) and a compatible temporal relationship with drugs, herbals, dietary supplements or vaccines should be considered as possible DI-ALH, especially for substances considered highly likely to induce this phenotype.[166,171] Of note, signs of hypersensitivity reactions, such as eosinophilia, rash or fever, are usually absent in DI-ALH cases.

Recently, a revised electronic version of RUCAM (RECAM, Revised Electronic Causality Assessment Methods) has been suggested for causality assessment.[178] The differential diagnosis between DI-ALH and idiopathic (classic) AIH is always

challenging, as in most cases, the clinical, biochemical, serological and histological features are indistinguishable. Regarding histology, the only exception is the finding of advanced fibrosis/cirrhosis which is less common in the DI-ALH group compared to classical AIH.[174,179,180] To date, no individual serologic biomarker has been identified for the establishment of a firm DI-ALH diagnosis. Recently, Björnsson and colleagues[172] proposed five criteria for the DI-ALH diagnosis, such as (1) substance as a trigger of liver injury with indicators of autoimmunity (elevation in any of ANA, SMA or IgG) and liver biopsy compatible with AIH according to the simplified criteria, (2) incomplete or no recovery or worsening of aminotransferases after drug cessation, (3) need for corticosteroids or spontaneous recovery, (4) no relapse for at least 6 months after corticosteroid withdrawal and (5) drugs potentially inducing DI-ALH with a chronic course. The first four criteria define probable DI-ALH, whereas three suggest possible disease.[166,172] However, external prospective validation of these criteria is still lacking.

The liver damage in DI-ALH usually manifests clinically within 3 months of drug exposure but can appear after more prolonged latency.[172,174,181,182] There are substantial differences in terms of treatment response and disease course that can be used in the differential diagnosis. In general, DI-ALH has a favourable disease course, as in the vast majority of cases the disease resolves either spontaneously within 6 months after withdrawal of the offending drug or after a short course of corticosteroids.[166,171,172] Absence of relapse in the long-term without the need for immunosuppression is in most instances typical of DI-ALH cases.[173,174,180,183–186] Conversely, patients with AIH have high potential for chronic progression or recurrence that requires long-term immunosuppressive therapy to prevent development of end-stage liver failure.[26] A proposed algorithm for the differential diagnosis between AIH and DI-ALH is provided in Fig. 2, although the evidence and grading of these suggestions is low.

Treatment and monitoring

Why and when should patients with AIH receive treatment?

Recommendations

- AIH treatment should be aimed at the attainment of complete biochemical, clinical, and histological remission of the disease **(LoE 2, strong recommendation, strong consensus).**
- AIH therapy is recommended to reduce morbidity and mortality and improve quality of life **(LoE 1, strong recommendation, strong consensus).**
- Immunosuppressive treatment is recommended in all patients with active disease including those with advanced fibrosis and/or compensated cirrhosis **(LoE 1, strong recommendation, strong consensus).**

Several old studies have already shown that untreated AIH bears a poor prognosis, with a mortality rate of about 55% during a follow-up period of 30-72 months.[52,187–191] Therefore, adequate immunosuppressive treatment should be given to all patients with active disease, including those with advanced fibrosis or compensated cirrhosis, in an attempt to achieve complete remission of the disease and prevent its progression to end-stage liver disease, HCC development and the need for LT.[71,73,85,192–201]

According to a recent report by the IAIHG,[163] CBR was defined as normalisation of AST, ALT, and IgG levels no later than 6 months after treatment initiation (Table 7). Recent, yet unpublished, data have questioned the role of IgG normalisation in the management of AIH, as the prognosis remains excellent when aminotransferases are normal and IgG is elevated, thus calling into question the role of IgG as part of the definition of CBR. Even though such a strategy may help prevent overtreatment simply because of IgG elevation, for the time being there is no robust data to support a different CBR definition. Insufficient response was defined as lack of CBR after 6 months of treatment initiation and was agreed to be applied for both first-line and second-line therapies. It should be emphasised that an insufficient response does not necessarily indicate an urgent need to change treatment, but it should alert the clinician, since it might have prognostic value.

The largest retrospective cohort study of patients with AIH in the world (n = 2,559) from the IAIHG recently confirmed that CBR within 6 months after immunosuppression is an independent prognostic factor for favourable patient outcomes, even though the same study revealed that 17% of patients who did not achieve CBR at 6 months attained it at 12 months, and this finding also had prognostic significance.[197] In this context, a recent retrospective study from South Korea in almost 300 patients with AIH, showed that those who achieved CBR within 12 months after treatment initiation had the highest chance of favourable outcomes.[193] Similarly, a multicentre retrospective cohort of 301 patients with AIH established that AST normalisation at 12 months was predictive of survival, independently of age, AST levels at diagnosis and cirrhosis.[202] Of note, in that study, IgG levels were not associated with survival in the first 12 months of treatment,[202] a finding which contrasts with another study.[203] Collectively these data indicate that the evaluation of CBR in clinical practice no later than 12 months is reasonable.[193,197,202] Identification of insufficient response requires the administration of predniso(lo)ne at a starting dose of at least 0.5 mg/kg/day with a maintenance dose of up to 10 mg/day and an appropriate dose of azathioprine or another immunomodulatory drug, while treatment adherence must also be confirmed.[163]

Non-response was defined as reduction of AST/ALT of <50% from baseline levels within 4 weeks after starting immunosuppression (Table 7).[163] However, a recent retrospective study in 370 patients (discovery cohort) and another 370 patients (validation cohort) revealed that a rapid aminotransferase reduction (≥80% from baseline) after 8 weeks of treatment was associated with AST/ALT normalisation at 6 and 12 months and led to significantly better outcomes, suggesting that the proposed 4-week cut-off for the definition of non-response may be too early.[204] Primary non-response should raise considerable concerns regarding problems with either adherence to treatment or the presence of an alternative diagnosis.

Remission was defined by the absence of necroinflammatory activity (mHAI <4/18) on liver biopsy either 12

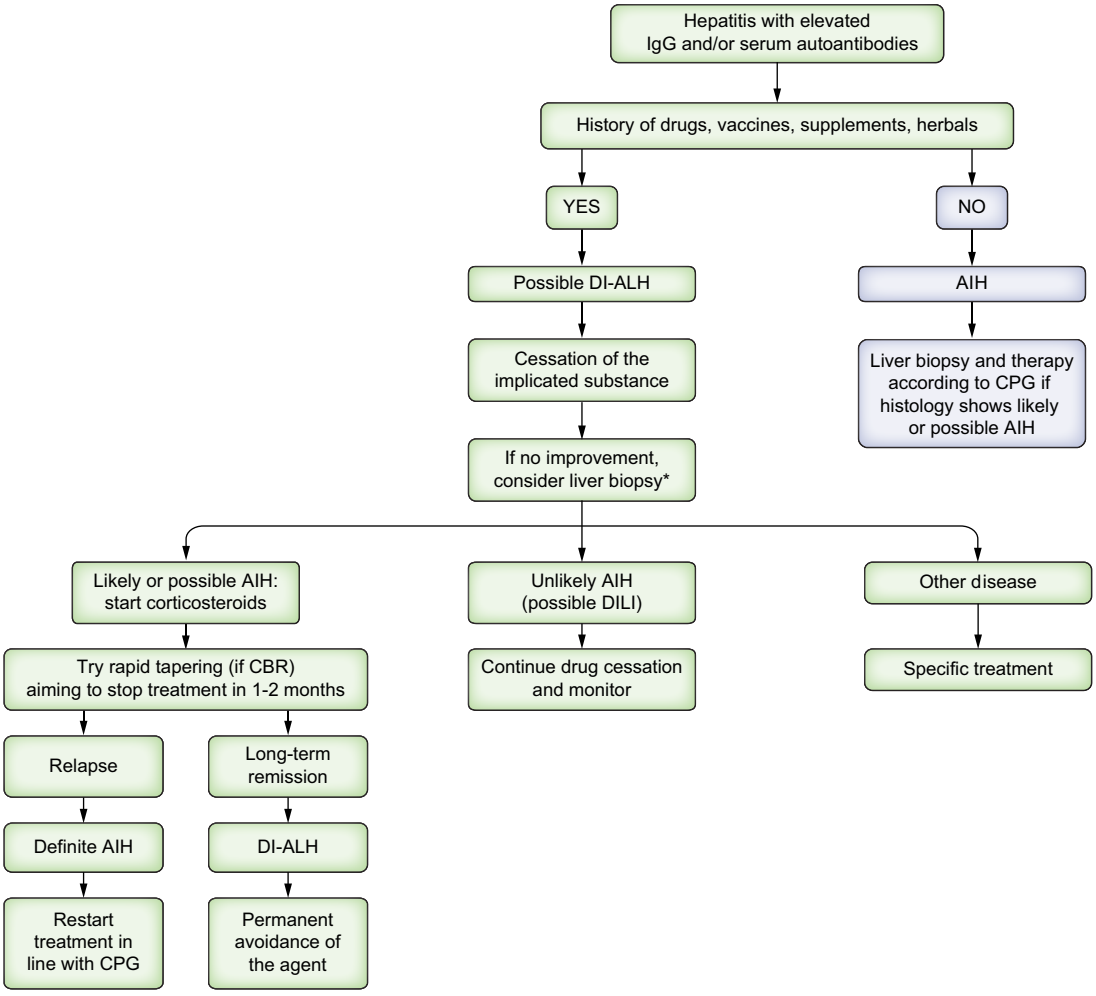

Fig. 2. Suggested algorithm for the differential diagnosis of DI-ALH and AIH. *The period of time to perform a liver biopsy depends on clinical judgement and varies according to the severity of ALT elevation. AIH, autoimmune hepatitis; ALT, alanine aminotransferase; CBR, complete biochemical response; CPG, clinical practice guidelines; DI-ALH, drug-induced – autoimmune-like hepatitis; DILI, drug-induced liver injury; IgG, immunoglobulin G.

Table 7. Endpoints and response criteria in AIH (modified from[163]).

Endpoints	Definitions
CBR	Normalisation of aminotransferase and IgG levels no later than 6-12 months after initiation of treatment
Insufficient response	Lack of CBR no later than 6-12 months after initiation of treatment with standard of care
Non-response	<50% reduction of aminotransferase levels from baseline after 4 weeks of treatment initiation
Remission (histological)	mHAI <4/18 on liver biopsy at any time during treatment
Intolerance to treatment	Occurrence of any adverse event due to therapy leading to drug cessation

AIH, autoimmune hepatitis; CBR, complete biochemical response; mHAI, modified hepatic activity index.

months after treatment initiation or at any time during treatment.[163] Finally, intolerance to treatment was defined as any adverse event potentially related to the immunosuppressive regimen leading to drug withdrawal (Table 7).[163]

Treatment initiation in patients with mild histological activity remains controversial, especially among the elderly, because side effects related to immunosuppression should always be counterbalanced with the risk of AIH progression.[31,50,52,205,206] In this group of patients, close follow-up without therapy could be justified, especially in those with contraindications to corticosteroid use (*e.g.* patients with uncontrolled diabetes, severe osteoporosis or several components of the metabolic syndrome including morbid obesity). Additionally, spontaneous resolution of AIH inflammatory activity may rarely occur. In these cases, as well as in those with burnt out cirrhosis (cirrhosis without inflammatory activity), immunosuppression can be withheld. However, as the course of AIH is unpredictable and fluctuates, careful long-term monitoring (*e.g.* measurement of aminotransferases and IgG every 3-6 months), including new liver biopsy if aminotransferase and/or IgG levels increase or fluctuate, is advised to avoid missing a subclinical relapse.[50,52,200]

What is the usual roadmap of the management of adult patients with AIH (pretreatment evaluation - induction therapy – predniso(lo)ne dose – tapering schedule – monitoring of biochemical data, treatment-related complications and fibrosis stage – follow-up visits)?

Pretreatment evaluation

Recommendations

- Vaccination against HAV and HBV is recommended for all susceptible patients with AIH **(LoE 5, strong recommendation, strong consensus).**
- All other potential vaccinations (influenza, SARS-CoV2, *Streptococcus pneumoniae*, *etc.*) should comply with national guidelines **(LoE 5, strong recommendation, strong consensus).**
- Screening for autoimmune thyroid and coeliac disease is recommended in all patients with AIH at diagnosis **(LoE 2, strong recommendation, strong consensus).**
- Dual energy X-ray absorptiometry (DEXA) determination is recommended in all adult patients with AIH at initiation of treatment **(LoE 3, strong recommendation, strong consensus).**

Before the initiation of immunosuppression, evaluation of HBV and HAV status, with appropriate vaccination for those unvaccinated or without previous virus exposure, is recommended but should not delay treatment initiation. Vaccination against influenza virus and SARS-CoV2 yearly, as well as Streptococcus pneumoniae should also be available to all patients according to local guidelines. Ideally, vaccination should be started before initiating immunosuppression. However, if immediate treatment is necessary, vaccination should be initiated as soon as immunosuppression is tapered to maintenance therapy to optimise vaccine response.

Autoimmune thyroid disorders and concurrent coeliac disease are common and usually asymptomatic, thus screening at diagnosis is recommended (determination of TSH and T4 levels along with anti-thyroid antibodies and coeliac-related antibodies).[41,43,44,46]

Assessment of bone mineral density by DEXA at diagnosis and during follow-up seems reasonable, as patients with AIH suffer from age-dependent worsening of the cortical bone microarchitecture.[207] This strategy may be able to identify patients with AIH at increased risk of osteoporosis. In this regard, a retrospective cross-sectional analysis has shown that about 20% of patients with AIH older than 50 years have osteoporosis.[208] In addition, a very recent large-scale study from South Korea in 7,062 patients with AIH reported a high incidence of osteoporotic fractures (17.5 per 1,000 person-years) compared to age- and sex-matched controls with the identification of female sex, presence of cirrhosis, older age, and long-term use of corticosteroids as the predominant risk factors.[209] Therefore, it seems reasonable to recommend using DEXA for case finding at baseline and during follow-up.

In two recent small, but prospective, studies, the effect of long-term oral corticosteroid use on intraocular pressure was investigated in children with AIH or other conditions.[210,211] Both studies found that almost two-thirds of patients – mostly asymptomatic – had raised intraocular pressure which resolved with antiglaucoma medication and predniso(lo)ne tapering. In this context, the American Academy of Ophthalmology, the European League Against Rheumatism and the National Institute for Health and Care Excellence recommend the baseline evaluation of intraocular pressure and periodic assessments during corticosteroid therapy. Therefore, a baseline examination along with periodic ophthalmic check-up, including intraocular pressure measurements, is recommended in patients with AIH for early recognition and intervention before irreversible vision loss.[210,211]

Induction therapy – predniso(lo)ne dose – tapering schedule

Recommendations

- In adults with AIH, predniso(lo)ne of at least 0.5 mg/kg/day, and potentially up to 1 mg/kg/day in more severe and advanced disease, in combination with azathioprine (whenever bilirubin is <6 mg/dl and ideally 2 weeks apart from corticosteroid start at an initial dose of 50 mg/day up to a final dose of 1-2 mg/kg/day) or mycophenolate mofetil (MMF, 1.5-2 g/day) should be the first-line treatments **(LoE 2, strong recommendation, consensus).**
- Induction therapy and tapering of corticosteroids should be individualised according to CBR status **(LoE 4, strong recommendation, strong consensus).**
- MMF is teratogenic and counselling of both female and male patients is recommended **(LoE 2, strong recommendation, strong consensus).**

The first-line induction therapy of AIH consists of predniso(lo)ne alone or in combination with azathioprine. The latter strategy is associated with considerably fewer side effects than predniso(lo)ne monotherapy.[6,85,190,212] The primary aim of these schedules is to achieve clinical and biochemical response as soon as possible while minimising exposure to corticosteroids. According to the previous EASL CPGs,[3] predniso(lo)ne doses should range between 0.5 and 1 mg/kg/day, followed by tapering under close monitoring of response. Rapid corticosteroid tapering (*e.g.* 5-10 mg/1-2 weeks) is desirable but should follow response (Fig. 3).[213,214] This strategy might increase adherence to treatment, which is of utmost importance, particularly in children, teenagers, and young adults.[85,194,215] However, a multicentre retrospective study in 451 adult patients with AIH reported that biochemical response (defined only by normalisation of ALT) at 6 months did not significantly differ between high- and low-dose schedules of predniso(lo)ne (≥0.5 mg/kg/day; median initial dose: 50 mg/day *vs.* <0.5 mg/kg/day; median initial dose: 20 mg/day).[216] However, these results should be interpreted with caution, as it was a retrospective study extending over four decades that excluded a substantial number of patients because of missing data, while no data on IgG levels or follow-up histology and long-term outcomes were available.[216] Furthermore, the two groups differed at baseline, in terms of significantly higher ALT, AST, and bilirubin levels, simplified score, and lower number of patients with cirrhosis in the high-dose group.[216] In a systematic review and meta-analysis of 25 studies including 3,305

patients, it has been shown that higher doses of predniso(lo)ne (1 mg/kg/day) resulted in higher biochemical response rates compared to lower doses (0.5 mg/kg/day), at the cost of higher rates of adverse events, particularly in those with acute severe or advanced AIH.[217] Based on the available data, a dose of at least 0.5 mg/kg/day is recommended with potential higher doses up to 1 mg/kg/day for those with severe and advanced disease.

Azathioprine (initial dose: 50 mg/day) is added, preferably after 2 weeks of initiation of corticosteroids when bilirubin is less than 6 mg/dl to avoid diagnostic uncertainties between non-response and azathioprine toxicity. Then, azathioprine is gradually increased up to 1-2 mg/kg/day according to its toxicity and response.[73,85,218–221] Azathioprine should never be used alone as induction therapy, because such a strategy was associated with high mortality.[187,188,220] Azathioprine should be given cautiously in patients with thiopurine methyltransferase deficiency, pregnancy, cytopenias, or malignancies and should be avoided in patients with acute severe AIH and decompensated cirrhosis.

Systematic reviews and prospective studies have shown that cumulative biochemical response occurs in 50-60% of patients or even fewer. Furthermore, nearly all patients who achieve long-term CBR experience relapse after discontinuing azathioprine.[212,222,223] In this regard, it should be noted that these conventional treatments are based on randomised-controlled trials (RCTs) conducted in the past five decades, carrying the inherent problem of not investigating for HCV, while they used different response criteria from those recently endorsed by the IAIHG,[163] with the last report published almost 30 years ago.[187,188,190,220,224] As an alternative first-line treatment option to azathioprine, MMF is a potent, non-competitive, and reversible inhibitor of isoform type-II of inosine-5'-monophosphate dehydrogenase that has been investigated in combination with predniso(lo)ne.[225–230] A number of observational and propensity matching studies support that MMF at a daily dose of 1.5-2 g (0.75-1.0 g bid) may serve as a safe and effective first-line treatment option for the induction and maintenance of CBR.[225–230]

Recently, a unique, multicentre, prospective, open-label, superiority RCT (CAMARO trial; NCT02900443) confirmed the previous real-world studies, as MMF proved superior to azathioprine in treatment-naive patients with AIH (CBR at 6 months 72.2% *vs.* 32.3%; $p = 0.004$).[231] Notably, these results were accompanied by more severe adverse events in the azathioprine-treated group (12.9% *vs.* 0%; $p = 0.03$), which subsequently led to higher rates of treatment withdrawal compared to the MMF group (25.8% *vs.* 5.1%), indicating the superior tolerability of MMF.[231]

A drawback of MMF is its teratogenicity and females of reproductive age should be informed in detail about its potential risks and the effective contraceptive measures that should be taken during treatment up to at least 12 weeks after drug withdrawal. Indeed, at screening, all these patients should have a negative pregnancy test, and they should be using or willing to apply two methods of birth control, such as hormonal contraceptives, condom by the partner, diaphragm, copper intrauterine device, sponge, or spermicide. Similar precautions for males under MMF are advisable.

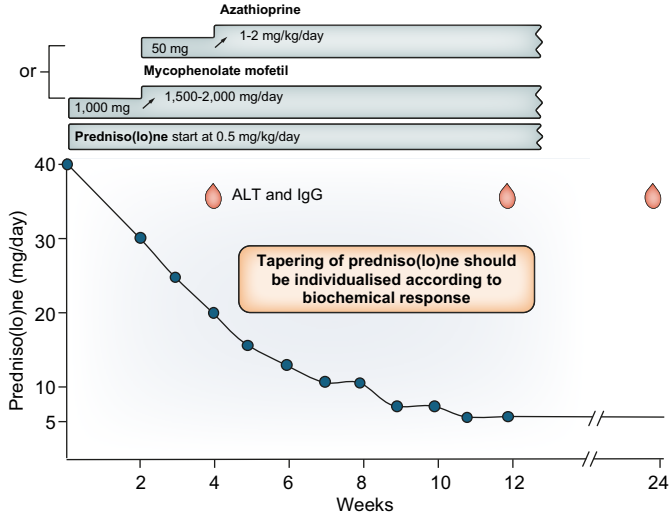

Fig. 3. Illustration of the first 24 weeks of the management roadmap of adult patients with new onset autoimmune hepatitis (*e.g.* an index case of 80 kg body weight). First-line therapy starts with predniso(lo)ne 0.5 mg/kg/day (up to 1 mg/kg/day in more severe cases), in combination with either mycophenolate mofetil (1,000 mg/day) at the same time as initiation of corticosteroids or azathioprine (50 mg/day) 2 weeks later. The figure depicts a tapering schedule for predniso(lo)ne that mirrors that of a recent clinical trial.[214] At week 2 the dose of mycophenolate mofetil should increase to its final full dose (1,500-2,000 mg/day), while azathioprine should increase to its final full dose (1-2 mg/kg/day) at week 4. ALT and IgG as efficacy parameters should be obtained at 4, 12, and 24 weeks, while choice and frequency of safety biomarkers may be tailored to the situation of the individual patient. ALT, alanine aminotransferase; IgG, immunoglobulin G.

Monitoring of biochemical data, treatment-related complications and fibrosis stage – follow-up visits

Recommendations

- Treatment-related adverse events should be pro-actively managed and, if possible, anticipated **(LoE 5, strong recommendation, strong consensus).**
- Laboratory and clinical assessment should be performed in an individualised manner depending on the severity of the disease, treatment response and tolerance (**LoE 2, strong recommendation, strong consensus).**
- Adequate calcium intake and supplementation of vitamin D should be considered in patients under long-term corticosteroids **(LoE 3, strong recommendation, strong consensus).**
- Regular non-invasive evaluation by transient elastography is recommended to monitor liver fibrosis **(LoE 3, strong recommendation, strong consensus).**

AST, ALT, prothrombin time, fasting glucose and full blood count should be monitored regularly (weekly) during the first

month of treatment, particularly in those being treated with azathioprine, as related toxicity most frequently occurs during the first 6 weeks after treatment initiation.[232] In the MMF-treated patients, monitoring of the same markers can be determined at 4 weeks after treatment initiation to evaluate for non-response, as MMF-related toxicity is rare.[163,223,229,230,233] Then, laboratory and clinical monitoring including IgG determination should be performed every 2-3 months to determine CBR at 6 and 12 months.[163] If CBR has been attained, follow-up every 3-6 months during maintenance therapy is advised to confirm sustained CBR. Given that thyroid disorders can also appear during follow-up, routine monitoring every 6-12 months seems reasonable.[43,44,234]

Up to 70% of patients with AIH, both children and adults, report side effects and low quality of life during corticosteroid therapy.[235,236] Indeed, high doses of corticosteroids can lead to metabolic complications, including weight gain, growth retardation, diabetes mellitus, hypertension, cataract, Cushingoid features and neuropsychiatric disorders, such as anxiety, insomnia, depression and even psychosis. Therefore, as in other autoimmune diseases under corticosteroid administration, a strategy of dietary restrictions, *i.e.* low carbohydrate and low salt diets, along with the administration of calcium and vitamin D supplements seems reasonable. In addition, follow-up for potential side effects to azathioprine or MMF is mandatory (see below).

Treatment-related adverse events should be pro-actively managed and, if possible, anticipated. Management may include rapid taper down of the steroid dose, as soon as serum aminotransferases improve, and other modifications (see below). In patients with concurrent metabolic syndrome, considerable attention is warranted, as corticosteroids may exaggerate many of its components and hepatic steatosis. A personalised approach with lower and more rapid tapering of corticosteroids, modification of the management of arterial hypertension, dyslipidaemia, and diabetes mellitus, along with lifestyle adaptations (physical exercise, weight loss) is recommended.[114,237–239]

In addition to HCC, assessing the risk of extrahepatic malignancies in long-term immune suppressed patients with AIH is clinically relevant. Extrahepatic cancers occur in up to 5% of patients with AIH with non-melanoma skin cancer and haematological cancers being the most frequent.[240] A Danish nationwide cohort study in a large cohort of patients with AIH (n = 1,805) demonstrated a 1.5 times higher 10-year risk of any non-hepatic cancer, only slightly increased with longer durations of immunosuppression.[241] To what extent the risk of extrahepatic malignancy is different from the healthy population is poorly studied. Nonetheless, it appears sensible to apply routine cancer screening measures for other malignancies in patients with AIH.

Progression of liver fibrosis is a major determinant of the prognosis of AIH and is assessed histologically. Physicians and patients alike are reluctant to repeat liver biopsies just to monitor the disease course. In these cases, serial liver stiffness measurements (LSM, *e.g.* every 12 months) by TE may offer a safe, reliable, and effective option for the non-invasive monitoring of fibrosis progression. TE correlates with fibrosis stage, with cut-offs for severe fibrosis or cirrhosis at 9 kPa and 12.5-16 kPa, respectively.[242–247] Of note, most studies agree that liver fibrosis can be accurately evaluated in patients with AIH after 6 months of initiation of immunosuppression.[242,245,246,248]

Should patients with AIH be treated with budesonide instead of predniso(lo)ne to reduce steroid-related side effects?

Recommendations

- Budesonide is not recommended as part of first-line treatment for AIH and is contraindicated in patients with cirrhosis **(LoE 2, strong recommendation, consensus).**
- Switching to budesonide may be suggested because of corticosteroid side effects in patients without cirrhosis who are predniso(lo)ne dependent **(LoE 3, weak recommendation, strong consensus).**

Budesonide, a synthetic glucocorticoid, has been used as an alternative to prednisolone in first- and second-line treatment in non-cirrhotic patients with AIH in view of its beneficial pharmacokinetic profile relative to predniso(lo)ne. It has a high hepatic first-pass clearance, which decreases its systemic bioavailability, and comes with a 15-fold higher affinity for the glucocorticoid receptor compared to predniso(lo)ne. Therefore, it is contraindicated in cirrhosis where there is also a high risk of portal vein thrombosis. These properties have led to the hypothesis that budesonide may be equally effective as predniso(lo)ne in non-cirrhotic AIH, but with fewer corticosteroid-related side effects.[249] A double-blind, multicentre, RCT compared budesonide (3 mg, t.i.d.) with prednisone (40 tapered to 10 mg/day) in combination with azathioprine (1–2 mg/kg/day) in treatment-naïve patients or in relapsers on prior standard of care.[250] The primary endpoint was AST and ALT normalisation after 6 months and the absence of predefined steroid-specific side effects. Budesonide was superior to prednisone at month 6 with respect to the primary endpoint (47/100 [47%] *vs*. 19/102 [18%]) and, similarly, ALT and AST normalisation was higher in budesonide-treated patients (60% *vs*. 39%).[250] This trial was mirrored in a paediatric population of 46 patients, wherein the proportion of patients who achieved the primary endpoint was comparable among groups: budesonide (3/19 [16%]) and prednisone (4/27 [15%]).[251] A subsequent retrospective case series in 381 treatment-naïve patients with AIH failed to replicate the initial claim of superiority of budesonide. Normalisation of serum aminotransferases and IgG at 6 months was significantly higher in patients treated with predniso(lo)ne (52%) than with budesonide (37%).[252] While budesonide was associated with a lower rate of corticosteroid-related side effects, the difference disappeared when patients with AIH and cirrhosis were excluded from the analysis.[252] A network meta-analysis concluded that the evidence to position budesonide in combination with azathioprine as the preferred option in treatment-naïve patients is lacking.[253] The evidence to support budesonide as a salvage treatment in those who are intolerant to or dependent on predniso(lo)ne is limited.[254]

When and how should treatment withdrawal be considered? Is a liver biopsy required?

Recommendations

- Due to the chronic nature of AIH, the majority of patients should receive long-term, often lifelong, immunosuppressive therapy **(LoE 2, strong recommendation, strong consensus).**
- A trial of stopping treatment should only be attempted in carefully selected patients if monotherapy with a low dose has been shown to maintain stable CBR for at least 2 years **(LoE 2, strong recommendation, strong consensus).**
- Immunosuppression should be reduced stepwise, as flares during dose reduction are frequent **(LoE 3, strong recommendation, strong consensus).**
- Patients with reactivity to SLA/LP autoantigen may need permanent immunosuppression **(LoE 3, weak recommendation, consensus).**
- Disease activity should be assessed individually using aminotransferase levels, IgG and/or liver biopsy prior to a trial of treatment cessation because residual activity predicts the likelihood of relapse **(LoE 2, strong recommendation, strong consensus).**
- Patient priorities should be included in the decision on treatment cessation **(LoE 5, strong recommendation, strong consensus).**
- Monitoring of relapse should be at least every 3 months in the first year after treatment cessation, and then adapted individually, considering that relapses may occur many years and even decades later **(LoE 3, strong recommendation, strong consensus).**
- After a relapse following first withdrawal, subsequent attempts are not recommended **(LoE 2, strong recommendation, strong consensus).**

As AIH arises in a genetically susceptible host, the disease risk remains a lifelong risk. For the majority of patients, the disease has already run a subclinical chronic course prior to making the diagnosis, but even in patients with an acute presentation the disease evolves into a chronic disease, therefore, long-term immunosuppression is required.[73,85,194,222,255,256] Furthermore, it may take many months, sometimes even longer, before the disease goes into remission during immunosuppressive therapy. A considerable number of patients with sustained CBR appear to have persistent histological activity (mHAI >3), however, prospective studies addressing this question are missing (mHAI >3).[162,257–259] The risk of relapse is high after stopping therapy, and potential variables that influence the relapse risk are:[82,204,212,230,260,261]

- Duration of CBR prior to treatment cessation
- Degree of CBR prior to treatment cessation
- Time to achieve continuous and sustained CBR
- Treatment duration
- Dose of immunosuppression prior to treatment cessation
- Past history of relapses

Observational studies have suggested that a duration of CBR of at least 24 months is predictive of successful tapering of immunosuppression.[230,261] Furthermore, observational studies and systematic reviews have shown that if aminotransferases are in the lower range of normal and similarly if IgG is below 12 g/L, the chance of a stable remission even without therapy is markedly higher.[258,261] It appears that elevated IgG levels predict relapse even when aminotransferases have been consistently normal. In addition, the presence of anti-SLA/LP antibodies characterises patients who may need permanent immunosuppressive therapy, as most of them relapse after treatment cessation.[82]

There has been considerable discussion on the role of liver biopsy prior to a trial of treatment cessation, and previous EASL guidelines recommended to consider liver biopsy prior to treatment withdrawal but refrained from providing a general recommendation.[3] Indeed, a clear positive or negative recommendation to perform a liver biopsy prior to treatment withdrawal cannot be given because strong evidence and prospective data are limited. It is thus uncertain whether liver biopsy is more reliable than AST/ALT and IgG measurements to confirm remission. However, it seems that the more inflammation is seen in a liver biopsy taken during CBR, the more likely the patient will relapse after stopping treatment, even though there are several limitations to these data.[256–259] In this context, it has been shown that, particularly in established cirrhosis, AST and IgG may be normal, but histology may show significant inflammatory activity, especially at the portal tract-parenchymal interface.[262] Therefore, it appears a wise compromise to perform a liver biopsy prior to a trial of treatment withdrawal at least in patients with cirrhosis.

However, patient priorities also need to be taken into account. Many patients will want to undertake a trial of treatment withdrawal independent of the predictive data, as they are hesitant to commit themselves to lifelong immunosuppressive therapy. If this is the case and the patient is thus determined to try treatment withdrawal in any case, liver biopsy is not justified. In these cases, LSM by TE can offer a safe and efficient non-invasive alternative method for monitoring fibrosis progression during CBR[242–248,263,264] (see above). Conversely, other patients may be hesitant to risk a new flare of their disease and thus may want histological confirmation of remission (defined as mHAI <4)[162] prior to trying treatment withdrawal and may thus wish to undergo liver biopsy. While this is a legitimate patient choice, patients need to be advised that even in the absence of histological inflammation, relapse is possible or even probable, although exact data on the relapse risk associated with residual hepatic inflammatory activity are lacking.

The large Dutch AIH network study also showed that patients on dual-drug immunosuppression (usually azathioprine with low-dose predniso(lo)ne) were twice as likely to relapse during the year after treatment cessation compared to patients on monotherapy, arguing strongly for trying to maintain a stable remission on low-dose monotherapy prior to a trial of treatment cessation.[222]

There is no clear-cut guidance on how to taper down the drugs when a trial of treatment withdrawal has been decided. Under real-life conditions, the tapering schedule up to complete withdrawal of corticosteroids varies largely (6-8 weeks to 3-4 months), whereas clinicians withdraw the immunomodulatory drugs either gradually or completely in one step.[222,230,258,259] After treatment cessation, up to 75% of patients may suffer from long-term myalgias and arthralgias (up to 12 months or more). Following withdrawal, all patients should be monitored closely for aminotransferase and IgG levels every 3-4 weeks for the first 3 months and thereafter in 3-month intervals during the first year when there is the highest relapse risk.[258,259] For the next 3 years, monitoring of the laboratory indices every 3-6 months seems rational, followed indefinitely by annual assessment.[222,265] Again, periodic annual assessment of fibrosis by LSM by TE may also be helpful to identify patients with fibrosis progression. Subsequent attempts at treatment withdrawal in case of relapse should be avoided, as further relapse episodes are very frequent and are related to worse outcomes.[258,259]

Transaminases may increase transiently (frequently <2x ULN) after treatment withdrawal. Thus, it is advisable to repeat testing to evaluate for potential normalisation. It is also important to exclude other causes of elevated aminotransferases, such as ALD, DILI, viral hepatitis, MASLD, hepatic or portal vein thrombosis, and biliary tract disease before a final diagnosis of relapse is established.

In sum, liver biopsy before withdrawal of immunosuppression seems generally desirable both in children and adults, as a considerable number of patients with AIH and a CBR may still have necroinflammatory activity at the histological level or even have progressed to cirrhosis, and thus should not stop immunosuppression because of the potential harmful effects of a relapse.[256–259] Of note, in this context, liver biopsies should be assessed by a specialised liver pathologist and not a general pathologist.

How should maintenance therapy be applied in patients with AIH who have achieved CBR to reduce the risk of relapse and side effects?

Statement

- In patients achieving CBR, maintenance treatment should be continued to reduce the risk of relapse and to prevent progression of liver disease **(LoE 2, strong consensus).**

Recommendations

- Maintenance treatment should consist of azathioprine or MMF as monotherapy or in combination with low-dose corticosteroids (predniso(lo)ne ≤5 mg/day). The dose of maintenance treatment should be adapted to sustain stable CBR **(LoE 2, strong recommendation, strong consensus).**
- During maintenance therapy, patients should be monitored for treatment-related complications **(LoE 5, strong recommendation, strong consensus).**
- Low-dose predniso(lo)ne monotherapy can be suggested only in patients with mild disease who achieved CBR and are intolerant to both azathioprine and MMF **(LoE 3, weak recommendation, consensus).**

After achievement of CBR, maintenance treatment should be continued to reduce the risk of relapse and, therefore, to prevent further progression of liver disease. Most patients require permanent maintenance therapy.

In one RCT,[266] combined treatment with azathioprine and prednisolone resulted in a relapse rate of 6% over 2 years (*vs.* 32% when azathioprine was stopped). Further data from a second RCT and a follow-up observational study showed that continuing azathioprine alone (at an increased dose of 2 mg/kg/day) reduced the relapse rate to zero over 12 months[267] and to 17% over 5 years.[220]

The efficacy of chloroquine *vs.* placebo in preventing relapse after treatment withdrawal has been tested in a recent RCT. While chloroquine was associated with a reduced 3-year relapse rate, adverse effects occurred in more than 50% of treated patients.[268]

In a recent multicentre UK audit including 1,267 patients with AIH, continuing corticosteroids beyond 3 months after attaining normal serum ALT levels was not associated with better clinical outcomes.[269]

The use of MMF as an alternative first-line maintenance therapy (alone or in combination with a low-dose of corticosteroids) resulted in similar efficacy in terms of sustained CBR.[227,229,230,270]

Hence, the most common maintenance treatment remains azathioprine 1-2 mg/day as monotherapy or in combination with low dose corticosteroids. Importantly, a successful maintenance treatment of AIH relies on finding the optimal individual treatment. In clinical practice, some people with AIH also receive small doses of predniso(lo)ne, and others receive predniso(lo)ne monotherapy, usually because attempts to phase out treatment have resulted in relapse. Patients with mild necroinflammatory activity at baseline biopsy who experienced intolerance to both azathioprine and MMF, but have attained CBR, can continue with predniso(lo)ne monotherapy at the lowest dose to maintain CBR. During azathioprine or MMF maintenance therapy, patients should be monitored for

treatment-related complications (see above). The duration of immunosuppressive treatment could be at least 4 years, with at least the last 2 years being in sustained CBR.[233,271]

Importantly, measurement of thiopurine metabolites can be used to optimise therapy and to distinguish true relapse from poor adherence (see below).[233] A meta-analysis including both adults and paediatric studies found a correlation between 6-thioguanine nucleotides (6-TGN) values and CBR.[272]

How should AIH relapse and flares be defined and managed?

Recommendations

- Patients should be monitored by measuring aminotransferases and IgG because of the high risk of flares and relapses **(LoE 2, strong recommendation, strong consensus).**
- Treatment adherence should be assessed in case of flares or relapses **(LoE 1, strong recommendation, strong consensus).**
- Re-biopsy can be performed to exclude other causes of elevated aminotransferases in patients with suspected flares or relapses of AIH **(LoE 2, weak recommendation, strong consensus).**
- Flares and relapses should be treated with short courses of corticosteroids and adjustment of maintenance therapy **(LoE 2, strong recommendation, strong consensus).**

Relapse in an index patient with AIH with previous CBR can occur after treatment withdrawal, whereas flares represent lack of CBR usually during tapering of corticosteroids in the induction phase or during maintenance therapy. However, rarely, flares of previously undiagnosed AIH can present as ACLF, which can be overlooked.[68,273] Although the precise definitions of relapse and flares are lacking, they should be considered when ALT increases more than 2-3 times the ULN and/or IgG is above the ULN, a finding which usually precedes that of ALT increase.[233] However, rechecking of aminotransferases for potential normalisation and appropriate exclusion of other causes of aminotransferase elevation, as well as problems in terms of adherence to treatment, are advisable before a working diagnosis of relapse or flare is considered.[6,274]

From the clinical point of view, recognition and appropriate management of relapses and flares is of major significance, as repeated events are associated with the development of progressive fibrosis resulting in end-stage liver disease, LT or liver-related death.[275,276] Re-biopsy of the liver is not usually needed to confirm relapse or flare, but it seems reasonable in case of ACLF and when there is suspicion of other causes during differential diagnosis.[68,273]

A recent systematic review between 1972 and 2018 found a wide range of relapse rates (25%-100%).[258] This was probably due to the considerable heterogeneity of the studies in terms of relapse definition, treatment schedules, treatment duration prior to discontinuation and the criteria used for CBR and histological remission.[258] Low relapse probability has been reported in several circumstances, such as DI-ALH or virus-associated AIH, normal IgG levels at diagnosis, absence of cirrhosis or extrahepatic autoimmunity, anti-SLA/LP seronegativity, shorter time to attain continuous and sustained CBR (*e.g.* in <6 months), longer duration of treatment (≥4 years), absence of previous relapses, and deeply normal ALT (below half the ULN) and IgG levels (<1,200 mg/dl) at the time of drug withdrawal.[82,141,212,213,222,230,258–261,277,278]

In previous small studies with short follow-up in children with AIH, the sustained immunosuppression-free CBR ranged between 45% and 87%.[194,279–281] A recent large study with long-term follow-up showed that 53% of children in whom treatment discontinuation was carried out under medical surveillance did not relapse during the study period.[85]

Flares and relapses are treated efficiently and quite easily with the initial regimens used during the induction therapy by slightly and transiently increasing the dose of corticosteroids. Very rapidly most patients re-achieve CBR with this schedule.[233,258,259]

How should non-adherence to treatment be investigated and managed in patients with AIH?

Recommendations

- Patient-centred consultations to assess for anxiety, depression and other reasons for suspected or confirmed non-adherence/concordance are recommended including assessment of capability, opportunity and motivation **(LoE 2, strong recommendation, strong consensus).**
- Early initiation of maintenance therapy to facilitate corticosteroid dose reductions and withdrawal is recommended to improve confidence in the relationship between caregiver and patient **(LoE 2, strong recommendation, strong consensus).**
- Testing of thiopurine metabolites is recommended to assess adherence to therapy. Undetectable or low levels of 6-TGN and 6-methylmercaptopurine (6-MMP) should trigger a discussion around medication management/side effects and allow for a benefit-risk discussion to optimise therapeutic management **(LoE 3, strong recommendation, strong consensus).**

A range of factors contribute to adherence/concordance with treatment which may be either intentional or unintentional. Behaviours which drive low rates of medication adherence are complex, and patients should be informed, supported and motivated to take the medication optimally. Therefore, recognising non-adherence to treatment and understanding its causes is critical in the management of patients. Whilst no single specific intervention can modify non-adherent behaviour, assessing capability to manage medications, assessment of motivation and attitudes to medication, as well as ensuring medication supply, are generic strategies to improve treatment compliance.

In AIH, many patients are required to continue corticosteroid therapy or immunosuppression for many years or even lifelong. This form of therapy is associated with a range of cosmetic and psychological effects that impact upon patient wellbeing. Patients with AIH who have higher depression and anxiety symptoms are more likely to be non-adherent to therapy.[282] It has been postulated that the association between treatment response, anxiety and depression could also represent a bidirectional relationship where specifically poor responses to therapy could worsen depression and anxiety symptoms. Similarly, avoidant relationship styles also have a significant impact on self-reported immunosuppressant medication adherence, as well as treatment response.[282] Therefore, awareness of these factors should be discussed in patient consultations. The interdependence between physicians and patients is not to be underestimated. Confidence in treatment, which is a relevant and readily modifiable determinant of health-related quality of life (HRQL), has also been identified as a key contributor to this in all autoimmune liver diseases including AIH.[283]

Early initiation of corticosteroid sparing therapies (maintenance therapy in the form of MMF or thiopurines, such as azathioprine, mercaptopurine [MP], or thioguanine [TG]) to facilitate corticosteroid dose reduction should be undertaken. In a large study of patients with a range of autoimmune liver diseases, treatment with azathioprine in AIH was associated with increased confidence in therapy.[283]

An obvious mechanism for assessing compliance with medication is testing for metabolites or drug levels where possible. This is pertinent for drugs such as azathioprine and MP where metabolite levels of 6-TGN and 6-MMP are increasingly measurable.[284] CBR was associated with a therapeutic window for 6-TGN levels of 225-450 pmol/8x10^8 erythrocytes. Moreover, not all patients on azathioprine monotherapy to maintain CBR required 2 mg/kg/day. For patients not achieving CBR, low levels or undetectable levels of metabolites are associated with poor compliance. Metabolite monitoring also allows drug toxicity to be identified and for treatment to be fine-tuned through manipulation of thiopurine prescribing, *i.e.* with the addition of allopurinol enabling an appropriate dose reduction of azathioprine.[285] A schema for interpreting azathioprine metabolite levels and assessing for non-adherence and dose optimisation is given in Fig. 4 (see also next section below on intolerance or non-response to first-line treatment).

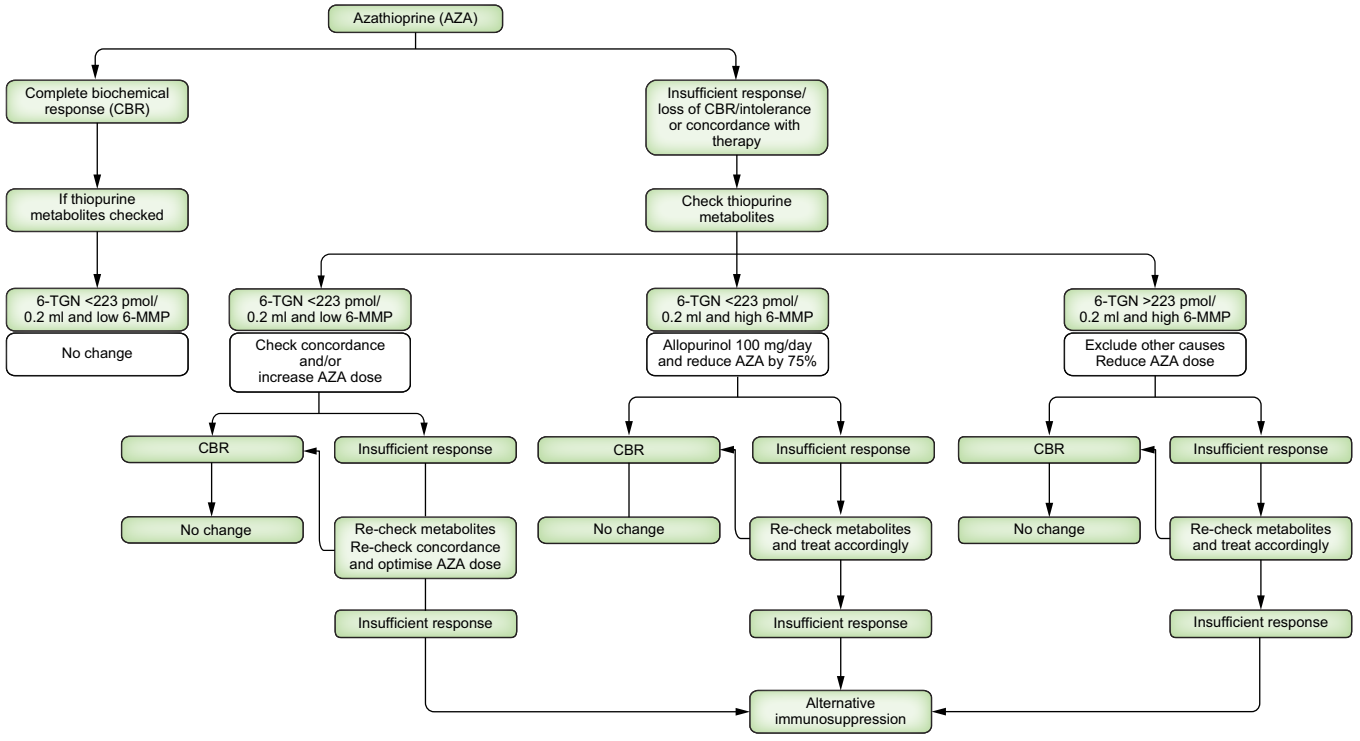

Fig. 4. Optimisation of azathioprine dosing in patients with AIH (adapted from ref.[303]). Thiopurine drugs (azathioprine and mercaptopurine) are catabolised to inactive metabolites by TPMT, which reduces concentrations of the active metabolite, 6-TGN (therapeutic range: 225-450 pmol/0.2 ml). Thiopurine metabolites have established value in assessing concordance with therapy as well as fine tuning of azathioprine doses. A schedule is given for the use of allopurinol 100 mg daily in conjunction with a previous (few days before) azathioprine reduction to 25% of its dose in order to shift metabolism of azathioprine towards less toxic metabolites. Measurement of 6-MMP (<5,700 pmol/0.2 ml) helps to differentiate patients who are suffering with hepatotoxicity, under-dosed or non-adherence (6-MMP levels appropriately low) from those demonstrating resistance to thiopurine drugs, *i.e.* preferentially metabolising thiopurine drugs to inactive 6-MMP rather than 6-TGN (6-MMP disproportionately increased). AIH, autoimmune hepatitis; 6-MMP, 6-methylmercaptopurine; 6-TGN, 6-thioguanine nucleotides; TPMT, thiopurine methyltransferase.

What are the treatment options for patients with AIH who are intolerant or do not respond to first-line treatment?

Intolerant

Recommendations

- MMF is recommended as the second-line treatment of choice in patients with intolerance or side effects to thiopurines **(LoE 2, strong recommendation, strong consensus).**
- MP or TG can be used in patients with intolerance to azathioprine **(LoE 4, weak recommendation, strong consensus**).

A recent retrospective study including 631 azathioprine-treated patients showed that approximately 15% of patients discontinued azathioprine due to adverse effects during the first year.[232] This discontinuation rate was independent of the time of azathioprine initiation (<2 weeks or ≥2 weeks). However, the results of the first prospective multicentre European Reference Network (ERN) registry showed that the rate of azathioprine intolerance was much higher (36.5%) during the first 6 months of therapy.[223] Common side effects include nausea, vomiting, and diarrhoea whilst myelotoxicity and hepatotoxicity, though possible, occur at a low frequency (<2%).[232]

In contrast, MMF (1.5-2.0 g/day) has been proven safer and much more tolerable than azathioprine with a discontinuation rate of 0-8%.[223,225,227,229–231,286] Additionally, a recent systematic review and meta-analysis,[286] and several retrospective observational studies, including a study from the Australian Liver Association Clinical Research Network, showed that MMF remains an excellent option for second-line treatment, as it was well-tolerated in patients who were intolerant to or experienced side effects related to azathioprine, demonstrating response rates of 62-92%,[287–291] even though an older study reported a response rate of 43%[292] (Table 8). Therefore, MMF should be considered as a potential second-line treatment in azathioprine-intolerant patients.

Various other treatment options have been assessed for individuals who are intolerant to azathioprine, such as MP, TG, cyclosporine and tacrolimus (TAC).[290,293,294] However, the outcomes of these treatments are limited by the small, retrospective nature of cohort studies conducted without control groups or standardised response criteria, thus making it difficult to make consistent recommendations for their use (Table 8).

MP is a non-enzymatically converted derivative of azathioprine and possesses the same mechanism of action and comparable efficacy. One small retrospective study in 20 azathioprine-intolerant patients showed that MP was more tolerable for up to 75% of patients due to the differences in their safety profiles.[293] However, CBR was achieved in 40% of patients (Table 8). MP is devoid of the imidazole component found in azathioprine, which is thought to be responsible for certain side effects. The standard starting dose of MP is 0.5 mg/kg/day and should be increased to 1-1.5 mg/kg/day or adjusted based on azathioprine metabolites (225-450 pmol/8x10^8 red blood cells) if tolerated.[293] TG is metabolised directly into 6-TG, and it is generally better tolerated than azathioprine or MP. This may be due to the absence of methylated azathioprine metabolites. The standard dose of TG is 20 mg/day, and this dose appeared to be effective in 66.7% of 33 azathioprine-intolerant patients according to a single retrospective observational study.[294]

TAC, a calcineurin inhibitor with a more potent immunosuppressive effect than either cyclosporine or MMF, has also been investigated as a second-line treatment in the setting of azathioprine intolerance. Indeed, in patients with intolerance to azathioprine or steroid monotherapy, one multicentre retrospective study reported normalisation of aminotransferases in 94.1% of 34 patients following TAC compared to 92% in 74 patients following MMF (Table 8).[290] However, this retrospective study included very heterogeneous groups of patients who were treated with different schemes and with irregular follow-up data, while clear-cut response rates for those intolerant to azathioprine were not provided. In this context, some other studies in the field including more systematic data have shown that although TAC is a potent immunosuppressant, it requires close follow-up, as it has a quite small therapeutic window and toxicity remains a problem.[295–297] A recent small study confirmed the limited effectiveness and the potential risks of TAC-related therapy in azathioprine-intolerant patients.[298] Therefore, its use should be potentially reserved for patients with insufficient response without other treatment options. Where TAC use is undertaken in intolerant patients, starting doses of 1 mg twice daily or 2 mg once daily (dependent on preparation) is recommended to achieve target trough levels of no more than 5 ng/ml with attention paid to renal function, blood pressure and other potential toxicity indices.[299]

Insufficient response

Recommendations

- In patients with insufficient response to thiopurine-based treatments, determination of 6-TGN and 6-MMP levels – if available – is recommended to confirm treatment adherence or sub-therapeutic drug levels (proposed cut-off: 223 pmol/8×10^8 red blood cells) **(LoE 3, strong recommendation, strong consensus).**
- After exclusion of non-adherence, intensification/optimisation of immunosuppression by increasing the dose of azathioprine up to 2 mg/kg/day (when 6-MMP is appropriately low) is recommended **(LoE 3, strong recommendation, strong consensus).**
- Addition of allopurinol (contraindicated in pregnancy) and reduction of the azathioprine dose to 25% (when 6-MMP is disproportionately increased) can be suggested as an alternative to the previous recommendation **(LoE 3, weak recommendation, strong consensus).**
- MMF may be used before initiating third-line therapies after unsuccessful intensification/optimisation of azathioprine-related therapies **(LoE 2, weak recommendation, consensus).**
- Tacrolimus, infliximab, rituximab and belimumab can be used as potential third-line rescue therapies in difficult-to-treat patients in expert centres (see recommended doses and monitoring in Table 11) **(LoE 4, weak recommendation, strong consensus).**
- Patients receiving these third-line therapies should be evaluated to estimate the risk of opportunistic infections and to ensure delivery of appropriate prophylaxis or vaccination **(LoE 3, strong recommendation, strong consensus).**

Table 8. Efficacy of treatment options for patients with azathioprine intolerance.

Author	Study	n*	Aim	Efficacy in patients with AZA intolerance	Side effects to second-line agent
Mercaptopurine					
Hübener *et al.*[293]	Retrospective	20	Complete response: AST, ALT, and IgG normalisation. Partial response: reduction in AST, ALT, and IgG to <2x ULN.	Complete response: 40% (8/20) Partial response: 35% (7/20)	Gastrointestinal (n = 5), anaemia (n = 2), alopecia (n = 1) and leucopoenia (n = 1)
Thioguanine					
van den Brand *et al.*[294]	Retrospective	33	Complete response: AST, ALT, and IgG normalisation. Incomplete response: reduction in AST, ALT, and IgG to <2x ULN.	Complete response: 66.7% (22/33) Incomplete response: 11% (3/33)	Headache (n = 3), myalgia/arthralgia (n = 2)
Mycophenolate mofetil					
Hennes *et al.*[292]	Retrospective	28	Response: reduction in AST, ALT to <2x ULN.	43% (12/28)	Nausea (n = 4), weight loss (n = 4), abdominal pain (n = 4), diarrhoea (n = 1)
Baven-Pronk *et al.*[289]	Retrospective	15	Complete response: AST and/or ALT normalisation. Incomplete response: reduction in AST and/or ALT to <2x ULN.	Complete response: 67% (10/15) Incomplete response: 6.7% (1/15)	Gastrointestinal (n = 5), rash (n = 3), fatigue (n = 3), alopecia (n = 2), leucopenia (n = 1)
Efe *et al.*[290]	Retrospective	56	Complete response: AST, ALT, and IgG normalisation.	92% (68/74 including 18 patients who started mycophenolate because of steroids intolerance)	Leukopenia (n = 6), gastrointestinal (n = 3), headache (n = 1)
Roberts *et al.*[291]	Retrospective	63	Complete response: AST, ALT, and IgG normalisation.	62% (39/63)	Gastrointestinal (n = 11), cytopenia (n = 3), infections (n = 4), neuropsychiatric (n = 3), skin cancer (n = 3)
Kolev *et al.*[287]	Retrospective	40	Complete response: ALT and IgG normalisation.	80% (32/40)	Leucopenia (n = 2), hair loss (n = 1), fatigue (n = 1), enteropathy (n = 1), recurrent topic infections (n = 1), headaches (n = 1)
Santiago *et al.*[286]	Systematic review/ meta-analysis	171		82% (95% CI: 77-87%)	
Tacrolimus					
Efe *et al.*[290]	Retrospective	22	Complete response: AST, ALT, and IgG normalisation.	94% (32/34 including 12 patients who started tacrolimus because of steroids intolerance)	Neurologic (n = 4), hypertension (n = 2), gastrointestinal (n = 2), renal failure (n = 1)

AST, aspartate aminotransferase; ALT, alanine aminotransferase; ULN, upper limit of normal.
*Number of patients with intolerance to azathioprine.

It has been estimated that 22-68% and 3-28% of patients have insufficient response to azathioprine[197,223,227,229–231,300] and MMF[223,225–231] respectively, when used as first-line therapy.[197,231,300] However, it is important to consider that some patients, especially those with advanced fibrosis or severe interface hepatitis, may require a longer time duration to achieve a CBR and the use of more potent immunosuppressive drugs could increase the risk of unnecessary side effects.[301]

In patients with insufficient response to azathioprine, the levels of its metabolites namely, 6-TGN, the active metabolite of azathioprine, and 6-MMP, which is not immunosuppressive but can reflect drug toxicity, should be determined before initiating alternative immunosuppression to evaluate whether biochemical activity is due to azathioprine underdose or non-adherence (Fig. 4).[233,284] In case of 6-TGN levels below 223 pmol/8×10^8 red blood cells and low 6-MMP, the patients should be investigated for non-adherence. If non-adherence has been excluded (high 6-MMP levels), a trial of optimisation of 6-TGN levels by increasing azathioprine dose up to 2 mg/kg/day or by adding allopurinol with simultaneous reduction of azathioprine to about 25% of the initial dose, seems rational (Fig. 4).[233,285,302,303] In patients with 6-TGN above 223 pmol/8×10^8 red blood cells along with high 6-MMP, an alternative or concurrent diagnosis should be excluded before reducing thiopurine dose and considering second- or third-line treatments (Fig. 4).[233,303] Particularly, viral infections (*e.g.* Epstein-Barr virus, cytomegalovirus), MASLD and/or MASH because of corticosteroids use, and DILI because of incidental consumption of supplements and/or herbals, should be carefully excluded before an index patient with AIH is defined as an insufficient responder.[6,233]

The cut-off of 6-TGN (223 pmol/8×10^8 red blood cells) has been suggested from previous experience in patients with IBD and LT recipients, as well as from two retrospective studies in patients with AIH,[285,304] although a recent UK study indicated that lower cut-offs might also be of clinical relevance.[284] Unfortunately, determination of 6-TGN/6-MMP is not widely available apart from in specialised laboratories, while it may also not always be covered by insurance.

It should be emphasised that repeated episodes of relapse during maintenance therapy, despite appropriate immunosuppressive therapy and adherence, should also be considered as insufficient response. Before initiating third-line treatment after unsuccessful intensification of azathioprine-related first-line therapies, MMF might be used because of its better safety and favourable tolerability, as recent systematic reviews and real-world studies have shown response rates ranging from 32% to 68% among insufficient responders, leading to a considerable reduction of patients who are real candidates for third-line interventions (Table 9).[229,230,286–288,290,291] Additionally, in patients with insufficient response to MMF as first-line therapy, switching to thiopurines should be tried before initiating third-line therapies.[229,230]

Evidence concerning the efficacy of TAC administration as second-line treatment in azathioprine insufficient responders is limited to small uncontrolled retrospective studies with diverse inclusion criteria, showing response rates ranging from 56% to 78% depending on the dose (1-6 mg/day), trough levels (around 6 ng/ml) and definition of response.[290,299] Approximately 12% of patients experience adverse events, primarily neurologic (Table 9). The efficacy of cyclosporine (2-5 mg/kg/day) in this scenario has also been explored in small, old uncontrolled case series showing variable results with response rates from 5% to 80% and significant side effects that are likely to impact patients' quality of life (hirsutism, gingival hyperplasia, neurological symptoms).[305–307] An ongoing phase IIIB, open-label, multicentre RCT (TAILOR study) will probably address this issue as it is investigating the effectiveness and safety of TAC *vs.* MMF as second-line treatment in patients with insufficient response to azathioprine.[308]

Third-line treatments should be considered in patients intolerant to first- or second-line agents and in insufficient responders who have progressive, active disease despite adherence to previous intensified first- and/or second-line agents. Patients with insufficient response to first- and/or second-line treatments are expected to exhibit lower rates of response to third-line therapies compared to intolerant patients and often need combinations with two or three drugs to achieve CBR.[233]

Several agents have been used as third-line therapies, although to date, robust data do not exist. In fact, only small uncontrolled case series have been published, where individual drugs (as monotherapies or combinations) have been used according to local expertise (Tables 10 and 11). These agents include mainly TAC, cyclosporine, rituximab, belimumab, ianalumab, infliximab and ustekinumab.[309–318] In this context, infliximab (anti-TNFα), rituximab (anti-CD20), and belimumab (anti-BAFF) have been shown to rescue some difficult-to-treat patients but are associated with an increased risk of infectious complications.[309,310,312,314,315,317] Ianalumab (a novel BAFF receptor-targeting antibody) has been evaluated in a phase II RCT in patients with insufficient response to azathioprine, but the results are still pending.

The administration of these drugs also required previous vaccination and the exclusion of latent infections that could be reactivated in the context of profound immunosuppression.[319,320] Therefore, they must be administered in reference centres with experience in the management of these patients.

How should specific forms of AIH and specific patient groups be managed?

Pregnant women with AIH

Recommendations

- Maintenance treatment with thiopurines (±corticosteroids) should be continued during pregnancy **(LoE 3, strong recommendation, strong consensus).**
- MMF should be withdrawn at least 3 months before conception **(LoE 2, strong recommendation, strong consensus).**
- In first presentations of AIH during pregnancy, standard therapeutic regimens (excluding MMF) should be utilised **(LoE 2 Strong recommendation, strong consensus).**
- Pregnancy should be closely monitored in patients with cirrhosis by a multidisciplinary team of obstetricians and hepatologists **(LoE 2, strong recommendation, strong consensus).**

Although AIH is associated with a slight decrease in fertility, particularly in patients with cirrhosis or poorly controlled disease,[321,322] pregnancy is a viable and safe option in most patients with AIH but requires close and multidisciplinary monitoring. A

Table 9. Studies evaluating treatment options in patients with insufficient response to azathioprine.

Author	Study	n	Aim	Efficacy in patients with insufficient response	Side effects to second-line agent
Mycophenolate					
Efe *et al.*[290]	Retrospective	47*	Complete response: AST, ALT, and IgG normalisation.	34% (16/47)**	Leukopenia (n = 6), gastrointestinal (n = 3), headache (n = 1)
Roberts *et al.*[291]	Retrospective	42	Complete response: AST, ALT, and IgG normalisation.	57% (24/42)	Gastrointestinal (n = 11), cytopenia (n = 3), infections (n = 4), neuropsychiatric (n = 3), skin cancer (n = 3),
Dalekos *et al.*[229]	Propensity matching trial	9	Complete response: AST, ALT, and IgG normalisation.	100% (9/9)	NA
Dalekos *et al.*[230]	Retrospective	16	Complete response: AST, ALT, and IgG normalisation.	68% (11/16)	NA
Kolev *et al.*[287]	Retrospective	10	Complete response: ALT and IgG normalisation.	50% (5/10)	
Santiago *et al.*[286]	Systematic review/ meta-analysis	124		32% (95% CI: 24-39%)	
Tacrolimus					
Efe *et al.*[290]	Retrospective	46*	Complete response: AST, ALT, and IgG normalisation.	56.5% (26/46)**	Neurological (n = 4), hypertension (n = 2), gastrointestinal (n = 2), renal failure (n = 1)
Aqel *et al.*[313]	Retrospective	11	Complete response: AST and ALT normalisation.	91% (10/11)	Headache (n = 4), neurological (n = 1), hypertension (n = 1)
Than *et al.*[311]	Retrospective	17	Not defined	29% normalisation of ALT and 50% normalisation of IgG	Headache (n = 2), abdominal pain (n = 1), psychosis (n = 1)
Ferre-Aracil *et al.*[299]	Retrospective	20	Complete response: AST, ALT, and IgG normalisation.	Not reported for patients with insufficient response; 78% (18/23) in the whole population	Diabetes (n = 1), tremor (n = 1), headache (n = 1), diarrhoea (n = 1), ototoxicity (n = 1)
Cyclosporine					
Sherman *et al.*[305]	Case series	6	Decrease in ALT >1.5x ULN.	67% (4/6)	Gingival hyperplasia (n = 6)
Fernandes *et al.*[306]	Case series	5	AST/ALT normalisation.	80% (4/5)	Hirsutism (n = 2), gingival hyperplasia (n = 2)
Malekzadeh *et al.*[307]	Retrospective	19	Complete response: AST, ALT, and IgG normalisation.	5% (1/19)	Paraesthesia (n = 4), gingival hyperplasia (n = 3), tremor (n = 1), hypertension (n = 1), diarrhoea (n = 1), hirsutism (n = 1)

AST, aspartate aminotransferase; ALT, alanine aminotransferase; IBD, inflammatory bowel disease; IgG, immunoglobulin G; NA, not available; ULN, upper limit of normal.
*Denotes insufficient response to standard of care (steroids alone or combined with azathioprine).
**Specific rates of complete response to tacrolimus or mycophenolate therapy in patients with insufficient response to azathioprine cannot be calculated precisely.

Table 10. Third-line treatment options.

Author	Study	n	Aim	Efficacy in patients with insufficient response	Side effects to second-line agent
Tacrolimus					
Aqel *et al.*[313]	Retrospective	11	Complete response: AST and ALT normalisation.	91% (10/11)	Headache (n = 4), neurological (n = 1), hypertension (n = 1)
Infliximab					
Weiler-Normann *et al.*[314]	Case series	11	Complete response: AST, ALT, and IgG normalisation.	54% (6/11)	Urinary tract infection (n = 2), ocular herpes (n = 2), recurrent herpes zoster infection (n = 2), pneumonia (n = 2)
Rituximab					
Burak *et al.*[318]	Case series	11	Decrease in ALT/AST and IgG.	Significant decrease	Dental abscess (n = 1)
Than *et al.*[312]	Case series	22	Not defined.	Significant decrease in ALT, AST, and IgG at 24 months; 59% (13/22) → corticosteroid dose reduction; 23% (5/22) → flare	Infections (n = 2), tongue cancer (n = 1)
Riveiro-Barciela *et al.*[315]	Retrospective	35	Complete response: AST, ALT, and IgG normalisation.	88.6% (31/35); Flare-free rate at 1st, 2nd and 3rd year: 86%, 73% and 62%, respectively	Infections (n = 5), anaphylaxis (n = 1), flu-like symptoms (n = 2)
Belimumab					
Arvaniti *et al.*[310]	Case series	2	Complete response: AST, ALT, and IgG normalisation.	100% (2/2)	Rectal fistula (n = 1)
Kolev *et al.*[309]	Case series	3	Complete response: AST, ALT, and IgG normalisation.	66.7% (2/3)	Headache episodes (n = 1)
Ustekinumab					
Terziroli Beretta-Piccoli *et al.*[317]	Case series in patients with concomitant IBD	5	AST and ALT normalisation.	80% (4/5)	None

AST, aspartate aminotransferase; ALT, alanine aminotransferase; IgG, immunoglobulin G.

Table 11. Dose recommendation for third-line treatment options.

Drug	Dose
Tacrolimus	0.1 mg/kg/12h (or equivalent on extended-release formulation). Recommended trough levels: 6 ng/ml
Rituximab	1,000 mg i.v. week 0 and 2. Readminister every 6 months if needed
Infliximab	Induction: 5 mg/kg weeks 0, 2, 6 and 10 Maintenance: 5 mg/kg every 8 weeks
Belimumab	10 mg/kg day 0, 14, 28 and then every 1-2 months.

recent meta-analysis of 14 studies with >1,400 patients found that patients with AIH were more likely to have gestational diabetes (odds ratio [OR] 2.84; 95% CI 1.78-4.54), hypertensive complications of pregnancy (preeclampsia, eclampsia, HELLP syndrome; OR 2.22; 95% CI 1.76-2.79), premature birth (OR 2.20; 95% CI 1.66-2.91), small for gestational age (OR 2.48; 95% CI 1.37-4.51), and low birth weight (OR 3.04; 95% CI 1.85-5.01).[323] These results were confirmed by a subsequent meta-analysis, which also found that preterm deliveries were more frequent in patients with portal hypertension.[324] However, neonatal mortality, stillbirth and congenital malformations were not significantly increased independently of the use of immunosuppression.[325–327] While AIH flares during pregnancy are rare (13%), postpartum flares occur in 41% of patients at a median time of 11 weeks after delivery.[321,323,325,328–330] Postpartum flares require intensification of immunosuppression. Importantly, immunosuppressive drugs commonly used in AIH (corticosteroids and thiopurines) are not associated with an increased risk of foetal complications during pregnancy and can be safely used during the breastfeeding period.[323] In contrast, MMF has shown teratogenic effects and is contraindicated during pregnancy and at least 3 months before conception.[331] Adequate immunosuppression during pregnancy is essential because CBR at conception and during pregnancy has been associated with reduced AIH flares and prematurity rates.[321,332] Rarely, AIH may present in pregnancy and standard diagnostic paradigms should be followed. In this circumstance, standard treatment regimens should be initiated as described in the treatment sections. However, MMF is contraindicated.

Acute severe AIH

Recommendations

- An early treatment trial with corticosteroids (predniso(lo)ne 0.5-1 mg/kg/day, or intravenous methylprednisolone at an equivalent dose) is recommended in patients with acute severe AIH without ALF or ACLF. Failure to improve after 3-7 days of treatment initiation should trigger referral to a LT centre **(LoE 3, strong recommendation, strong consensus).**
- Direct evaluation (discussion with a LT centre) for LT is recommended in patients with acute severe AIH with ALF or ACLF, as data on the role of corticosteroids in these patients is very limited and outcomes are poor (**LoE 3, strong recommendation, strong consensus**).
- If corticosteroids are given to patients with acute severe AIH with ALF or ACLF, strict surveillance for infections and close monitoring of their efficacy is recommended **(LoE 2, strong recommendation, strong consensus).**

The effectiveness of corticosteroids in addressing acute AIH has been well established and extensively demonstrated in various studies.[333,334] Treatment should be administered as recommended to patients with an insidious or chronic presentation. However, managing patients with acute severe AIH (icteric, INR ≥1.5 but <2, without hepatic encephalopathy and without chronic lesions on liver biopsy), with ALF (INR >2 and hepatic encephalopathy) or ACLF, can be challenging, and the most crucial decision is whether and when to initiate corticosteroid treatment.[67,335] In general, adult patients with acute severe AIH accompanied by ALF or ACLF have the worst prognosis, with response rates to corticosteroids of between 8% and 41%, and they should thus be referred for LT as soon as possible.[67,68,335–337]

In contrast, a significant number of patients with acute severe AIH undoubtedly benefit from treatment, as evidenced by a transplant-free survival rate ranging from 52% to 95.2%.[66,270,337–341] However, a proportion of patients fail to respond to corticosteroid treatment and may die or require LT. A separate concern is that significant corticosteroid exposure can lead to post-LT infectious complications. Several retrospective studies have searched for early predictors of corticosteroid non-response, either at presentation or after 3-7 days of treatment, aiming to decide the right time to consider LT. Age, presence of ascites and hepatic encephalopathy, INR, model for end-stage liver disease (MELD) score, and organ failure at presentation (defined by the Chronic Liver Failure Consortium organ failure score), delta (Δ) INR at day 0-3, Δ bilirubin at day 0-3, and Δ MELD score at day 0-7 have been found to predict corticosteroid treatment response.[337–339,341] Indeed, the survival and prognostic factors for acute severe AIH (SURFASA) score – [6.80 + 1.92*(D0-INR) + 1.94*(Δ%3-INR) + 1.64*(Δ%3-bilirubin)] – derived from a retrospective multicentre French cohort found that with a score higher than 1.75, the risk of dying or being transplanted was between 85% and 100%.[337] Another large study from a Spanish cohort in 242 consecutive patients developed a nomogram to predict the treatment response at diagnosis and on day 7[341] (see below).

Another issue of debate is the optimal dose and route of corticosteroid administration. Most patients (>70%) who participated in the previous studies received a high dose of predniso(lo)ne (1 mg/kg/day) intravenously;[66,270,334,338–341] however, there are no specific studies comparing high-*vs.* low-dose predniso(lo)ne (≤0.5 mg/kg/day) in this context. Pragmatically, 0.5 mg/kg/day of prednis(ol)one, or an equivalent dose of intravenous methylprednisolone, is an appropriate starting dose in this setting, since it balances the likelihood of response against the infection risk seen at doses of 1 mg/kg/day.

Studies on the management of acute severe AIH as a specific entity in children and/or adolescents are lacking. In contrast, the management of acute severe AIH with ALF has been described in the past, indicating that corticosteroids can be effective, although LT is still required in a fair number of patients.[61,62,67,80,335,342–344]

Patients with DI-ALH

Recommendations

- In suspected cases of DI-ALH, the potential causative agent should be immediately withdrawn **(LoE 2, strong recommendation, strong consensus).**
- In patients with severe hepatitis or impaired liver function or no improvement of liver tests within 30 days of discontinuation of the implicated agent, a short course of predniso(lo)ne is recommended (**LoE 4, strong recommendation, strong consensus**).
- Predniso(lo)ne at an initial dose of 0.5 mg/kg/day followed by rapid tapering until complete withdrawal within 1-2 months is recommended (**LoE 5, strong recommendation, strong consensus**).

There is no consistent evidence on how to treat patients with DI-ALH. However, a joint expert opinion consensus by the IAIHG and the Prospective European Drug-Induced Liver Injury Network has proposed a guidance on management of the DI-ALH.[166] The first and most important step in the management of these patients is the discontinuation of the causative agent, which leads to spontaneous recovery in approximately half of patients after a median of 70 days.[173,186] The indication for corticosteroid treatment in patients with DI-ALH should be individualised but corticosteroids are probably indicated in symptomatic patients and those with no improvement or worsening of liver tests after discontinuation of the implicated agent.[166] According to a study from two large DILI registries (6.4% of the 724 patients enrolled met the criteria for DI-ALH), the benefit of corticosteroid treatment was more evident in severe cases that fulfilled the nR-based Hy's law (ALT >3x ULN and total bilirubin >2x ULN) and had no biochemical resolution within 30 days.[345]

The optimal dose and duration of corticosteroid treatment is also unknown, but generally a short course (1-2 months) of predniso(lo)ne at an initial dose of 0.5 mg/kg/day leads to resolution of the syndrome in most cases (Fig. 2).[166,172] When predniso(lo)ne is considered, liver biopsy seems very helpful in confirming AIH-like lesions at the histological level and excluding other entities.[166,171,346,347]

Elderly patients with AIH

Recommendations

- Elderly patients with at least moderate activity should receive standard immunosuppression as described before **(LoE 3, strong recommendation, strong consensus).**
- A watch-and-wait strategy is recommended in elderly asymptomatic patients with mild activity and without advanced fibrosis **(LoE 4, strong recommendation, strong consensus).**

- Due to the potential risk of aggravating osteoporosis, and/or cardiovascular risk factors, rapid tapering of corticosteroids is recommended **(LoE 5, strong recommendation, strong consensus).**

Several retrospective studies have shown that elderly patients (≥65 years) with AIH have similar chances of achieving CBR as younger patients, but lower relapse rates.[31,55,205,206,348,349] According to a systematic literature review and more recent publications, treatment-related adverse events were similarly reported in all age groups.[31,33] However, owing to the retrospective nature of the studies, these data should be interpreted with caution, and elderly patients should be carefully monitored to prevent and treat corticosteroid-related adverse events, especially osteoporosis, which can already be present in this patient population.

Therefore, in asymptomatic elderly patients with mild disease at the histological level, the initiation of treatment can be withheld, particularly if other comorbidities are present. In contrast, in those with at least moderate necroinflammatory activity on liver biopsy, immunosuppression is recommended, but again the dose and tapering schedules of immunosuppressants should be carefully considered according to the concurrent comorbidities.

Patients with AIH and decompensated cirrhosis

Recommendations

- Patients with AIH-related decompensated cirrhosis should be evaluated for LT **(LoE 2, strong recommendation, strong consensus).**
- Corticosteroid treatment should be considered in patients with AIH-related decompensated cirrhosis with signs of disease activity (elevated aminotransferase levels and/or mHAI ≥4) **(LoE 4, strong recommendation, strong consensus).**

Owing to the insidious course of the disease, approximately 30% of patients with AIH have cirrhosis at diagnosis. Moreover, failure to achieve treatment response can also lead to disease progression and its advanced stage of decompensated disease.

Only three retrospective studies have evaluated the efficacy and safety of immunosuppressive treatment in patients with decompensated cirrhosis; therefore, it is difficult to make strong recommendations.[350–352] In general, these studies showed that treated patients had significantly higher aminotransferase and albumin levels, indicating that physicians are more inclined to treat patients with active disease and relatively preserved liver function. The median predniso(lo)ne dose in treated patients ranged from 20 mg to 30 mg per day. Only a small number of patients started maintenance therapy with azathioprine or MMF, but there was no information regarding the dose or the time of initiation.

Wang *et al.*[351] found that, among the 62 treated patients, 60% recompensated. Patients who recompensated had higher levels of aminotransferases, higher white blood cell and platelet counts, mild ascites (*vs*. gross ascites), and a rapid decrease in bilirubin and MELD score after 7 days of treatment. Nine patients died, seven due to infectious complications. Sharma *et al.*[350] found that 30% of patients with mild ascites (n = 38) and 4% of those with gross ascites (n = 24) achieved biochemical response defined as normalisation of aminotransferase levels. Nineteen patients experienced infectious complications, primarily spontaneous bacterial peritonitis and pneumonia.

Recently, a multicentre retrospective study from the IAIHG tried to identify baseline predictive factors to guide treatment decisions in this group of patients with AIH.[352] The study concluded that patients with hepatic encephalopathy grade 3 or 4 should be immediately considered for LT, as the treatment benefit is limited in this group. In contrast, patients without hepatic encephalopathy or with hepatic encephalopathy grades 1-2 at diagnosis showed a 60% LT-free survival rate after initiating treatment. In this subgroup, the MELD-Na score was useful in guiding further treatment decisions, as patients with a baseline MELD-Na ≤28 had significantly better LT-free survival rates compared to those with a MELD-Na >28. These results suggest that treatment can be considered for patients without hepatic encephalopathy or with hepatic encephalopathy grades 1-2 and a MELD-Na ≤28 at diagnosis. However, even in this subgroup, one third of patients died or required LT. Additionally, a reduction of MELD-Na at 4 weeks of treatment was the most important predictor of survival in the latter group, refining prognosis and guiding further therapeutic decisions.[352]

Although the possibility of recompensation exists, patients with AIH-related decompensated cirrhosis should be referred to a transplant centre for evaluation of LT. The decision to initiate immunosuppression should consider the potential risks of infectious complications, both before and after transplantation.

Patients with AIH/PBC or AIH/PSC variants

Recommendations

- The management of variant syndromes should be directed at the predominant component of the syndrome **(LoE 4, strong recommendation, strong consensus).**
- In patients with AIH/PBC, the initial treatment regimen should be determined according to biochemical parameters and liver histological findings. Combination of standard immunosuppressive therapy with UDCA (13-15 mg/kg/day) can be used in those with moderate or severe hepatitis, while UDCA monotherapy can be used in those with mild hepatitis followed by addition of immunosuppressive therapy if they do not achieve CBR **(LoE 4, weak recommendation, strong consensus).**
- Immunosuppressive treatment with or without UDCA is suggested for adult and paediatric patients with the AIH/PSC variant **(LoE 4, weak recommendation, strong consensus).**

Treating patients with variants syndromes of autoimmune liver diseases is challenging, as RCTs assessing the best treatment

options for these entities are lacking.[3,90,93,94,353,354] As a result, progression to end-stage liver disease is not a rare course, despite combined or second-line therapies. For these reasons, patients with variant syndromes should be referred to experienced centres and/or managing physicians should consult with other experts via the ERN RARE-LIVER CPMS (clinical patient management system) platform. Therapy for cholestatic variants of AIH includes the management for classic AIH with immunosuppression and UDCA.[3,90,93,94,353,354] The treatment approach is highly dependent on which disease process represents the dominant component and follows a set order. Recommendations, however, rely on expert opinions due to the lack of prospective RCTs.

In patients with the AIH/PBC variant, the initial treatment regimen can be determined according to the histological findings.[3,90,93,94,353,354] Immunosuppressive treatment is initially indicated if AIH is the predominant component of the disease (moderate or severe hepatitis based on the mHAI score is mandatory), followed by the addition of UDCA if there is no response. However, it is not certain if patients with AIH who develop PBC features will benefit from this addition, but such an approach seems reasonable, as theoretically combination therapy may protect them from the long-term complications of PBC (development of ductopenia and biliary-related cirrhosis). In contrast, UDCA monotherapy is indicated initially if the cholestatic component is predominant (only mild hepatitis), followed by immunosuppressive agents if there is no response. CBR is expected in most patients with AIH/PBC, however, they have a more severe disease course than those with classic PBC, as most of these patients present with advanced fibrosis at diagnosis.[3,90,94,355] In case of no response to UDCA, second-line treatment for the cholestatic component could be considered according to the PBC CPGs.[94,98]

A multicentre retrospective study of 88 patients with AIH/PBC revealed that patients with severe interface hepatitis at the histological level required standard or second-line immunosuppressive treatments in addition to UDCA to reach CBR and were less likely to respond to UDCA monotherapy.[356] At the same time, in most patients with less severe AIH activity, UDCA alone was able to induce CBR.[356] Of note, these patients seem to need lower doses of immunosuppressants and maintain CBR after treatment discontinuation at higher rates compared to patients with AIH alone. Recently, a systematic review and meta-analysis showed similar favourable results of the combination therapy.[357]

Patients with the AIH/PSC variant can be treated with a combination of immunosuppressive treatment with UDCA, if the simplified score is >5 and the mHAI >3,[358] as the beneficial role of immunosuppression has been confirmed.[60,93,353,354,359–363] Small retrospective studies have also suggested that administration of azathioprine might increase survival without increasing the risk of cholangiocarcinoma in patients with PSC.[359,364] Biochemical response is, however, variable and patients with AIH/PSC have a worse disease prognosis compared to those with AIH or the AIH/PBC variant, as liver fibrosis may progress even during combination therapy.[3,60,90,359–361,363] In contrast, variant patients appear to have better outcomes than patients with PSC alone, although a recent very large multicentre study, including 7,121 patients with PSC, showed a similar risk, albeit a significantly lower incidence of hepatobiliary malignancy.[365] In this context, predniso(lo)ne (0.5 mg/kg/day tapered to 10-15 mg/day) with UDCA (13-15 mg/kg/day) has improved survival and reduced the frequency of LT compared to classic PSC.[363]

Patients with AIH and liver-related comorbidities

MASLD

Recommendations

- Patients with AIH and concomitant MASLD should receive standard treatment for AIH **(LoE 3, strong recommendation, strong consensus).**
- A personalised multidisciplinary approach to predniso(lo)ne administration targeting its lowest effective dose, lifestyle modifications, and strict management of metabolic syndrome components are recommended **(LoE 2, strong recommendation, strong consensus).**

As shown in a recent study from the IAIHG in 640 patients with AIH, the prevalence of concurrent MASLD was similar to that of the general population.[114] Therefore, concomitant MASLD in patients with AIH represents a common problem in everyday clinical practice.[237] Recent retrospective studies have shown that patients with AIH and concomitant MASLD more frequently have cirrhosis at diagnosis and a higher risk of decompensation than those without MASLD.[114,366] There is no clear information on the best therapeutic regimen for these patients; however, given the diversity in the mechanisms of action of corticosteroids, they can cause a wide range of time- and dose-dependent adverse events that can aggravate the components of metabolic syndrome. Therefore, it is advisable to use a low corticosteroid dose for these patients. In fact, two recent retrospective studies observed that patients with AIH-MASLD were more likely to receive low doses of predniso(lo)ne and/or unconventional treatments such as UDCA or azathioprine monotherapy.[238,367] The impact of these regimens on the probability of achieving a CBR is not clear[238,366–368] and is difficult to evaluate because the presence of steatosis can impede the complete normalisation of liver tests. In these cases, a follow-up liver biopsy might be necessary.

The treatment of MASLD requires the implementation of lifestyle changes aimed at achieving weight loss, including diet modification, exercise, and behavioural therapy.[168] However, there is no evidence for the impact of these measures on the evolution of AIH. There are no data on the efficacy and safety of pharmacological therapies to induce weight loss or treat MASH in patients with concomitant AIH-MASLD. However, if considered, the administration should follow international guidelines.

Viral hepatitis

Recommendations

- Patients with chronic viral hepatitis and autoimmune features should receive antiviral therapy **(LoE 4, strong recommendation, strong consensus).**
- Immunosuppressive treatment is recommended if there is evidence of persistent liver inflammation despite adequate viral control **(LoE 4, strong recommendation, strong consensus).**

Following the introduction of highly effective antivirals for treating hepatitis C, the focus has shifted towards HBV and hepatitis D virus (HDV) infections. A recent single-centre study evaluated the presence of autoantibodies and IgG levels in 40 patients with chronic HDV infection, 70 patients with chronic HBV infection, and 46 patients with AIH as the control group.[116] The frequency of ANA and SMA positivity was significantly higher in patients with chronic HDV than in patients with HBV (67% *vs.* 43% and 16% *vs.* 3%, respectively), but lower than that in patients with AIH (96% and 50%, respectively). Median IgG levels were also higher in patients with HDV infection (16.9 g/L *vs.* 12.7 g/L in HBV). SMA of F-actin reactivity were detected only in patients with AIH. Liver biopsy was available in 12 patients with HDV and 3 with HBV infection. The median mHAI in patients with HDV was higher (6.5/18) than that in patients with HBV, but lower than that in patients with AIH (9/18).[116] The findings of this study corroborated previous research, which had stressed the presence of autoimmune characteristics, such as increased IgG levels and the presence of anti-LKM3 in individuals with persistent HDV infection.[369] However, the relevance of this phenomenon remains unclear. Approximately 50% of patients with HEV infection have at least one positive autoantibody. Data from the Swiss AIH Cohort Study Group found that 33% of 48 patients with acute HEV infection tested positive for ANA, and 21% were positive for SMA as well. However, none of these patients developed AIH.[370]

Depending on the prevalence of viral hepatitis in an index area, concurrence of AIH with viral hepatitis infections, although rare, can exist.[117,371,372] Distinguishing between the above-mentioned autoimmune reactions in viral hepatitis and genuine AIH is of paramount importance, as coexisting autoimmune liver disease would necessitate immunosuppressive therapy, which carries the risk of impairing the control of viral hepatitis. However, establishing the diagnosis of AIH in patients with viral hepatitis is very difficult and challenging because there are no pathognomonic histological features of AIH.[116,117,373]

There are no clear recommendations regarding the best treatment for these patients. The administration of interferon-based therapies is contraindicated in patients with autoimmune features because of the risk of triggering or worsening autoimmunity.[374] However, the approval of bulevirtide has revolutionised the management of chronic HDV infection, allowing for the treatment of more complicated cases, such as those with autoimmune features. To date, only one case report has shown excellent results (resolution of inflammation and disappearance of plasma cells) in HDV-positive patients with cirrhosis and histological features of AIH.[375] These promising results must be confirmed in larger cohorts. Likewise, in patients with HCV infection, oral antiviral treatment resolves autoimmune features.[376,377]

Hepatitis B reactivation

Recommendations

- HBV surface antigen (HBsAg)-positive patients with AIH undergoing immunosuppressive treatment should receive antiviral therapy **(LoE 2, strong recommendation, strong consensus).**
- Anti-HBV core antigen (anti-HBc)-positive patients (HBsAg negative) at high risk of reactivation should undergo HBV prophylaxis **(LoE 2, strong recommendation, strong consensus).**
- Anti-HBc-positive patients (HBsAg negative) with low or moderate risk of reactivation require HBsAg and HBV DNA monitoring every 3 months. In case of HBV reactivation, antiviral therapy should be initiated **(LoE 2, strong recommendation, strong consensus).**

The specific risk of HBV reactivation in AIH is unknown. Nevertheless, according to the HBV status (positivity for HBsAg and anti-HBc) and the type of immunosuppressive therapy, patients can be classified as having a high (<10%), moderate (1%-10%) or low (<1%) risk of reactivation.[378] HBsAg-positive patients should receive antiviral therapy due to a high risk of reactivation. In contrast, in patients with negative HBsAg and positive anti-HBc, HBV prophylaxis is recommended when receiving high-risk immunosuppression (B cell-depleting agents or infliximab) and should be maintained for at least 18 months after stopping immunosuppression. Patients with low or moderate risk of reactivation need to be frequently monitored (every 3 months) for HBsAg seroconversion and the emergence of HBV DNA. In this case, guidelines recommend starting antiviral therapy.[379]

Alcohol-related liver disease (ALD)

Recommendations

- Treatment of alcohol use disorder aimed at alcohol abstinence is recommended and should follow specific guidelines **(LoE 2, strong recommendation, strong consensus).**
- Immunosuppressive treatment for the AIH component should follow the current treatment guidelines of AIH **(LoE 5, strong recommendation, strong consensus).**

ALD is a major cause of cirrhosis worldwide. Its diagnosis requires documenting high-risk alcohol consumption and exclusion of other causes of liver disease. However, like other liver diseases, it can rarely co-exist with AIH. Unfortunately, this area is underexplored, and only one study has reported on 12 patients with ALD-AIH. These patients had lower aminotransferase levels, a higher frequency of AST/ALT ratio >1 than patients with AIH, and more frequently developed cirrhosis and liver-related deaths. The treatment response was similar to that of patients with classic AIH.[115]

However, it is also important to bear in mind that up to 69% of patients with ALD can have positive autoantibodies, especially those with advanced liver disease (where high IgG levels can also be found) and no other signs of AIH.[380] Therefore, a careful evaluation of liver biopsy is mandatory in this setting. The indications and impact of immunosuppressive treatment on the autoimmune component in patients presenting with features of AIH and alcohol-related hepatitis (AH) is unknown, and the indications for corticosteroids should probably follow those recommended for patients with AH.

What are the most effective treatment strategies for inducing and maintaining remission of AIH in the paediatric population, including those with the AIH/PSC variant and patients younger than 6 years old?

Recommendations

- Treatment of AIH in children should follow the same guidance as in adults except for tailored weaning of predniso(lo)ne to a maintenance dose of 2.5-5 mg/day to avoid corticosteroid-related side effects including growth failure **(LoE 2, strong recommendation, strong consensus).**
- In younger children or those with developmental delay, dispersible tablets and syrups should be considered to avoid incorrect dosing **(LoE 2, strong recommendation, strong consensus).**
- Second- and third-line agents such as MMF and calcineurin inhibitors are recommended for treatment refractory cases with close monitoring for side effects including teratogenicity of MMF **(LoE 3, strong recommendation, strong consensus).**
- If not included in the national programme, hepatitis A and B vaccines should be given; live vaccination should be considered with caution and after discussion with the medical teams **(LoE 3, strong recommendation, strong consensus).**

The recommendation for medical treatment of children with AIH does not differ from adults[80] and randomised control studies are lacking in children.[251,381] In a recent pan-European survey including 36 centres from 22 countries, all reported using predniso(lo)ne as first-line treatment, in association with azathioprine in 21, whilst 11 used azathioprine as second-line treatment.[382] Biochemical remission on predniso(lo)ne, with or without azathioprine, has been reported in 75-95% within the first year after diagnosis.[57,71,85,194,383] The current treatment in paediatrics is summarised in Table 12.[80] Children receiving immunosuppression are at an increased risk of vaccine-preventable infections,[384] but their response to both live and inactivated vaccines can be less effective.[385] Thus, children who have not completed the national immunisation programme prior to starting treatment should complete vaccination prior to treatment start, unless the child has ALF.[386] In the latter case, the vaccination programme should be initiated as soon as immunosuppression is tapered to maintain therapy.[386] As in adults, vaccination against HAV and HBV is recommended if not included in the national programme. Vaccination with live vaccines should be cautiously considered only after discussion with the medical teams, as live vaccines were previously contraindicated during immunosuppressive treatment. However, recent studies suggest they may be safe,[384] even though severe side effects have (albeit rarely) been reported.

MMF is the preferred agent to be used as second/third-line treatment followed by calcineurin inhibitors[80,381,382,387,388] (Table 12). Two studies reported similar response rates with induction using cyclosporine[381] or TAC;[387] however, in the only randomised study, patients treated with cyclosporine achieved remission later than those receiving standard treatment.[381,388] Cyclosporine was also used in 15 children with LKM1 and/or LC1-related AIH, including as primary treatment in 8 with sustained response.[388]

In children, it is recommended to screen for the presence of a cholangiopathy at diagnosis and if a diagnosis of AIH/PSC is made to add UDCA to the treatment regimen.[80,389] As in adults, screening for autoimmune thyroid diseases and concurrent coeliac disease is mandatory.[47,234] The prevalence of LKM1 and/or LC1-related AIH is higher in paediatrics compared to adults, accounting for 10% of cases, presents at a younger age and more frequently with ALF.[57]

One of the challenges for younger children, under the age of 6 years, is not being able to swallow tablets; they thus rely on other medication formulations including dispersible tablets or syrups.

Table 12. Treatment of AIH in paediatrics.

		Dosage	Comments
First line	Predniso(lo)ne	1-2 mg/kg/day max 60 mg daily	• Close monitoring of blood tests to avoid corticosteroid-related side effects • Tapering to maintenance dose of 2.5-5 mg/day • Paediatric experience with budesonide is limited
	Azathioprine	1 mg/kg/day- titrate up to max 2-2.5 mg/kg/day	• Started after 2 weeks as part of first-line treatment or second-line treatment when insufficient response to predniso(lo)ne • Caution with jaundiced patients as hepatotoxic • TPMT levels can be checked prior to starting • Azathioprine metabolites: 6-MMP/6-TGN ratio can be monitored during treatment
Second line	MMF	5-10 mg/kg bid increase to 20 mg/kg bid (max 1,000 mg bid)	• Used as replacement of azathioprine in treatment refractory AIH • Estimated adverse events 48% • Metabolites not routinely measured • **Teratogenic**
Third line	TAC	Initial dose: 0.05 mg/kg/day (in 2 divided doses) Aim for trough levels around 5 ng/ml	• Rarely used as a second-line agent • Estimated adverse events 42% • Nephrotoxicity and diabetic risk
	Cyclosporine	Initiate dose: 4 mg/kg/day (in 2 divided doses) Aim for trough levels 200-250 ng/ml, decreasing after remission	• Occasional use as induction treatment • Estimated adverse events 78% • Cosmetic side effects and nephrotoxicity

Despite age-appropriate formulations for both predniso(lo)ne and azathioprine being approved by the European Medication Agency and available on the commercial market, 44% of paediatricians across Europe ask parents or caregivers to manipulate predniso(lo)ne and azathioprine tablets by crushing them, increasing the risk of dosage inconsistency and drug errors.[390]

Whilst overall outcomes on medical treatment in paediatric AIH are excellent, side effects of long-term corticosteroid treatment on growth[391] and azathioprine-related malignancy risk need to be considered and treatment tailored.[392]

In Europe, only 58% of centres who treat children with AIH routinely perform thiopurine methyltransferase phenotyping prior to starting azathioprine. Measurement of azathioprine metabolites is used routinely in 54% whilst the remainder of centres use it in the context of unsatisfactory response to treatment, suspected non-adherence or possible side effects.[382] Although the concentration of TGN varies independently of weight-adjusted dose and does not correlate with ALT or AST,[281] it has been suggested that a TGN to MMP ratio <4 can optimise the remission rate with the help of allopurinol.[393] TGN is incorporated into leucocyte DNA as DNA-TG. As seen for acute lymphatic leukaemia, DNA-TG may be a more precise measure for monitoring TG treatment in AIH.[394]

It is estimated that 7-15% of paediatric patients are on either MMF or calcineurin inhibitors.[194] A systematic review found 15 studies including 76 children with a median of 3 (range 1-18) cases per study.[297] Five studies included MMF, six calcineurin inhibitors, one both MMF and calcineurin inhibitors, and the remaining three studies included rituximab, sirolimus and budesonide, respectively. The response rate for MMF was 36%, with higher rates of 84% and 50% for cyclosporine and TAC, respectively, whilst estimated adverse events were the highest with cyclosporine (82%) compared to TAC (42%) and MMF (38%).[297] Due to the low number of studies and low number of cases in each study, the results should be interpreted with caution.[395,396] Of importance for paediatricians is to inform pubertal females regarding the teratogenicity of MMF, including a risk of birth defects (24% incidence) and spontaneous abortion.[397]

Relapse of AIH is common and frequent episodes are associated with inferior outcomes.[194] Whilst those diagnosed as children can outgrow their treatment when growing up, suboptimal adherence to treatment should be explored, especially in adolescents where this is more common. The absence of corticosteroid-related effects at onset of treatment or undetectable or low metabolite levels can raise suspicion and warrants further non-judgmental exploration of mental health and psychosocial circumstances, which can contribute to suboptimal adherence.

Biological therapy represents an underexplored opportunity for the treatment of paediatric AIH. Since the publication of the first paediatric case treated with infliximab in 2013,[398] the only relevant publication has been a small case series of 11 patients with combined AIH/PSC and IBD treated with infliximab due to severe IBD.[399] The main finding was that the treatment was hepatologically safe. The use of rituximab has been reported in two case studies,[318,400] including eight patients, with promising results.

Approximately 10% of paediatric patients with autoimmune liver diseases will decompensate and require transplantation, which is associated with overall good outcomes.[401]

The AIH/PSC variant is common in paediatrics with up to 20% of autoimmune liver disease cases having either small or large duct disease. Association is mainly with ANA and SMA autoantibodies. The PSC component can be present at AIH diagnosis or develop after.[64] The prevalence of IBD is higher in comparison with AIH.[64,96] Overall outcomes are inferior to those of patients with AIH alone and recurrence after LT is a concern.[194,402,403]

There is no solid evidence on treatment withdrawal in children with AIH. In general, discontinuation of treatment in paediatric patients with LKM1/LC1-related AIH is less likely.[57] The ESPGHAN position paper[80] recommends extending treatment in children for at least 3 years and to consider withdrawal if aminotransferases and IgG levels are persistently normal and autoantibody negative for at least a year. In addition, liver biopsy before withdrawal is strongly advised to exclude residual inflammatory activity.[80] However, a recent long-term study (n = 117; median follow-up: 20 years)[85] showed that treatment withdrawal was successful in 53% of children without a liver biopsy if treatment discontinuation was performed under strict medical surveillance. Deep normal aminotransferase levels and prothrombin ratio ≥70% were identified as the best prognostic markers of successful treatment cessation.[85,86] Inherent problems of this study include its retrospective nature, extending up to three decades, along with different treatment schedules and response criteria.[85] Therefore, ESPGHAN recently published a commentary recommending that because of insufficient evidence, liver biopsy prior to a trial of treatment withdrawal in children with AIH should remain.[404]

How should complications of cirrhosis (portal hypertension, HCC) be monitored and managed in paediatric and adult patients with AIH?

Recommendations

- Upper gastrointestinal (GI) endoscopy screening to determine the presence of varices needing treatment (VNT) is recommended in patients with AIH-related cirrhosis and LSM ≥20 kPa or platelet count ≤150x 10^9/μl **(LoE 3, strong recommendation, strong consensus).**
- Patients with lower LSM but indirect signs of portal hypertension (splenomegaly, increased portal diameter, collateral veins) should undergo upper GI endoscopy screening **(LoE 3, strong recommendation, strong consensus).**
- Although the prevalence of HCC is lower in patients with AIH-related cirrhosis compared to cirrhosis of other aetiologies, patients with AIH-related cirrhosis should be screened for HCC with liver ultrasound with or without alpha-fetoprotein determination on a 6-monthly basis **(LoE 3, strong recommendation, strong consensus).**
- HCC management in AIH should follow specific HCC guidelines **(LoE 2, strong recommendation, strong consensus).**
- Immunotherapy for HCC can be considered in patients with well-controlled disease **(LoE 4, weak recommendation, strong consensus).**

Cirrhosis is a critical determinant of treatment response, disease progression, and subsequent risk of decompensation and HCC. Consequently, regular upper GI endoscopy

screening for clinically significant portal hypertension (CSPH) and HCC should be conducted in patients with AIH, similar to other aetiologies of liver disease.[1,199,405,406]

Portal hypertension

The Baveno VII consensus states that; firstly, the presence of a LSM by TE ≤15 kPa in combination with a platelet count ≥150x10^9/μl rules out the presence of CSPH with sensitivity and negative predictive value >90% in patients with cirrhosis and, secondly, a LSM ≥25 kPa is enough to rule in CSPH with a specificity and positive predictive value >90%, which is considered the group of patients with a high risk of having upper GI endoscopic signs of portal hypertension and a higher risk of decompensation. In these patients, the consensus recommends starting non-selective β-blockers (especially carvedilol) to prevent the first episode of decompensation. In patients with contraindications to β-blockers, LSM ≥20 kPa or platelet count ≤150x10^9/μl should prompt upper GI screening endoscopy to detect oesophageal VNT.[407] It is important to note that these recommendations are based on studies conducted on patients with viral, alcohol, and MASLD-related liver diseases, and it is unclear whether they can be safely extrapolated to patients with AIH. A recent multicentre study analysing patients with AIH-related cirrhosis found that up to 52% of patients with clear signs of portal hypertension had an LSM below the recommended cut-off points, especially long-term after treatment initiation;[264] therefore, the LSM cut-off point to rule out CSPH recommended by the Baveno VII consensus should be carefully validated in patients with AIH. Moreover, since many patients with cirrhosis and AIH are managed with immunosuppressant regimens (thiopurines and MMF which may also further lower the platelet count), competing factors for low platelets need to be considered. Despite this, owing to the presence of a low platelet count in most patients with known VNT, the Baveno VII criteria were found to be useful for selecting patients for upper GI endoscopy screening.[264]

Although, there is a clear need for larger studies validating Baveno recommendations in patients with AIH, in the meantime, it seems prudent to consider collectively clinical, analytical, elastographic, and ultrasound signs of portal hypertension to recommend upper GI endoscopic screening for VNT.

Hepatocellular carcinoma

The risk of HCC development in patients with AIH-related cirrhosis remains below the cut-off recently proposed for surveillance strategies (0.5% instead of 1.0% annually)[408] and therefore, surveillance with ultrasonography and/or determination of alpha-fetoprotein every 6 months may not be cost-effective. However, as prospective studies to determine whether patients with AIH require screening programmes are lacking, and the surveillance recommendations have not been validated in patients with AIH-related cirrhosis, personalised surveillance strategies could be adopted, taking into consideration the presence of additional risk factors.[110]

Studies on the modification of immunosuppressive therapy as a potential adjunct treatment strategy in patients with AIH after the diagnosis of HCC are lacking.[409] In addition, AIH-associated HCC cases are underrepresented in studies on systemic therapies both because of the low incidence of HCC in patients with AIH and their exclusion because of concerns regarding the potential exacerbation of the underlying AIH or severe drug-related adverse events.[410–412] Recently, a pan-European retrospective study assessed the outcomes of patients with AIH- and PBC-associated HCC who were treated with tyrosine kinase inhibitors or trans-arterial chemoembolisation (TACE).[413] Despite several inherent limitations, this study showed comparable median overall survival with better tolerability in patients with AIH- or PBC-associated HCC undergoing tyrosine kinase inhibitor or TACE therapy compared to HCC cases of other aetiology, even though a trend toward shorter median overall survival in patients with AIH was observed.[413]

What are the indications for LT in adult and paediatric patients with AIH and how should these patients be managed after LT?

Indications for LT in AIH

Recommendation

- Patients with AIH and decompensated cirrhosis, acute severe AIH or AIH-related ALF (including ACLF) should be managed and evaluated for LT in reference centres **(LoE 2, strong recommendation, strong consensus).**

A recent examination of the European Liver Transplant Registry found that AIH constituted 8% of LTs performed between 1998 and 2017.[414] The indications for LT in patients with AIH are identical to those for other liver diseases, including decompensated cirrhosis, failure of response in acute severe AIH, ALF, and ACLF.[415] The identification of the optimal timing for LT in these groups of patients who have an increased risk of complications, particularly infectious complications, is of utmost importance.[66,337,341] Acute severe AIH is discussed in detail elsewhere. Models to predict response at day 3 and day 7 following corticosteroid initiation, including the SURFASA score, have demonstrated a high level of accuracy in predicting death or LT.[337] Another multicentre study from Spain developed a nomogram composed of older age, MELD score, encephalopathy, and ascites at the time of treatment initiation, which was highly predictive of corticosteroid response. A decrease in the MELD score on day 7 was the best predictor of response during follow-up.[341] Although both studies require validation in larger and preferably prospective cohorts, they underscore the importance of promptly evaluating treatment response to anticipate the need for LT in patients with low likelihood of improvement.

Management of AIH after LT

Recommendation

- In patients undergoing LT for AIH, low-dose predniso(lo)ne in combination with a calcineurin inhibitor (mainly TAC) can be used as maintenance immunosuppression to prevent AIH recurrence **(LoE 4, weak recommendation, strong consensus).**

- Plasma cell-rich rejection hepatitis should be considered as a cause of late graft dysfunction in patients transplanted for a liver disease different from AIH who present with liver enzyme abnormalities and histological features resembling AIH with or without IgG elevation and/or positive autoantibodies **(LoE 3, strong recommendation, strong consensus).**
- AIH recurrence and plasma cell-rich rejection hepatitis should be treated with predniso(lo)ne at the same doses recommended for AIH in non-LT patients **(LoE 4, strong recommendation, strong consensus).**

According to a recent analysis of data from the European Liver Transplant Registry, the 5-, 10-, and 15-year survival rates of recipients transplanted for AIH were 79%, 71%, and 60%, respectively. The most common causes of death were infections, neoplasia and rejection. After adjustment for age and sex, fatal infections and rejection were more frequent in patients with AIH than in those transplanted for other indications, including PBC, PSC, and alcohol-related cirrhosis.[414] Graft survival was 73%, 63%, and 60% at 5-, 10-, and 15-year follow-up, respectively, and disease recurrence was one of the major causes of graft failure.

Recurrent AIH

The diagnostic criteria for AIH recurrence after LT are the same as those for non-transplanted patients. However, the accuracy of serological markers in LT recipients is limited, and the diagnosis should be mainly based on histological criteria (interface hepatitis with lymphocytic infiltrate with or without plasma cells and lobular hepatitis with or without central vein endotheliitis) after excluding other causes of graft dysfunction.[416,417] The recurrence rate ranges between 17% and 42% depending on the sample size of the study and the use of per-protocol or clinically indicated liver biopsies.[416,418,419] A recent study by the IAIHG evaluating a multicentre retrospective cohort of patients transplanted for AIH observed recurrence rates of 20% and 31% at 5 and 10 years after LT, respectively.[419] Age at LT ≤42 years, use of MMF during the first year of LT (but not the use of MMF for longer periods), donor/recipient mismatch, donor/recipient cytomegalovirus status mismatch, and high IgG levels before LT were associated with a higher rate of disease recurrence. Cohort studies have shown that low levels of immunosuppression and cessation of corticosteroids after LT are associated with a higher chance of AIH recurrence. A study from the UK showed that long-term maintenance of low-dose predniso(lo)ne after transplantation was associated with a lower rate of recurrence.[420] However, the decision to maintain this treatment should consider the potential risks of long-term corticosteroid use. In these cases, a low dose of MMF in combination with a backbone immunosuppressive agent (generally TAC) could be a potential therapeutic strategy to prevent AIH recurrence in the long-term.[416] However, this strategy needs to be validated in prospective, multicentre studies.

The management of patients who present with AIH recurrence after LT is empirical, as no studies have compared different treatment options. However, initiation (or augmentation of the dose) of predniso(lo)ne at the dose recommended for non-transplanted patients seems to be the most appropriate therapeutic strategy.

Plasma cell-rich rejection hepatitis (previously termed "De novo AIH").

This entity, first described in children, resembles AIH but occurs in approximately 5% to 10% of children and 1% to 2% of adult patients transplanted for other aetiologies of liver disease, usually >6 months after LT.[415] It is generally accepted that this entity represents a late cause of graft dysfunction in patients without AIH. In 2016, the Banff Working Group in Liver Allograft Pathology recommended that this entity be entitled "plasma cell-rich rejection hepatitis",[421] but this requires validation, since there are some differences between the initial descriptions of *de novo* AIH in children and cases described in adults, particularly relating to the presence of detectable autoantibodies and elevated IgG, which are not entirely necessary for the diagnosis of plasma cell-rich rejection hepatitis.[421,422] Histologically, the diagnosis is based on the presence of at least one of the following criteria: 1) portal and/or perivenular plasma cell-rich (>30%) infiltrates with interface hepatitis and/or perivenular necroinflammatory activity involving the majority of portal tracts and/or terminal hepatic veins, and 2) lymphocytic cholangitis.[421] Risk factors for *de novo* AIH (or plasma cell-rich rejection hepatitis) are receiving a female graft, older donors,[423] and the presence of donor/recipient mismatch for glutathione-S-transferase T1.[424] The treatment consists of the administration of predniso(lo)ne at the dose recommended for patients with classical AIH, in combination with the adjustment of baseline immunosuppression (which may include the addition of azathioprine).

Quality of life and support

How can the wellbeing of patients with AIH be improved?

Recommendations

- Mental health and HRQL assessments are recommended in the routine management of all patients with AIH, with signposting to other services if needed **(LoE 2, strong recommendation, strong consensus).**
- Treatment of AIH, particularly with corticosteroids, has a significant impact on HRQL and adherence and, as such, dose reductions or withdrawal of corticosteroids should be considered when appropriate **(LoE 2, strong recommendation, strong consensus).**
- Patient involvement in daily care and research should be encouraged **(LoE 3, strong recommendation, strong consensus).**

Exploration of HRQL in AIH is based on both patient surveys and personal communication. Overall, HRQL in AIH is inferior to that of the general population and this relates to treatment and mental health difficulties.[235,425–431] Whilst response to treatment predicts HRQL with lower scores for those with insufficient *vs*. complete response, corticosteroid treatment and its side effects play a major role in HRQL perception.[235,283,426,427] A survey on health utility in 990 adults with AIH found that corticosteroid treatment was associated with impaired HRQL even when controlling for biochemical activity.[427] Semi-structured interviews with 13 patients highlighted that aside

from the negative experience of corticosteroid treatment, fatigue, stigma related to the liver disease and loss of control were the main factors impacting on HRQL.[235] Three studies in paediatrics have shown that HRQL is affected by symptoms including abdominal pain and fatigue as well as medication-related factors including dislike of medication and corticosteroids.[432–434]

Mental health difficulties, such as depression and anxiety, are a concern in adult and paediatric AIH and are more likely to affect females.[428,435,436] Illness perceptions including concerns about disease progression, stigma associated with liver disease and disease duration have been shown to be relevant in adults and adolescents.[283,428,436] In adolescents with autoimmune liver disease being more worried and emotionally affected by the condition was negatively associated with adherence to treatment.[437]

In a large cohort of adults with AIH, PSC and PBC (n = 1,170), Wunsch *et al.* identified treatment confidence, treatment with azathioprine and being looked after in a LT centre as modifiable factors associated with HRQL.[283] In addition, improved patient-physician relationships contributed to treatment confidence.

Regarding interventions, a small study including 17 adults with AIH demonstrated the positive effect of mindfulness on stress and self-control, as well as on liver function tests, cytokines and corticosteroid requirement, whilst another study reported that zinc supplementation improved HRQL in those on corticosteroid treatment.[438,439]

What other interventions should be provided to improve the HRQL of patients with AIH?

Recommendation

- Involvement with patient support groups (PSGs) can be offered, among other interventions, to patients with AIH to improve their HRQL **(LoE 5, weak recommendation, strong consensus).**

It is notable that a key contributor to patient HRQL in all autoimmune liver diseases is 'confidence in treatment'.[283] This includes the ability of patients to connect with their liver team. This same study identified depression as a key symptom for many patients, which needs to be recognised along with anxiety as a barrier to improved HRQL. These data indirectly highlight the need for clear CPGs that are both easy to access and implement, so that the patient-physician relationship can be enhanced. Conversely, a key step towards patient empowerment includes a patient-friendly summary of CPGs.

Patient empowerment represents the concept of patients being active participants in their own healthcare process with the intention of optimising outcomes of healthcare interventions through this participation. Active participation involves interplay between multiple elements including access to healthcare, informed decision-making, engagement, and having the ability to act and make decisions in the process according to one's own values as a patient. PSGs can provide a platform for patients with AIH to support each other by sharing information and guidance on managing their health conditions. PSGs can also advocate on behalf of patients on the key issues that are important to them as a patient cohort.

A recent study has highlighted the impact of corticosteroid dose on HRQL with daily predniso(lo)ne dose inversely related to both the worry domain score and SF-36 mental health component.[439] A recent survey in patients with AIH performed in the UK highlighted the lack of support networks and the need for patient empowerment. Indeed, 74% of patients who had access to a specific AIH or liver support group rated the help that the PSG provided highly.[235]

PSGs can provide a point of contact for patients, answering questions, addressing problems, providing a safety net, as well as finding information on referral centres when needed. Patients and caregivers might also need advice on practical daily life issues (*i.e.* travel, vacation, family planning, financial advice, access to benefits). Whilst entirely dependent on the scope and size of the individual PSG, these resources enhance the patient journey. Finally, internet-based apps and AI-based chatbots are particularly helpful for younger patients and are widely used.[440,441] However, the accuracy and reliability of the information provided in AIH needs to be demonstrated.[442]

Patient empowerment is a top priority for Europe's healthcare systems and contributes to improved healthcare across Europe's national realities. Along this line, PSGs can provide a platform for individuals with AIH to support each other, share information, and receive guidance on managing their health conditions.

How should the transition of care from paediatric to adult services be organised and managed for patients with AIH?

Recommendations

- Young people aged 16-25 years should receive specialised care with support from a multidisciplinary team to address their developmental needs and improve outcomes **(LoE 2, strong recommendation, strong consensus).**
- Transition of care from paediatric to adult services should not solely depend on age, and service provision should include collaboration between paediatric and adult services with inclusion of parents/carers **(LoE 2, strong recommendation, strong consensus).**

Transition to adulthood is complex and includes, aside from transitioning from paediatric to adult healthcare settings, the biological and neurodevelopmental changes associated with puberty. Overall outcomes for young adults with liver disease are inferior to those of both older and younger patients, highlighting the need for specialised care provision for this patient population.[443]

Adolescence is known to continue into the mid-20s, hence, age should not be the main determinant when deciding on the timing of transfer of care. Mental health problems and suboptimal adherence to treatment are common.[444] Considering that, in autoimmune liver diseases, failure to sustain remission of the disease is linked with mental health problems, illness perceptions and poorer outcomes, an individualised approach to patient care is recommended.[437]

To address the complex needs of young adults, services providing transitional care should have access to a multidisciplinary team who have a special interest in young adults.

Surveys in the UK and Europe have shown that the provision of transition services is available in just over half of the centres, with overall resources, interest from healthcare authorities and lack of professional training mentioned as limitations.[445,446]

Models of care are determined by organisational factors such as (co-)location of paediatric and adult services and age at transfer of care, *i.e.* 16 or 18 years. Healthcare providers report poor communication and coordination of care between paediatric and adult healthcare providers, reluctance of paediatric providers to transfer and lack of allied healthcare professional support, such as social and psychological support, as barriers to successful transition.[445,446] Young adults are keen to have a 'key' person involved in the transition of their care, prefer a gradual process and to be seen as a person living with a disease. The psychosocial screening tools HEADSS and THRxEADS are useful to encourage engagement and personalise patient care.[447,448]

Whereas young adults should be encouraged and nurtured into increased responsibility for the management of their condition, this is unlikely to be achieved by the age of transition from paediatric to adult services. Parents/carers should and can be actively involved in the process, as transition entails a change in their role from primary carer to a more supportive role.[443]

Future directions

The diagnosis of AIH is still based on the combination of several parameters, namely IgG elevation, circulating autoantibodies, and histopathology indicating portal or lobular hepatitis, usually in the absence of other liver diseases. Unfortunately, there is not yet a specific diagnostic marker, resulting in considerable underestimation or under-recognition of the disease in several circumstances. The detection of autoantibodies using the recommended assays and cut-offs, and their interpretation along with histological findings remain the backbone for a timely diagnosis. Response to first and/or second-line immunosuppressive therapy is quite efficient in most patients with almost normal life expectancy and good quality of life among responders. Still, many experience significant morbidity and mortality, mainly because of underestimation or misdiagnosis, side effects or drug intolerance, relapses and flares, insufficient response and poor concordance or poor delivery of care.

In March 2017, the ERN on Hepatological Diseases was launched among other ERNs, forming a Europe-wide network for centres of excellence in the clinical management of rare liver diseases in children and adults, including the management of patients with AIH. In this regard, ERN Rare-Liver is expected to play a significant role in improving the holistic management of patients with AIH. Moreover, in-depth research on the pathogenetic and diagnostic aspects of AIH will lead to the improvement of our understanding of the disease and its timely diagnosis. In recent years, the standardisation of immunoassays for the detection of autoantibodies, determination of pIgG, AI-based digital pathology and metabolomics have gained attention, as all these parameters could play an important role in improving the diagnostic workup of patients with suspected AIH (Table 13).[157,159,223,449] Particularly, metabolomics proposes different metabolic pathways in patients with AIH compared to other liver diseases, including patients with MASLD, even though it is not known whether any of these metabolites can affect immune responses and the development of AIH.[159] Last but not least, non-invasive imaging testing, such as multiparametric MRI and TE, is expected to further enhance the follow-up of patients with AIH perhaps without the need for repeat liver biopsies (Table 13).[450–452]

Even though most patients with AIH achieved CBR under long-term or lifelong immunosuppression, patients would prefer a finite therapy and cure, not only disease remission, and there is a strong need to avoid corticosteroid administration. The development of small molecules targeting a wide range of autoimmune diseases has facilitated the design of clinical trials investigating the merits of these drugs in AIH. Several phase II/III trials are currently underway investigating the effectiveness of novel molecules, such as ianalumab, a BAFF receptor inhibitor, in patients with insufficient response or intolerance to azathioprine (NCT03217422, phase II/III randomised placebo-controlled trial). JKB-122, a TLR4 antagonist which has been shown to reduce liver inflammation in animal models of AIH, will be tested as an adjunct therapy to standard treatment with prednisolone and azathioprine (NCT04371718, phase II trial), while zetomipzomib, a selective inhibitor of immunoproteasome, will be investigated in patients with insufficient response to first-line treatment (NCT05569759, phase IIa study). In the coming years, it seems that the future of AIH both regarding diagnosis and management is promising, but more efforts and new ideas are still warranted (Table 13). The recent data on MMF as an efficient first-line treatment may further enhance these efforts by minimising the number of patients with insufficient response. However, in AIH, the ultimate goal should ideally be the development of therapies which are fully corticosteroid-free because corticosteroids have a significant impact on HRQL and compliance. In addition, a high burden of

Table 13. Future directions and challenges.

Field	
Diagnostics	• Standardised immunoassays for autoantibodies • Polyreactive IgG (pIgG) • Metabolomics • AI digital pathology
Non-invasive imaging for monitoring	• Multiparametric magnetic resonance imaging • Transient elastography
Therapeutics	• MMF as first-line treatment • Phase II/III trials: *e.g.* ianalumab, JKB-122, zetomipzomib • Corticosteroid-free regimens • Cell-based therapies
Patient focus	• Patients prefer a cure, not only remission • High burden of health-related quality of life, especially in low socioeconomic groups • Inclusion of patient-reported outcomes in future studies • Special populations: *e.g.* paediatrics, advanced liver disease, variant syndromes
Management networks	• ERN Rare-Liver supports the holistic management and fosters research

AI, artificial intelligence; ERN, European Reference Network; MMF, mycophenolate mofetil.

health-related unmet needs is observed in all patients with AIH and especially in those with low socioeconomic status (Table 13).[453] Therefore, patient-reported outcomes should be a focus of future studies in AIH. The field is in need of a core outcome set including endpoints and for a range of clinical situations of AIH that will facilitate development of investigator-initiated and industry-driven RCTs. Research efforts should also address the unique challenges faced by specific patient groups, including paediatric populations, those with variant syndromes or advanced liver disease. Tailored therapeutic strategies for these subgroups are essential for improving outcomes.

Finally, moving from "one-size-fits-all" treatment to personalised treatment strategies will improve efficacy and minimise adverse events. Progress in the field of AIH will require a multidisciplinary approach that combines advanced research, innovative technologies, and a strong focus on patient-centred care.

Appendix. Delphi round consensus on the statements and recommendations of the present CPGs.

Recommendation/statement	Consensus
The clinical manifestations of AIH vary from asymptomatic to acute liver failure and they present at any liver fibrosis stage regardless of age, sex, and ethnicity **(LoE 2)**	100%
Subclassifying adult patients with AIH into different subtypes according to autoantibody profile cannot not be recommended **(LoE 3, weak recommendation)**	86%
The diagnosis of a variant syndrome of AIH and one of the cholestatic immune-mediated diseases PSC or PBC should be considered whenever there are concomitant cholestatic features **(LoE 2, strong recommendation)**	91%
The possibility of underlying or associated sclerosing cholangitis should be considered in every case of childhood AIH **(LoE 2, strong recommendation)**	97%
Magnetic resonance cholangiography is recommended for the initial work-up of all childhood AIH cases independently of elevated cholestatic enzymes, as well as of young adults with cholestasis or those not achieving complete biochemical response (CBR), and should be repeated when there is remaining disease activity or cholestatic features upon follow-up **(LoE 3, strong recommendation)**	94%
Investigation for PBC-specific autoantibodies is recommended, before any other test, in all adults with AIH and biochemical features of cholestasis **(LoE 2, strong recommendation)**	90%
Magnetic resonance cholangiography is recommended in adults with cholestatic features, either at diagnosis or during follow-up when testing for PBC-specific autoantibodies is negative **(LoE 3, strong recommendation)**	94%
Long-term complications of AIH are related to disease progression and cancer risk as in any other aetiology of liver disease **(LoE 2)**	91%
Surveillance and early recognition of disease complications are recommended in all patients with AIH **(LoE 5, strong recommendation)**	97%
Monitoring for complications, including portal hypertension, and hepatocellular carcinoma (HCC) is recommended in patients with AIH-related cirrhosis as per dedicated guidelines **(LoE 3, strong recommendation)**	100%
The diagnosis of AIH should be based on a distinct IgG elevation, the presence of autoantibodies, and a likely or possible liver histology **(LoE 2, strong recommendation)**	91%
A careful exclusion of all known causes of acute and chronic liver diseases is recommended for AIH diagnosis, although coexistence with metabolic dysfunction-associated steatotic liver disease (MASLD), alcohol-related liver disease (ALD) or viral hepatitis is possible **(LoE 3, strong recommendation)**	100%
The simplified diagnostic criteria are recommended in clinical practice to help in the diagnosis of AIH if rodent tissue sections are used for ANA and SMA detection **(LoE 3, strong recommendation)**	100%
The updated simplified diagnostic criteria can be applied if HEp-2 cells or ELISAs are used for ANA and SMA detection **(LoE 3, weak recommendation)**	89%
The International AIH Pathology Group (IAHPG) consensus histological criteria can be applied when using the simplified scoring system, as they may increase the sensitivity of AIH diagnosis **(LoE 3, weak recommendation)**	93%
In paediatric patients, the revised 2018 ESPGHAN scoring system can be used **(LoE 3, weak recommendation)**	100%
In cases involving acute forms of AIH, AIH variants, concurrent liver disease, and drug-induced autoimmune-like hepatitis (DI-ALH), the diagnostic scores should be applied with caution **(LoE 3, strong recommendation)**	100%
AIH should be suspected in all patients with elevated aminotransferases of unknown aetiology, irrespective of the level of increase, especially in the presence of elevated IgG levels and circulating autoantibodies **(LoE 2, strong recommendation)**	100%
AIH should also be suspected in all patients with cirrhosis of unknown aetiology, even in the absence of aminotransferase elevations **(LoE 3, strong recommendation)**	100%
Normal IgG levels should not exclude the diagnosis of AIH **(LoE 3, strong recommendation)**	100%
First screening for ANA, SMA, anti-LKM1 and anti-LC1 should be performed by IFT on triple rodent tissue sections in parallel with anti-SLA/LP testing by solid phase assays **(LoE 2, strong recommendation)**	100%
In case of a negative IFT result, serum should be re-tested at a lower dilution (1:40 in adults, 1:10 in children) **(LoE 2, strong recommendation)**	97%
Clinical laboratories should comply with AIH guidelines both regarding the cut-offs of reporting and the techniques they use **(LoE 3, strong recommendation)**	100%
Liver biopsy is required to establish the diagnosis of AIH **(LoE 1, strong recommendation)**	100%
The histology report should include grading of necroinflammatory activity, staging of fibrosis and classification of the findings as likely, possible or unlikely AIH **(LoE 2, strong recommendation)**	100%
Differential diagnosis of AIH should include various causes of liver diseases depending on the presentation (acute hepatitis, chronic hepatitis or cirrhosis) as well as extrahepatic entities, such as coeliac disease and SLE **(LoE 1, strong recommendation)**	100%

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Recommendation/statement	Consensus
DILI associated with an autoimmune phenotype, *i.e.* the presence of autoantibodies, high IgG levels and/or histological evidence of autoimmunity in the liver should be considered as possible DI-ALH **(LoE 2, strong recommendation)**	97%
Differential diagnosis between DI-ALH and AIH should be established by treatment response and disease course. Resolution after withdrawal of the implicated agent with or without a short course of corticosteroids and no relapse in the long-term may indicate DI-ALH instead of classic AIH **(LoE 3, strong recommendation)**	97%
AIH treatment should be aimed at the attainment of complete biochemical, clinical, and histological remission of the disease **(LoE 2, strong recommendation)**	94%
AIH therapy is recommended to reduce morbidity and mortality and improve quality of life **(LoE 1, strong recommendation)**	97%
Immunosuppressive treatment is recommended in all patients with active disease including those with advanced fibrosis and/or compensated cirrhosis **(LoE 1, strong recommendation)**	100%
Vaccination against HAV and HBV is recommended for all susceptible patients with AIH **(LoE 5, strong recommendation)**	100%
All other potential vaccinations (influenza, SARS-CoV2, Streptococcus pneumoniae etc.) should comply with national guidelines **(LoE 5, strong recommendation)**	97%
Screening for autoimmune thyroid and coeliac disease is recommended in all patients with AIH at diagnosis **(LoE 2, strong recommendation)**	94%
Dual energy X-ray absorptiometry (DEXA) determination is recommended in all adult patients with AIH at initiation of treatment **(LoE 3, strong recommendation)**	96%
In adults with AIH, predniso(lo)ne of at least 0.5 mg/kg/day and potentially up to 1 mg/kg/day in more severe and advance disease in combination with azathioprine (whenever bilirubin is <6 mg/dL and ideally 2 weeks apart from corticosteroids start at initial dose of 50 mg/day to a final dose of 1-2 mg/kg/day) or mycophenolate mofetil (MMF, 1.5-2 g/day) should be the first-line treatments **(LoE 2, strong recommendation)**	82%
Induction therapy and tapering of corticosteroids should be individualised according to CBR status **(LoE 4, strong recommendation)**	94%
MMF is teratogenic and counselling of both female and male patients is recommended **(LoE 2, strong recommendation)**	97%
Treatment-related adverse events should be pro-actively managed and, if possible, anticipated **(LoE 5, strong recommendation)**	97%
Laboratory and clinical assessment should be performed in an individualised manner depending on the severity of the disease, treatment response and tolerance **(LoE 2, strong recommendation)**	97%
Adequate calcium intake and supplementation of vitamin D should be considered in patients under long-term corticosteroids **(LoE 3, strong recommendation)**	97%
Regular non-invasive evaluation by transient elastography is recommended to monitor liver fibrosis **(LoE 3, strong recommendation)**	97%
Budesonide is not recommended as part of first-line treatment for AIH and is contraindicated in patients with cirrhosis **(LoE 2, strong recommendation)**	82%
Switching to budesonide may be suggested because of corticosteroid side effects in patients without cirrhosis who are predniso(lo)ne dependent **(LoE 3, weak recommendation)**	91%
Due to the chronic nature of AIH the majority of patients should receive long-term, often lifelong immunosuppressive therapy **(LoE 2, strong recommendation)**	97%
A trial of stopping treatment should only be attempted in carefully selected patients if monotherapy with a low dose has been shown to maintain stable CBR for at least 2 years **(LoE 2, strong recommendation)**	94%
Immunosuppression should be reduced stepwise, as flares during dose reduction are frequent (**LoE 3, Strong recommendation**)	100%
Patients with reactivity to SLA/LP autoantigen may need permanent immunosuppression **(LoE 3, weak recommendation)**	87%
Disease activity should be assessed individually using aminotransferase levels, IgG and/or liver biopsy prior to a trial of treatment cessation because residual activity predicts the likelihood of relapse **(LoE 2, strong recommendation)**	91%
Patient priorities should be included in the decision on treatment cessation **(LoE 5, strong recommendation)**	100%
Monitoring of relapse should be at least every three months in the first year after treatment cessation, and then adapted individually, considering that relapses may occur many years and even decades later **(LoE 3, strong recommendation)**	97%
After a relapse following first withdrawal, subsequent attempts are not recommended **(LoE 2, strong recommendation)**	94%
In patients achieving CBR, maintenance treatment should be continued to reduce the risk of relapse and to prevent progression of liver disease **(LoE 2)**	97%
Maintenance treatment should consist of azathioprine or MMF as monotherapy or in combination with low dose corticosteroids (predniso(lo)ne ≤5 mg/day). The dose of maintenance treatment should be adapted to sustain stable CBR **(LoE 2, strong recommendation)**	91%
During maintenance therapy, patients should be monitored for treatment-related complications **(LoE 5, strong recommendation)**	97%
Low-dose predniso(lo)ne monotherapy can be suggested only in patients with mild disease who achieved CBR and are intolerant to both azathioprine and MMF **(LoE 3, weak recommendation)**	85%
Patients should be monitored by measuring aminotransferases and IgG because of the high risk of flares and relapses **(LoE 2, strong recommendation)**	100%
Treatment adherence should be assessed in case of flares or relapses **(LoE 1, strong recommendation)**	100%
Re-biopsy can be performed to exclude other causes of elevated aminotransferases in patients with suspected flares or relapses of AIH **(LoE 2, weak recommendation)**	91%
Flares and relapses should be treated with short courses of corticosteroids and adjustment of maintenance therapy **(LoE 2, strong recommendation)**	97%
Patient-centred consultations to assess for anxiety, depression and other reasons for suspected or confirmed non-adherence/concordance are recommended including assessment of capability, opportunity and motivation **(LoE 2, strong recommendation)**	100%
Early initiation of maintenance therapy to facilitate corticosteroid dose reductions and withdrawal is recommended to improve confidence in the relationship between caregiver and patient **(LoE 2, strong recommendation)**	97%
Testing of thiopurine metabolites is recommended to assess for adherence to therapy. Undetectable or low levels of 6-TGN and 6-methylmercaptopurine (6-MMP) should trigger a discussion around medication management/side effects and allow for a benefit-risk discussion to optimise therapeutic management **(LoE 3, strong recommendation)**	97%
MMF is recommended as the second-line treatment of choice in patients with intolerance or side effects to thiopurines **(LoE 2, strong recommendation)**	97%
MP or TG can be used in patients with intolerance to azathioprine **(LoE 4, weak recommendation)**	94%

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Recommendation/statement	Consensus
In patients with insufficient response to thiopurine-based treatments, determination of 6-TGN and 6-MMP levels -if available- is recommended to confirm treatment adherence or sub-therapeutic drug levels (proposed cut-off: 223 pmol/8×10^8 red blood cells) **(LoE 3, strong recommendation)**	97%
After exclusion of non-adherence, intensification/optimisation of immunosuppression by increasing the dose of azathioprine up to 2 mg/kg/day (when 6-MMP is appropriately low) is recommended **(LoE 3, strong recommendation)**	94%
Addition of allopurinol (contraindicated in pregnancy) and reduction of the azathioprine dose to 25% (when 6-MMP is disproportionately increased) can be suggested as an alternative to the previous recommendation **(LoE 3, weak recommendation)**	94%
MMF may be used before initiating third-line therapies after unsuccessful intensification/optimisation of azathioprine-related therapies **(LoE 2, weak recommendation)**	83%
Tacrolimus, infliximab, rituximab and belimumab can be used as potential third-line rescue therapies in difficult-to-treat patients in expert centres (see recommended doses and monitoring in Table 11) **(LoE 4, weak recommendation)**	91%
Patients receiving these third-line therapies should be evaluated to estimate the risk of opportunistic infections and to ensure delivery of appropriate prophylaxis or vaccination **(LoE 3, strong recommendation)**	97%
Maintenance treatment with thiopurines (±corticosteroids) should be continued during pregnancy **(LoE 3, strong recommendation)**	97%
MMF should be withdrawn at least 3 months before conception **(LoE 2, strong recommendation)**	97%
In first presentations of AIH during pregnancy, standard therapeutic regimens (excluding MMF) should be utilised **(LoE 2 Strong recommendation)**	100%
Pregnancy should be closely monitored in patients with cirrhosis by a multidisciplinary team of obstetricians and hepatologists **(LoE 2, strong recommendation)**	100%
An early treatment trial with corticosteroids (predniso(lo)ne 0.5-1 mg/kg/day, or intravenous methylprednisolone at equivalent dose) is recommended in patients with acute severe AIH without ALF or ACLF. Failure to improve after 3-7 days of treatment initiation, should trigger referral to a LT centre **(LoE 3, strong recommendation)**	91%
Direct evaluation (discussion with a LT centre) for LT is recommended in patients with acute severe AIH with ALF or ACLF, as data on the role of corticosteroids in these patients is very limited and outcomes are poor **(LoE 3, strong recommendation)**	97%
If corticosteroids are given to patients with acute severe AIH with ALF or ACLF, strict surveillance for infections and close monitoring of their efficacy is recommended **(LoE 2, strong recommendation)**	100%
In suspected cases of DI-ALH, the potential causative agent should be immediately withdrawn **(LoE 2, strong recommendation)**	97%
In patients with severe hepatitis or impaired liver function or no improvement of liver tests within 30 days of discontinuation of the implicated agent, a short course of predniso(lo)ne is recommended **(LoE 4, strong recommendation)**	94%
Predniso(lo)ne at an initial dose of 0.5 mg/kg/day followed by rapid tapering until complete withdrawal within 1-2 months is recommended **(LoE 5, strong recommendation)**	91%
Elderly patients with at least moderate activity should receive standard immunosuppression as described before **(LoE 3, strong recommendation)**	100%
A watch-and-wait strategy is recommended in elderly asymptomatic patients with mild activity and without advanced fibrosis **(LoE 4, strong recommendation)**	94%
Due to the potential risk of aggravating osteoporosis, and/or cardiovascular risk factors, rapid tapering of corticosteroids is recommended **(LoE 5, strong recommendation)**	100%
Patients with AIH-related decompensated cirrhosis should be evaluated for LT **(LoE 2, strong recommendation)**	100%
Corticosteroid treatment should be considered in patients with AIH-related decompensated cirrhosis with signs of disease activity (elevated aminotransferase levels and/or mHAI ≥4) **(LoE 4, strong recommendation)**	100%
The management of variant syndromes should be directed at the predominant component of the syndrome **(LoE4, strong recommendation)**	100%
In patients with AIH/PBC, the initial treatment regimen should be determined according to biochemical parameters and liver histological findings. Combination of standard immunosuppressive therapy with UDCA, (13-15 mg/kg/day) can be used in those with moderate or severe hepatitis, while UDCA monotherapy can be used in those with mild hepatitis followed by addition of immunosuppressive therapy if they do not achieve CBR **(LoE4, weak recommendation)**	100%
Immunosuppressive treatment with or without UDCA is suggested for adult and paediatric patients with the AIH/PSC variant **(LoE4, weak recommendation)**	94%
Patients with AIH and concomitant MASLD should receive standard treatment for AIH **(LoE 3, strong recommendation)**	97%
A personalised multidisciplinary approach to predniso(lo)ne administration targeting its lowest effective dose, lifestyle modifications, and strict management of metabolic syndrome components are recommended **(LoE 2, strong recommendation)**	97%
Patients with chronic viral hepatitis and autoimmune features should receive antiviral therapy **(LoE 4, strong recommendation)**	100%
Immunosuppressive treatment is recommended if there is evidence of persistent liver inflammation despite adequate viral control **(LoE 4, strong recommendation)**	100%
HBV surface antigen (HBsAg)-positive patients with AIH undergoing immunosuppressive treatment should receive antiviral therapy **(LoE 2, strong recommendation)**	100%
Anti-HBV core antigen (anti-HBc)-positive patients (HBsAg negative) at high risk of reactivation should undergo HBV prophylaxis **(LoE 2, strong recommendation)**	91%
Anti-HBc-positive patients (HBsAg negative) with low or moderate risk of reactivation require HBsAg and HBV DNA monitoring every 3 months. In case of HBV reactivation, antiviral therapy should be initiated **(LoE 2, strong recommendation)**	91%
Treatment of alcohol use disorder aimed at alcohol abstinence is recommended and should follow specific guidelines **(LoE 2, strong recommendation)**	97%
Immunosuppressive treatment for the AIH component should follow the current treatment guidelines of AIH **(LoE 5, strong recommendation)**	97%
Treatment of AIH in children should follow the same guidance as in adults except for tailored weaning of predniso(lo)ne to a maintenance dose of 2.5-5 mg/day to avoid corticosteroid-related side effects including growth failure **(LoE 2, strong recommendation)**	100%
In younger children or those with developmental delay dispersible tablets and syrups should be considered to avoid incorrect dosing **(LoE 2, strong recommendation)**	100%

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(*continued*)

Recommendation/statement	Consensus
Second- and third-line agents such as MMF and calcineurin inhibitors are recommended for treatment refractory cases with close monitoring for side effects including teratogenicity of MMF **(LoE 3, strong recommendation)**	100%
If not included in the national programme, hepatitis A and B vaccines should be given; live vaccination should be considered with caution and after discussion with the medical teams **(LoE 3, Strong Recommendation)**	97%
Upper gastrointestinal (GI) endoscopy screening to determine the presence of varices needing treatment (VNT) is recommended in patients with AIH-related cirrhosis and LSM ≥20 kPa or platelet count ≤150× 10^9/μL **(LoE 3, strong recommendation)**	91%
Patients with lower LSM but indirect signs of portal hypertension (splenomegaly, increased portal diameter, collateral veins) should undergo upper GI endoscopy screening **(LoE 3, strong recommendation)**	94%
Although the prevalence of HCC is lower in patients with AIH-related cirrhosis compared to cirrhosis of other aetiologies, patients with AIH-related cirrhosis should be screened for HCC with liver ultrasound with or without alpha-fetoprotein determination on a 6 monthly basis **(LoE 3, strong recommendation)**	97%
HCC management in AIH should follow specific HCC guidelines **(LoE 2, strong recommendation)**	100%
Immunotherapy for HCC can be considered in patients with well-controlled disease **(LoE 4, weak recommendation)**	100%
Patients with AIH and decompensated cirrhosis, acute severe AIH or AIH-related ALF (including ACLF) should be managed and evaluated for LT in reference centres **(LoE 2, strong recommendation)**	100%
In patients undergoing LT for AIH, low-dose predniso(lo)ne in combination with a calcineurin inhibitor (mainly TAC) can be used as maintenance immunosuppression to prevent AIH recurrence **(LoE 4, weak recommendation)**	91%
Plasma cell-rich rejection hepatitis should be considered as a cause of late graft dysfunction in patients transplanted for a liver disease different from AIH who present with liver enzyme abnormalities and histological features resembling AIH with or without IgG elevation and/or positive autoantibodies **(LoE 3, strong recommendation)**	100%
AIH recurrence and *plasma cell-rich rejection* hepatitis should be treated with predniso(lo)ne at the same doses recommended for AIH in non-LT patients **(LoE 4, strong recommendation)**	100%
Mental health and HRQL assessments are recommended in the routine management of all patients with AIH with signposting to other services if needed **(LoE 2, strong recommendation)**	100%
Treatment of AIH, particularly with corticosteroids, has a significant impact on HRQL and adherence and, as such, dose reductions or withdrawal of corticosteroids should be considered when appropriate **(LoE 2, strong recommendation)**	97%
Patient involvement in daily care and research should be encouraged **(LoE 3, strong recommendation)**	97%
Involvement with patient support groups (PSG) can be offered, among other interventions, to patients with AIH to improve their HRQL **(LoE 5, weak recommendation)**	100%
Young people aged 16-25 years should receive specialised care with support from a multidisciplinary team to address their developmental needs and improve outcomes **(LoE 2, strong recommendation)**	97%
Transition of care from paediatric to adult service should not solely depend on age and service provision should include collaboration between paediatric and adult services with inclusion of parents/carers **(LoE 2, strong recommendation)**	100%

Abbreviations

6-MMP, 6-methylmercaptopurine; 6-TGN, 6-thioguanine nucleotides; ACLF, acute-on-chronic liver failure; ALD, alcohol-related liver disease; ALF, acute liver failure; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AMA, anti-mitochondrial antibodies; ANA, antinuclear antibodies; anti-dsDNA, antibodies to double-stranded DNA; anti-HBc, anti-HBV core antigen; anti-SLA/LP, antibodies against soluble liver antigens/liver pancreas; AI, artificial intelligence; AIH, autoimmune hepatitis; AIH-1, type 1 AIH; AIH-2, type 2 AIH; AIH-3, type 3 AIH; ASC, autoimmune sclerosing cholangitis; AST, aspartate aminotransferase; CBR, complete biochemical response; CPGs, clinical practice guidelines; CSPH, clinically significant portal hypertension; DEXA, dual energy X-ray absorptiometry; DILI, drug-induced autoimmune-like hepatitis; DILI, drug-induced liver injury; EASL, European Association for the Study of the Liver; ESPGHAN, European Society for Paediatric Gastroenterology Hepatology and Nutrition; ERN, European Reference Network; GI, gastrointestinal; GGT, gamma-glutamyltransferase; HAV, hepatitis A virus; HBC, hepatitis B core antigen; HCC, hepatocellular carcinoma; HDV, hepatitis D virus; HEV, hepatitis E virus; HCV, hepatitis C virus; HRQL, health-related quality of life; IBD, inflammatory bowel disease; IFT, indirect immunofluorescence testing; IAIHG, International Autoimmune Hepatitis Group; INR, international normalised ratio; IgG, immunoglobulin class G; LC1, liver cytosol type 1; LKM1, liver kidney microsomal type 1; LT, liver transplantation; MELD, model for end-stage liver disease; MASLD, metabolic dysfunction-associated steatotic liver disease; MASH, metabolic dysfunction-associated steatohepatitis; MMF, mycophenolate mofetil; MP, mercaptopurine; mHAI, modified hepatic activity index; OCEBM, Oxford Centre for Evidence-based Medicine; PBC, primary biliary cholangitis; pANNA, perinuclear staining of anti-neutrophil nuclear antibodies; PSG, patient support group; PSC, primary sclerosing cholangitis; RCT, randomised-controlled trial; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SMA, smooth muscle antibodies; SLE, systemic lupus erythematosus; SURFASA, survival and prognostic factors for acute severe AIH; TAC, tacrolimus; TG, tioguanine; UDCA, ursodeoxycholic acid; ULN, upper limit of normal; TE, transient elastography; Δ, delta.

Conflict of interest

Please refer to the accompanying ICMJE disclosure forms for further details.

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Supplementary data

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Author names in bold designate shared co-first authorship

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