

The Saudi Association for the Study of Liver Diseases and Transplantation clinical practice guidelines for management of autoimmune hepatitis

Abdulrahman A. Aljumah, Badr Al Jarallah¹, Ali Albenmoussa², Abdullah Al Khathlan³, Adnan Al Zanbagi⁴, Mohammed Al Quaiz⁵, Bandar Al-Judaibi⁶, Khalid Nabrawi⁷, Waleed Al Hamoudi⁸, Mohammed Alghamdi⁹, Hind Fallatah¹⁰

Division of Hepatology, Hepatobiliary Sciences and Organ Transplant Center, King Abdulaziz Medical City and King Saud Bin Abdulaziz University for Health Sciences, Ministry of National Guard Health Affairs, Riyadh, Saudi Arabia, ¹Department of Medicine, Division of Gastroenterology, Al Qassim University, Al Qassim, Saudi Arabia, ²Department of Gastroenterology, Prince Sultan Military Medical City, Riyadh, Saudi Arabia, ³Department of Medicine, Division of Gastroenterology, King Fahad Medical City, Riyadh, Saudi Arabia, ⁴Department of Medicine, Division of Gastroenterology, King Abdullah Medical City, Makkah, Saudi Arabia, ⁵Department of Medicine, Section of Gastroenterology, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia, ⁶Department of Medicine, University of Rochester, Rochester City, New York State, USA, ⁷Department of Internal Medicine, Aseer Central Hospital, Abha, Saudi Arabia, ⁸Department of Medicine, Division of Gastroenterology, King Saud University, Riyadh, Saudi Arabia, ⁹Department of Internal Medicine, King Fahad Military Medical City, Dhahran, Saudi Arabia. ¹⁰Department of Medicine, Division of Gastroenterology and Hepatology, King Abdulaziz University, Jeddah, Saudi Arabia,

Address for correspondence: Dr. Abdulrahman A. Aljumah, Division of Hepatology, Hepatobiliary Sciences and Organ Transplant Center, King Abdulaziz Medical City and College of Medicine, King Saud Bin Abdulaziz University for Health Sciences, Ministry of National Guard Health Affairs, P. O. Box 225264, Riyadh 11324, Saudi Arabia.
E-mail: draljumah@hotmail.com

INTRODUCTION

Autoimmune hepatitis (AIH) is a chronic and progressive inflammatory liver condition of unknown etiology. It is a common cause of chronic hepatitis, liver cirrhosis, and end-stage liver disease worldwide.^[1] AIH is a complex disease that represents a challenge in diagnosis and management due to the diversity of the clinical presentation, wide spectrum of the disease, and variable response to treatment.^[2] Its diagnosis is based on histologic abnormalities, characteristic clinical and laboratory findings, abnormal levels of serum globulins, and the presence of one or more characteristic autoantibodies and exclusion of other known causes of chronic liver diseases. The characteristics of AIH include female predilection, elevations of aminotransferases,

non-specific or organ-specific autoantibodies, increased levels of immunoglobulin-G (IgG), and interface hepatitis on liver biopsy.^[3] Several international studies have investigated this disease; however, only limited data is available from the middle-eastern region. In the Kingdom of Saudi Arabia (KSA), although the prevalence of AIH among patients with liver disease is not known, it may be much less as compared to North America and European countries. We applied a systematic methodology to develop guidelines for the management of AIH by reviewing the available evidence, local data, and published international data. A comprehensive literature search of published articles on different aspects of the pathophysiology, epidemiology, diagnosis, and management of AIH was performed. All available literature on the topic was studied

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critically, and the available evidence was then classified according to its importance. International scientific associations' guidelines including, but not limited to, the European Association for the Study of the Liver,^[1] the American Association for the Study of Liver Disease,^[4] and the Asia-Pacific Association for the Study of the Liver^[5] were reviewed. Selected aspects of these guidelines were adopted and modified according to the need for local practice. Part of these guidelines were based on the experience of the authors in the specified topic. The purpose of these guidelines is to provide clinical and systematic approach guidance to gastroenterologists, hepatologists, and general internists in KSA on the diagnosis and treatment of AIH in order to improve the care of affected patients. It should also give physicians in primary and secondary care facilities the privilege to initiate a diagnostic and therapeutic approach on AIH patients before referring them to tertiary care centers. These guidelines are intended to be flexible and simple. The recommendations in these guidelines are based on the best available evidence and are tailored to patients being managed in KSA. They are graded on the basis of evidence as follows:

Grading of Recommendations:

Grade A: Recommendation based on at least one high-quality randomized controlled trial or at least one high-quality meta-analysis of methodologically sound randomized controlled trials

Grade B: Recommendation based on high-quality case-control or cohort studies or a high-quality systematic review

Grade C: Recommendation based on non-analytic studies (case reports or case series)

Grade D: Recommendation based on expert opinion only.

These guidelines have been endorsed and approved by The Saudi Association for the Study of Liver diseases and Transplantation (SASLT) and represent the position of the Association.

EPIDEMIOLOGY OF AIH

AIH is the most common form of autoimmune liver disease,^[4] affecting more females than males, with a female:male ratio of 3.6:1.^[4,6] Saudi studies addressing AIH have reported similar levels of female predominance, with the percentage of female patients ranging from 60.8% in the central region to 75.7% in the western region.^[7-9] In the largest Saudi multicenter study of AIH, Aljumah *et al.*^[9] reported a

female:male ratio of 3:2. The age of presentation for AIH exhibits a wide range that extends from adolescence and early adulthood to extreme old age.^[6,10] In KSA, the mean age of presentation for AIH patients is 32.3–45.4 years, although this age varies greatly as Saudi individuals older than 65 years of age have also presented with this disease.^[7-9] Comparison with international reports indicate that Saudi patients and patients from India and Italy have similar ages of presentation for AIH.^[11,12] There is a poor documentation of the prevalence of AIH worldwide. However, it has been estimated to range between 100 and 400 cases per 1 million in different regions from Europe and North America.^[3,13,14] In comparison, the international prevalence among patients with liver disease is between 11% and 20%.^[15] In Asian and African countries, where viral hepatitis is endemic, the prevalence of AIH is not precisely known. Although the prevalence of AIH among Saudi patients with liver disease is not known, it is anticipated to be lower compared to North America and European countries. In one study of 112 liver transplant (LT) patients, 14.3% of LT indications were due to AIH.^[16]

Summary Points:

- The prevalence of AIH in KSA is not known
- The prevalence of AIH among LT patients from KSA is 14.3%
- AIH can affect a wide spectrum of age groups, ranging from adolescents to those aged more than 60 years. However, young females are more frequently affected
- AIH affects females twice as much as males.

CLINICAL PRESENTATION

Clinical features of AIH

The clinical spectrum of presentation for AIH varies from an asymptomatic elevation of liver enzymes with typical positive immunological markers to severe forms of advanced chronic liver disease, acute hepatitis, and fulminant liver failure.^[1,4,6,17] AIH studies from KSA have shown that one-fifth to one-fourth of patients were asymptomatic; such patients are diagnosed when evaluated for abnormal liver enzymes.^[7-9] Another one-fifth of the patients present with either no specific symptoms or only abdominal pain.^[8,9] Jaundice, the most frequently reported presentation, has been observed in more than 50% of Saudi AIH patients.^[7,9] Chronic presentations were seen in 37.7% of Saudi AIH patients,^[9] while cirrhosis with or without decompensation has been reported in 28.8–45.5% of patients.^[7,9] In KSA, acute presentations of AIH have been reported in 7.5–36.4% and fulminant presentation occurred in 2.8% of patients.^[7,9] The summary of findings from the major studies on AIH from

KSA is illustrated in Table 1. Another uncommon presentation of AIH involves cholestatic but not hepatocellular elevation of liver enzymes, which raises the possibility of other cholestatic liver diseases.^[18,19] This presentation is also not commonly reported in KSA.^[7,8] Hepatocellular carcinoma (HCC) is rarely reported as a complication of AIH.^[1,20] In KSA, one study has reported that out of 235 patients, only 3 patients (1.3%) developed HCC in AIH-related cirrhosis compared to 178 patients (75.7%) with viral hepatitis.^[21]

Summary Points:

- AIH has a wide spectrum of presentation, ranging from asymptomatic liver function abnormality to severe acute or chronic advanced liver disease
- One-third of AIH patients have acute presentation
- Jaundice is the most commonly presenting symptom
- AIH should be considered in all patients with acute or chronic liver disease in the absence of other etiology.

Classification of AIH

AIH is classified into two types: AIH type 1 and AIH type 2. AIH type 1, which is the more commonly reported form of AIH in international reports, accounts for 90–95% of cases and is characterized by positivity for anti-nuclear antibody (ANA) and/or anti-smooth muscle antibody (ASMA). Anti-soluble liver antigen (SLA)/liver pancreas (LP) is detected in one-third of patients with AIH type 1 and can be considered as the only positive marker found in AIH patients.^[1,4,5,17]

AIH type 2 is characterized by the presence of anti-liver kidney microsomal type 1 (LKM1), anti-liver cytosolic antigen type 1, and/or anti-LKM3. This form accounts for less than 10% of AIH patients, predominantly affects children, and commonly involves acute presentation.^[1,4,17,20] In studies addressing AIH from KSA, most of the reported patients had AIH type 1,^[7-9,22] and only 7.6% cases had LKM1-positive AIH type 2.^[9]

Table 1: Clinical presentation, laboratory findings, and treatment response of autoimmune hepatitis in three major studies from Saudi Arabia

Parameters	Study		
	Fallatah et al. ^[7]	Abdo ^[8]	Aljumah et al. ^[9]
Total number of patients	33	39	212
Age: mean±SD (range)	32.3 years (10-65)	45.4 years	36.2±16.8 years
Gender, n (%)			
Male	8 (24)	14 (35)	83 (39.2)
Female	25 (76)	25 (65)	129 (60.8)
Clinical presentation, n (%)			
Asymptomatic	7 (21)	10 (27)	95 (45)
Jaundice	17 (52)	18 (46)	141 (67)
Abdominal pain	NR	NR	22
Acute hepatitis	12 (36)	3 (8)	65 (31)
Fatigue/non-specific	2 (6)	8 (21)	77 (36)
Fulminant hepatic failure	NR	NR	6 (2.8)
Associated autoimmune disorders, n (%)	6 (18.1)	23 (59)	55 (26)
Laboratory findings*			
ALT	378 (median)	286 (mean)	328 (mean)**
AST	400 (median)	277 (mean)	364 (mean)**
Bilirubin	151 (median)	92. (mean)	131 (mean)**
ANA	19 (58)	18 (47)	132 (62.4)
ASMA	24 (72)	12 (30)	133 (63)
ANA + ASMA	NR	5 (13)	82 (39)
LKM1	0 (0)	NR	16 (7.6)
IgG	16 (48)	NR	177 (83)
Advanced fibrosis and cirrhosis	15 (45.5)	15 (38)	61 (28.8)
Treatment regimen, n (%)	2 (6) No treatment 30 (91) PD + Aza 1 (3) MMF***	20 (51) PD 19 (49) PD + Aza	200 (94) PD + Aza 9 (4.2) MMF*** 5 (2) Tac***
Response rate, n (%)			
Complete response	17 (54.8)	18 (46)	158 (75)
Partial response	11 (35.5)	12 (30)	19 (9)
No response	3 (0.9)	9 (23)	35 (17)

*Only autoantibodies with significant level was reported; **Liver tests means were extrapolated from the original data of the study; ***Patients initially received PD + AZA. MMF or Tac was used if no response to standard therapy. AIH: Autoimmune hepatitis; SD: Standard deviation; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ANA: Anti-nuclear antibody; ASMA: Anti-smooth muscle antibody; Anti-LKM: Liver/kidney microsomal antibody; IgG: Immunoglobulin G; NR: Not reported; PD: Prednisone/prednisolone; Aza: Azathioprine; MMF: Mycophenolate mofetil; Tac: Tacrolimus

AIH and other autoimmune diseases

Associations between AIH and other forms of organ-specific disorders are not uncommon, and approximately one-fifth of AIH patients have another autoimmune disease.^[1,4,17] Such diseases include autoimmune thyroid diseases, type 1 diabetes mellitus, rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), inflammatory bowel diseases, and other disorders.^[1,4,9,17] Saudi studies of AIH have shown varying associations between AIH and other autoimmune disorders, with percentages for such associations ranging from 18%, as reported by Fallatah *et al.*, to nearly 60%, as reported by Abdo *et al.*^[7-9,23] In KSA, the most commonly reported autoimmune diseases associated with AIH are autoimmune thyroid disorders and diabetes.^[8,9] SLE and RA have also been reported.^[7] Moreover, AIH can be associated with primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC).^[24-26] AIH overlap syndrome has been reported in 20% of patients with autoimmune liver disease.^[27] An overlap can be observed between any of the clinical or laboratory features of the two overlapping conditions. The relationship between the two disorders and the presentations of overlapping disorders can vary. The two disorders can manifest sequentially, co-exist without a clear distinction, or present as discrete conditions.^[24-26] (See section on “Difficulties in the diagnosis”).

Summary Points:

- AIH is commonly associated with other organ-specific autoimmune diseases in more than one-third of patients
- Autoimmune thyroid disorders and diabetes are the most commonly diagnosed autoimmune diseases among AIH from KSA
- In the presence of suggestive symptoms, it is worthwhile investigating for coinciding autoimmune disease in AIH patients.

DIAGNOSIS

Diagnostic criteria and scoring systems

The diagnosis of AIH is made based on a combination of biochemical, serological, and histological findings. The scoring system developed by the international AIH group in 1993 and revised in 1999 is the most widely used scoring system in clinical trials; however, its complexity makes it cumbersome to use in real-life practice [Table 2].^[28,29] This comprehensive system incorporates several clinical, biochemical, serological, and histological tests together with the response to treatment. A simplified scoring

system has been suggested for clinical use, and it consists of 4 criteria based on which the diagnosis of definite or probable AIH can be made [Table 3].^[30] The original scoring system has a higher sensitivity than the simplified one (100% vs. 85–95%), while specificity was higher in the simplified system (90–99% vs. 73–90%).^[31,32] The diagnostic accuracy of these systems varies according to the clinical presentation, variant of AIH, and concomitant liver diseases (see section on “Difficulties in the diagnosis” below). The simplified scoring system has been verified in several retrospective trials from different countries and found to be appropriate for clinical use with acceptable accuracy. Utilizing these scoring systems requires exclusion of other liver diseases that may resemble AIH and can get high scores.^[33] The designation of definite and probable AIH by these two systems may reflect the differences in clinical features between them without a difference in their prognosis or response to treatment.^[34]

Recommendations:

- AIH patients should be managed by an expert gastroenterologist or hepatologist whenever possible (Grade C)
- Diagnosis of AIH requires exclusion of other causes of liver diseases (Grade B)
- There is no single pathognomonic test for the diagnosis of AIH (Grade C)
- Both the original international AIH group score and the simplified score combined several diagnostic criteria and can be used for the diagnosis of AIH with acceptable accuracy (Grade B)
- Response to treatment has important diagnostic value in the management of AIH (Grade C).

Laboratory and histological assessment

Biochemical changes

Initial assessment of patients investigated for possible AIH should include the measurement of total and direct bilirubin, alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), aspartate transaminase (AST), alanine transaminases (ALTs), and serum immunoglobulins. There is no specific biochemical pattern for AIH, but the classical change is a hepatitis liver function test (LFT) abnormality with predominant rise in transaminases that can be mildly elevated and may reach thousands.^[7,9] Bilirubin can be normal, but jaundice was reported in up to 66% cases.^[9] Jaundice at presentation carries poor prognosis.^[35] ALP can also be elevated, but GGT rise is more frequently encountered.^[9,36] Cholestasis can be the presenting feature of AIH, and it is either related to the disease

Table 2: The revised international autoimmune hepatitis scoring system

Parameter	Result	Score	Parameter	Result	Score
Sex	Female	+2	HLA	DR3 or DR4	+1
ALP:AST (ALT) ratio	>3	-2	Immune disease	Thyroiditis, colitis, others	+2
	<1.5	+2	Other markers	Anti-SLA, anti-actin, anti-LC1, p-ANCA	+2
IgG level above normal	>2	+3	Histological features	Interface hepatitis	+3
ANA, ASMA, anti-LKM1	1.5-2	+2		Plasmacytic infiltrate	+1
	1-1.5	+1		Rosette formation	+1
	>1:80	+3		None of the above	-5
	1:80	+2		Biliary changes	-3
	1:40	+1		Other changes	-3
	<1:40	0	Treatment response	Complete	+2
AMA	Positive	-4		Relapse	+3
Viral markers	Positive	-3	Pre-treatment score	Definite diagnosis	>15
	Negative	+3		Probable diagnosis	10-15
Drugs	Yes	-4	Post-treatment score	Definite diagnosis	>17
	No	+1		Probable diagnosis	12-17
Alcohol	<25 g/day	+2			
	>60 g/day	-2			

HLA: Human leukocyte antigen; ALP: Alkaline phosphatase; AST: Aspartate transaminase; ALT: Alanine transaminase; anti-SLA: Anti-soluble liver antigen; anti-LC1: Anti-liver cytosol antibody type 1; p-ANCA: Perinuclear anti-neutrophil cytoplasmic antibodies; IgG: Immunoglobulin G; ANA: Anti-nuclear antibodies; ASMA: Anti-smooth muscle antibodies; anti-LKM: Anti-liver/kidney microsome antibodies; AMA: Anti-mitochondrial antibodies

Table 3: The simplified scoring system for autoimmune hepatitis

Parameter	Result	Score
ANA or ASMA	≥1:40	+1
	≥1:80	+2
Anti-LKM	≥1:40	+2
Anti-SLA	Positive	+2
Serum IgG	>1 ULN	+1
	>1.1 × ULN	+2
Histology	Compatible with AIH	+1
	Typical AIH	+2
Viral serology	Negative	+2
Definite diagnosis		≥7
Probable diagnosis		6

ANA: Anti-nuclear antibodies; ASMA: Anti-smooth muscle antibodies; anti-LKM: Anti-liver/kidney microsome antibodies; anti-SLA: Anti-soluble liver antigen; IgG: Immunoglobulin G; ULN: Upper limit of normal; AIH: Autoimmune hepatitis

or indicates an overlapping PBC, PSC, or autoimmune cholangiopathy.^[18] Serum IgG is an important diagnostic tool that has been incorporated in the international AIH scoring system.^[29] It also has a prognostic value since it was found to correlate with the severity of inflammation and fibrosis.^[9,37] The level of serum transaminases was not found to reflect the severity of the disease but they are best used to monitor disease activity, and thus biochemical remission is widely used as a surrogate marker for response to treatment.^[38] Moreover, increased AST/ALT ratio was found to correlate with cirrhosis^[8]

Auto-antibodies

The presence of circulating autoantibodies is an essential element in the definition of AIH.^[39] These antibodies are important diagnostic tools, but they are not specific and their absence does not exclude AIH. ANA and ASMA are the hallmark of type 1 AIH, while anti-LKM1 is the marker

for type 2 AIH.^[40,41] A positive titer for ANA and ASMA is $\geq 1:40$ in adults, and a titer of 1:20 is clinically significant in children. Positive ANA and ASMA can be found in 80% and 65% of AIH patients, respectively.^[42] In Saudi patients, ANA was found to be positive in 62.4% cases and ASMA in 63% cases; they were both positive in 38.7% cases and both negative in 17.2% cases.^[9] Positive ANA was found in up to 30% and ASMA was found positive in 3–15% of patients with liver diseases other than AIH including non-alcoholic steatohepatitis, hepatitis C virus (HCV), PSC, and PBC.^[43,44] This might create diagnostic difficulty, and thus correlation with other findings is necessary to establish the diagnosis. The level of ANA does not seem to correlate well with disease severity, and it cannot be used to monitor disease for progression and response to treatment.^[40,45] Anti-LKM1 in AIH was found in about 3% of adults and in up to 32% of pediatric age group.^[41,46] Although anti-LKM1 has a specific target (cytochrome P450 2D6), it remains not pathognomonic for AIH and was reported in 10% of patients with HCV infection.^[39] The prevalence of anti-LKM1 in KSA was reported to be 7.6%.^[9] In the absence of conventional autoantibodies, several other autoantibodies can be useful in the diagnosis of AIH including anti-actin-F, anti-SLA/LP, and anti-asialoglycoprotein.^[47-50]

Histology

Histological assessment is an essential part in the diagnosis of AIH. Liver biopsy is strongly recommended to confirm the diagnosis, exclude other causes of hepatitis, and assess the extent of fibrosis. Although biopsy is a crucial step in the diagnosis of AIH, its unavailability or presence of contraindications should

not delay the initiation of treatment if urgently indicated.^[1,4,51,52] The liver biopsy is better evaluated by an expert gastrointestinal and liver pathologist, and on some occasions liver biopsy needs to be evaluated by two pathologists. Liver biopsy can be done percutaneously or through trans-jugular access in patients with severe coagulopathy.^[53] The classical histological features of AIH are interface hepatitis, plasma cell infiltration, rosette formation, and emperipolesis (active penetration of the cytoplasm of a hepatocyte by another cell, usually a lymphocyte and rarely a plasma cell which remains intact)^[54] Emperipolesis was observed in 65% of patients with AIH and was associated with more severe necroinflammation and more advanced fibrosis.^[55] Different stages of fibrosis can be found at the time of diagnosis, and bridging fibrosis and cirrhosis are frequent findings even in asymptomatic patients.^[9,56] Bridging necrosis, centrilobular necrosis, massive or sub-massive hepatic necrosis, lymphoid follicles, a plasma cell-enriched inflammatory infiltrate, and central perivenulitis are more frequently seen in patients with acute severe presentation including acute liver failure.^[57,58] These findings, however, are not specific for AIH and can be found in viral hepatitis, drugs and herbal extract-induced hepatitis, and other immune-mediated liver diseases; their absence does not exclude AIH.^[54,59] If there is a lack of classical features, then an alternative diagnosis should be sought; but AIH should still be considered as a differential diagnosis. Neither serological markers nor the clinical symptoms predict the histological severity of AIH.^[45] Some laboratory tests are suggested to correlate with inflammation, particularly ALT and IgG, but their normalization is not a reliable marker for histological remission.^[37] Aljumah *et al.*^[9] showed an association among serum IgG, ALT level, and platelet count, and the presence of advanced fibrosis on liver biopsy. Bile duct injury in AIH can be seen in up to 10% of cases. This may suggest the presence of co-existing PBC or PSC, particularly if there is ductopenia or severe cholangitis.^[60] The presence of IgG4-related hepatitis was suggested by a limited number of small studies. However, the evidence is not sufficient to treat this group of patients as a separate entity.^[61] A repeat liver biopsy is not always needed but should be considered if there is an increase in liver enzymes in spite of adequate immunosuppression and prior to discontinuation of treatment.^[62] The presence of portal plasma cell infiltrates on liver biopsy prior to withdrawal of treatment was found to predict relapse with a sensitivity of 31% and positive predictive value of 92%.^[63]

Recommendations:

- Initial assessment of patients suspected to have AIH should include full blood count, LFT, coagulation profile, serum immunoglobulins, and autoantibodies (Grade B)
- Autoantibodies have important diagnostic and prognostic value in patients suspected to have AIH, but they lack the sensitivity and specificity (Grade B)
- Autoantibodies are not sufficient to make the diagnosis of AIH, and they should be interpreted within the clinical presentation and correlated with other biochemical and histological findings (Grade B)
- Elevated serum IgG is important in the diagnosis of AIH and it correlates with the disease severity (Grade B)
- Liver biopsy is necessary to establish the diagnosis of AIH and exclude other causes of liver dysfunction, but it should not delay the treatment if urgently indicated (Grade B).

Genetic considerations

One of the principles that explain the pathogenesis of AIH is that it is an autoimmune disorder triggered by an environmental factor in a genetically susceptible patient, which leads to the loss of tolerance to autoantigens.^[64] However, this relationship between genetics and the autoimmune process is still poorly understood. Most of the research into genetics and AIH is directed toward human leukocyte antigens (HLA) within the major histocompatibility complex, which is located on chromosome 6.^[65] Unfortunately, data on the genetic characteristics in the Saudi population is limited, and most studies are from other places in the world. In North American Caucasians, there is a strong association between AIH and HLA-DRB1*0301 (DR3) and HLA-DRB1*0401 (DR4) alleles.^[66] Other associations have been found in South America, especially DRB1*1301.^[67] In a recent genome-wide association study on a large cohort of patients from Netherlands, an association between AIH type 1 and multiple variants in the major histocompatibility complex region were identified as likely risk factors.^[68] In Asia, the main AIH association is with HLA-DR4 and genotypes DRB1*0405 and DQB1*0401.^[69] This variation in the association between AIH and different alleles may explain the different clinical presentations in terms of the age of onset and disease behavior among different geographical areas. The variation in the HLA alleles does not lead to increased susceptibility to AIH. In fact, one allele, HLA-DRβ1*1501, is associated with “protection” from AIH, especially in Caucasians.^[70] One rare genetic

disease involves AIH with multiple endocrine organ failure, mucocutaneous candidiasis, and ectodermal dystrophy. This is collectively labeled as “autoimmune polyendocrine syndrome type 1.” This syndrome is not associated with HLA variants but rather a mutation on chromosome 21 by mutations in the autoimmune regulator gene.^[71] Despite the aforementioned association between HLA variability and AIH, the exact mechanisms by which these variations increase, or decrease, the susceptibility to AIH are still not well understood.

Difficulties in the diagnosis

Difficulties in the diagnosis of AIH can be attributed to multiple factors, including the presence of atypical clinical or biochemical features. This can be explained by another active process in the liver (PSC, PBC, autoimmune cholangiopathy) or the existence of an alternative etiology that may explain the biochemical/histological findings (drug-induced hepatitis). Currently, there exist no acceptable, agreed-upon definitive diagnostic criteria used to define overlap syndromes. However, it has been suggested that those syndromes should be regarded as a distinct disorder and that diagnoses should be established based on each patient’s most dominant clinical feature. Diagnostic criteria for AIH/PBC overlap have been previously proposed; however, these criteria have limitations and cannot be accurately applied to all patients.^[25,72,73] There are ongoing diagnostic challenges for AIH overlapping with PSC and PBC, which will be discussed in the next section.

AIH with primary biliary cholangitis:

The prevalence of overlap between the features of PBC and AIH is estimated to be 7–10% in patients with AIH.^[27,74] Although there is no standardized approach to diagnose such overlap, the “Paris criteria” has been proposed to serve as a tool to diagnose AIH–PBC overlap. Details of the Paris criteria are listed in Table 4. These criteria carry good sensitivity and specificity (92% and 97%, respectively)

Table 4: Paris AIH-PBC overlap criteria modified by EASL

PBC	AIH
2 are needed	Mandatory: Moderate to severe lymphocytic piecemeal necrosis (interface hepatitis)
ALP > 2 ULN “OR” GGT > 5 ULN	“Plus”
Positive AMA	One of
Florid duct lesions on liver biopsy	ALT 5-fold ULN
	IgG 2-fold ULN “OR” positive ASMA

PBC: Primary biliary cholangitis; AIH: Autoimmune hepatitis; ALP: Alkaline phosphatase; EASL: European Association for the Study of the Liver; GGT: Gamma-glutamyl transferase; ULN: Upper limit of normal; AMA: Anti-mitochondrial antibodies; IgG: Immunoglobulin G; ASMA: Anti-smooth muscle antibodies

for the diagnosis of AIH–PBC overlap syndrome.^[75] Serological overlap is a term that is used to describe the presence of an isolated serological marker of one disease without its histological features.^[4] Such serological overlap has a prevalence of 5% in patients with AIH, although older studies reported more frequent detection of anti-mitochondrial antibody in AIH (20%).^[76] Females are more commonly affected by this form of overlap; the male:female ratio among patients with AIH/PBC overlap is 2:8.^[24] The clinical presentations of AIH/PBC do not significantly differ from those of isolated AIH; however, AIH/PBC patients frequently present with malaise and lethargy.^[24] In this variant of overlap syndromes, the disease may evolve into isolated AIH or PBC or continue as overlap syndrome.^[25] This form of serological overlap does not negatively influence the response of AIH to corticosteroids.^[76]

AIH with primary sclerosing cholangitis:

AIH/PSC overlap was first described in three patients by Gohlke *et al.*^[77] It typically affects children, adolescents, and young adults with a male:female ratio among the patients with this overlap being 2:1.^[24,77] The prevalence of overlap between AIH and PSC is increased in young patients and children, reaching 6–14% in some reports.^[26,27,78] Children who are diagnosed with AIH have a particularly high prevalence of co-existing AIH with PSC. This has led to the introduction of the term “autoimmune sclerosing cholangitis.”^[79] Based on that diagnosis, it is recommended that all children should be evaluated by a cholangiogram to rule out the presence of an overlap between PSC and AIH.^[1] Typically, in cases involving AIH/PSC overlap, AIH is first diagnosed, and PSC is diagnosed several years later.^[80,81] Two patterns of PSC exist; the large duct PSC can reliably be with imaging like magnetic resonance cholangiopancreatography (MRCP). On the other hand, small duct PSC requires a histological diagnosis in the setting of a normal cholangiography. However, injury of the bile ducts can naturally occur in AIH, which makes the diagnosis of AIH–PSC difficult.^[60] AIH/PSC patients commonly present with jaundice.^[24] Compared with PSC patients, patients with AIH/PSC overlap syndrome can benefit from immunosuppression and ursodeoxycholic acid.^[81] On the other hand, AIH/PSC overlap patients exhibited significantly reduced survival compared with patients with alone, but better survival than patients with PSC alone.^[24,81,82]

Drug-induced autoimmune liver injury:

Approximately 9% of patients diagnosed with AIH have drug-induced liver injury (DILI).^[83] Many drugs can induce liver injuries that are indistinguishable from classic AIH.

Drugs can induce liver injury via different mechanisms, including drug-induced autoimmunity.^[84] Multiple drugs have been documented to induce an immune reaction that either mimics AIH or triggers AIH. Among those medications, two are clearly associated with drug-induced autoimmune liver injury; minocycline and nitrofurantoin induce histological changes in the liver that fulfill the diagnostic criteria for AIH.^[83,85,86] When compared with classical AIH, no major differences exist except for the advanced stage in classical AIH. Most patients with drug-induced AIH are women (80–90%); the median time to onset of clinical symptoms (jaundice) from drug exposure is 40 days (range 20–117), and features of hypersensitivity (fever, rash, and eosinophilia) are present in 15–20% of patients.^[87] The serological markers for AIH are also positive in patients with minocycline and nitrofurantoin, with ASMA positive in 45–55% and ANA positive in 73–91%.^[83] Thus, any patient being evaluated for the presence of AIH should be asked about medication history. Histological findings that are particularly suggestive of drug-induced injury are portal neutrophils and intracellular cholestasis, whereas portal plasma cells and hepatocyte rosettes favor classic AIH. In drug-induced AIH, fibrosis may be present, but cirrhosis is rare. Keys to diagnosis include the collateral sequence between drug exposure and the onset of disease and the lack of recurrence after discontinuation of the drug.^[83,87] Patients with drug-induced immune liver injury will not likely require long-term immune suppression. On the other hand, patients with classical AIH will usually relapse; thus, differentiating between those two entities is important.^[83] Some data suggest that patients with drug-induced AIH may have a late relapse.^[88]

Khat (Gat or Qat):

Khat or Qat, also known as *Catha edulis*, is a flowering plant native to the African Horn of the southern Arabian Peninsula (mainly Somalia and Yemen, and to a less extent, southern KSA). For people from those regions, Khat chewing is a common social habit that causes excitement, euphoria, and loss of appetite. Khat contains cathinone, which is a monoamine alkaloid and an amphetamine-like stimulant.^[89] Khat is a hepatotoxic agent that has been reportedly linked to AIH in young males from Khat chewing regions. Multiple case series have been published that link Khat use to AIH. One series of seven patients with severe hepatitis and chronic Khat use showed that 3 out of 7 had positive serological markers for AIH (ASMA) and that 3 of them scored 9, 1 scored 10, and 1 scored 12 on the AIH probability scoring system.^[90] Another case series of six patients who had active hepatitis while using Khat revealed that 83% fulfilled the probable diagnosis of AIH.^[91] Moreover, severe cases of Khat-induced liver injury

have been reported to cause death or require LT.^[92,93] Data from KSA in a of three young patients who used Khat for a prolonged period showed clinical and serological features of AIH and one showed biopsy-proven AIH.^[94] The prognosis of Khat-induced hepatotoxicity/AIH seems to be dependent on early diagnosis, early treatment, and most importantly abstinence from using Khat.

AIH and viral infection:

Several hepatotropic and non-hepatotropic viruses are thought to trigger AIH.^[17] These viruses include the hepatitis A, B, and C viruses and the Epstein–Barr virus.^[2,17,95] However, chronic hepatitis virus infection with hepatitis B virus (HBV), HCV, and/or hepatitis D virus (HDV) has been found to be associated with immune response and with positive immune markers for AIH, leading to the misdiagnosis of AIH in certain patients.^[2,95] Similar to our findings for cholestasis and AIH, we identified only one Saudi report of AIH triggered by a viral infection, namely, varicella-zoster infection.^[96]

TREATMENT

The aim of the therapy is to achieve clinical, biochemical, and histological remission and prevent further progression of the liver disease. In those with established active cirrhosis, treatment prevents clinical deterioration and may cause reversal of cirrhosis.

Indications for treatment

Absolute indications

Patients with AIH and moderate or severe inflammation (defined as one or more of serum AST >5 times normal, serum globulins >2 times normal, liver biopsy showing confluent necrosis) should be offered treatment.^[3,97-99] Patients with biopsy-proven cirrhosis due to AIH should also be considered for treatment.

Other indications

Patients who do not meet the above criteria, but have fatigue or arthralgia, should be treated to control the symptoms.^[4,56] Younger patients with less severe disease may be offered treatment with the intention of preventing cirrhosis.^[4] However, patients with the right context of possible AIH, particularly in the presence of suggestive biochemical and serological markers, should be offered treatment with steroids. Currently, there is accumulating evidence to suggest that AIH with even low transaminases and/or serum IgG that is not reaching the diagnostic criteria may insidiously progress to cirrhosis. Elderly patients with mild interface hepatitis and mild elevation of transaminases may be observed, as the outcome of untreated patients was similar to those who were treated.^[10,100]

No indication to treat

There is no justification to treat patients with normal transaminases and IgG and minimal activity on biopsy. However, it should also be taken into consideration that untreated AIH has a fluctuating, unpredictable disease behavior, and a substantial proportion of asymptomatic patients may become symptomatic during the course of their disease and thus long-term follow-up is recommended.^[56,100] Patients with burned-out cirrhosis (normal liver enzymes and absent histological activity on liver biopsy) are not considered for treatment but are rather considered for LT as they are unlikely to benefit from the treatment.^[101]

Induction therapy

The survival benefit of corticosteroid therapy with or without azathioprine has been long established by key early studies and was confirmed by more recent studies.^[98,99,102] The use of prednisolone plus azathioprine provides the best option to control the disease and minimize the side effects. The dosing of prednisolone and the timing of azathioprine introduction varies between different studies and guidelines. In a recent double-blind randomized trial, budesonide (9 mg/day) plus azathioprine (1–2 mg/kg/day) was compared to the conventional prednisolone (40 mg/day) plus azathioprine (1–2 mg/kg/day) in non-cirrhotic AIH. The study showed that budesonide in combination with azathioprine resulted in induction and maintenance of remission in such patients with fewer side effects.^[103]

Medications and doses

Prednisolone: the induction dose varies between trials, ranging between 30 and 60 mg, or up to 0.5–1 mg/kg/day. For adult patients, prednisolone is given as a single daily dose orally. Alternatively, budesonide may be preferred in patients without cirrhosis.

Azathioprine: The dose and timing of introducing azathioprine vary in the literature. Till now, 50–100 mg or 1–2 mg/kg/day as a single dose are considered appropriate maintenance doses.^[4,104] We advise to delay the introduction of azathioprine by a week or two to confirm the response to steroids and avoid the dilemma of azathioprine hepatic toxicity versus steroid resistance in patients having worsening of LFT after initiation of treatment and in patients presenting with hyperbilirubinemia.

Induction of remission

We recommend a daily oral dose of 40–60 mg prednisolone for 2 weeks, followed by azathioprine at a starting dose of 50 mg that needs to be increased slowly to a maximum of 2 mg/kg daily. The dose of

steroids should be adjusted according to the biochemical response. Tapering of steroid should be individualized, aiming to taper off steroids in 6–12 months.^[105] Usually by 6 months, the patient should be administered a dose of prednisolone of 10 mg daily or less and azathioprine of 1–2 mg/kg daily.

Maintenance therapy

After achieving clinical and biochemical responses, azathioprine should be titrated to 1–2 mg/kg/day along with withdrawing corticosteroid therapy. Azathioprine therapy is the main maintenance therapy that helps to prevent the side effects of steroids. Data on azathioprine therapy up to 67 months showed 83% remission rate.^[102,106,107]

Withdrawal of azathioprine after achieving remission has been associated with a high relapse rate (50–90%).^[10,108,109] It is recommended to continue a maintenance dose of azathioprine of 1–2 mg/kg daily for life. If the patients have a contraindication to azathioprine, then they can be kept on the smallest dose of steroid required to maintain remission. Alternatively, mycophenolate mofetil (MMF) can be given as maintenance medication if azathioprine is contraindicated or the patient develops toxicity. Patient involvement in the selection of treatment options and the possible side effects expected from each option can improve compliance to treatment and help in effective disease management.

Monitoring during induction and maintenance therapy

Clinical and biochemical monitoring early in the course of treatment is important to confirm response to corticosteroid therapy and recognize steroid-resistant cases. The initial follow-up needs to be done within 2–4 weeks of starting therapy depending on the severity of the case. It involves monitoring for encephalopathy, worsening jaundice, and/or presence of ascites. Laboratory parameters include ALT/AST, bilirubin, albumin, IgG, and international normalized ratio (INR). With prolonged duration of the therapy, monitoring can be extended to 3- to 6-month intervals to ensure normalization of laboratory indices. Flares and relapses are frequent even after complete remission; hence, lifelong monitoring is warranted. Recent reports have shown that non-invasive measurement using transient elastography (FibroScan) can be used to assess regression/progression of cirrhosis or fibrosis in patients with AIH.^[110] Calcium and vitamin D are required during prolonged steroid therapy to minimize the side effects on the bones.

Remission

Remission is defined as the resolution of clinical condition, normalization of laboratory indices (ALT/AST, IgG, bilirubin, albumin, and INR), and resolution of histological activity. Clinical and biochemical remission are the first clues of response to a treatment after 3–8 months.^[98] Histological remission is the only measure of complete remission. It lags 3–8 months behind laboratory remission.^[98] The average duration of treatment to achieve complete sustained remission is about 18–24 months.^[111–113] Interface hepatitis is present in up to 55% of patients who achieve normal liver enzymes and normal IgG.^[113] The majority of patients show a biochemical response to the usual treatment with corticosteroid therapy. Non-responsive patients to immunosuppressive therapy represent a very small proportion of patients and should lead to questioning the diagnosis and compliance to treatment. Saudi reports on AIH have shown variable complete response rate from 45% in Abdo *et al.*'s study to 74.5% in Aljumah *et al.*'s study.^[8,9] Compared to international figures, this lower response rate may be explained by the presence of a large number of patients with advanced disease among the Saudi cohorts of AIH.^[7–9]

Continuing treatment without response to initial treatment or at 6–12 months of follow-up in fully compliant patients was reported in 15–20% of AIH patients.^[114,115] This should raise the possibility of treatment failure or alternative diagnosis, and an alternative treatment option can be used.^[114–116]

Discontinuation of therapy

Giving the patient who sustained remission, the chance to be off medications at some point is debatable, and the evidence is not yet conclusive.^[109,111–113,117,118] However, we do not recommend discontinuation of maintenance therapy. Due to the high rate of relapse after discontinuation of therapy (up to 90%), it is recommended to keep the lowest possible dose of azathioprine for life. Inadequate therapy can achieve a sustained response in only 20% of patients.^[1,109,119–121] In the cases of treatment withdrawal, the risk of relapse should be discussed with the patients, and the patient should share the decision of treatment withdrawal if deemed necessary. Termination of therapy should be gradual with close monitoring during withdrawal time. Liver biopsy is mandatory before discontinuation of therapy to prove histological remission before stopping the treatment.^[4,114] Patients off medication should be monitored clinically and biochemically for recurrence of symptoms and elevated liver enzymes as delayed relapses can develop even after several years after discontinuing azathioprine.^[108,114,118]

Recommendations:

- Treatment of AIH is indicated in patients with evidence of active moderate to severe inflammation and patients with active symptoms (Grade B)
- Immune suppression with steroids or azathioprine is the mainstay for treatment of AIH (Grade A)
- A rational treatment strategy includes initial induction therapy with large dose of steroids followed by gradual reduction to smaller maintenance doses (Grade B)
- Maintenance of AIH remission is achieved in most patients with azathioprine 1–2 mg/kg/day or azathioprine and small dose of prednisolone (Grade B)
- Continuation of maintenance therapy is important after initial biochemical remission since histological remission can take up to 8 months after biochemical remission (Grade B)
- Discontinuation of therapy after complete remission is discouraged as more than 90% of patients will have relapse (Grade B).

Relapse after discontinuation of therapy and possible treatment options

According to the International Autoimmune Hepatitis Group, relapse of AIH is defined as the reappearance of ALT elevation >3 times the upper limit of normal, but may also present with milder ALT elevations and/or an increase in IgG levels.^[121,122] An ALT elevation is highly predictive of relapse and is enough to diagnose it without histological evidence. Many predictors have been described as indicators of increasing chance of relapse including persistent elevation of transaminases or slow response to treatment, biopsy-proven inflammation, and inadequate duration of treatment.^[105,113,123,124] Progression to cirrhosis, death from liver failure, and requirement for LT are common in relapsers compared to patients with sustained clinical, biochemical, and histological remission.^[106] Relapse off medication depends on the patient's profile during therapy. Patients who showed normal biochemical profile on treatment have 3–11 times higher chance of sustained remission compared to patients who had abnormal biochemical profile on treatment. However, normalization of biochemical profile does not mean that the patient is immune to relapse.^[113] About 50–90% of AIH patients may relapse after drug withdrawal, and typically occurs in the first 12 months after stopping therapy.^[108,118,125] It has been shown that 13–20% of responders in KSA had relapse while on maintenance therapy.^[7,8]

Corticosteroids and azathioprine are equally effective in achieving remission among relapsers. However, close

monitoring after treatment withdrawal may help in detecting early relapsers to initiate therapy promptly to avoid the requirement of high doses of immunosuppressants. Due to the concern of poor outcomes among AIH patients with multiple relapses, an indefinite treatment regimen is advisable.^[109,126,127]

Steroid-dependent patients

Patients who require a maintenance dose of corticosteroid to achieve normal transaminases require revision of histology, MRCP to rule out PSC, and possibly repeating liver biopsy to check for the possibility of an overlap syndrome. Administration of budesonide should be considered if the patient is not cirrhotic to minimize the side effects related to long-term corticosteroid use. Other medications such as ursodeoxycholic acid may also be tried.^[1,4]

Treatment failure

Treatment failure is defined as the clinical, laboratory or histological deterioration in AIH patients despite complete adherence to the optimal doses of immunosuppression. It is expected that 10% of patients will fail to show improvement on adequate doses of corticosteroids. Clinicians need to wait for a response to the treatment for up to 3–6 weeks to call it a failure, except in rapidly deteriorating cases.^[4,120,128] Risk factors associated with treatment failure include patients of younger age, acute presentation, higher serum bilirubin, higher model for end-stage liver disease (MELD) score, and HLA DRB1*03 positive.^[120,128,129] They may be expected to show clinical or laboratory deterioration within few days of starting the treatment in the absence of sepsis or hepatotoxicity. In reports from KSA, the number of treatment failure cases of AIH varied from 9.6% in Fallatah *et al.*'s report to 23% in Abdo *et al.*'s report.^[7,8] However, the largest Saudi cohort by Aljumah *et al.*^[9] showed a failure rate of 16.5%. Most (25–29%) of these patients had advanced cirrhosis.^[7,9] Another group of treatment failure included patients who had severe acute hepatitis or fulminant liver failure, representing 7.6% and 2.8%, respectively, from the national data.^[8,9] It is important to recognize this group of treatment failure patients to consider an alternative therapy including timely LT, which is needed in 60% of such patients.^[120,128-131] Another group of treatment failure patients include those who do not have acute severe presentation but show poor or minimal response to conventional therapy after several weeks.^[1] Possible treatment options for treatment failure include high corticosteroid dose of 60 mg daily, or 30 mg daily dose in addition to 150 mg azathioprine.^[111,112,117,121] Corticosteroid and azathioprine can be reduced to conventional doses

after the biochemical response.^[4,111] The use of other medications like tacrolimus and cyclosporine is limited to anecdotal cases.^[132,133]

Incomplete response

Incomplete response occurred in 13% of patients who failed to achieve full clinical, biochemical, and histological remission with the conventional therapy for 3 years.^[112,117,134] However, it is important to evaluate non-compliance before labeling a patient as an incomplete responder, and it is not essential to wait for 3 years to make such a diagnosis. Once the diagnosis has been established, alternative therapeutic strategies must be considered. Treatment with long-term corticosteroids is not advisable due to the potential side effects. However, a short course of prednisone with gradual tapering by 2.5 mg/month to reach a dose between 5 and 10 mg/day might be acceptable to achieve a complete normalization of ALT and AST.^[135] An alternative treatment option would be to increase the dose of azathioprine to 2 mg/kg/day to avoid the usage of corticosteroids.^[107] However, in some patients, it might be necessary to use the therapeutic dose of azathioprine (2 mg/kg/day) with a small dose of prednisolone such as 5 mg/day to achieve the desired response. Likewise, immunosuppressive therapies such as MMF and calcineurin inhibitors have been used in small case series with variable success among patients of AIH with incomplete response. These potent therapies have their own side effects and should be considered a second line of therapy among incomplete responders.^[112,117,136] Partial or incomplete response was encountered in 9–34.4% of AIH patients in Saudi reports, and most of these patients had advanced disease.^[7-9] The majority of these patients responded after adjustment of the doses of immunosuppression, and only 2–5% were switched to MMF or tacrolimus.^[7,9]

Recommendations:

- Ensuring full compliance with the standard therapy is mandatory before defining treatment failure or incomplete response (Grade B)
- High dose prednisolone together with azathioprine is a possible treatment option in the case of incomplete response or failure of standard therapy (Grade B)
- MMF, as a second line therapy, can replace azathioprine in cases of non-response or treatment failure (Grade B)
- Calcineurin inhibitors (tacrolimus and cyclosporine) are other alternative second-line therapies for non-responders or incomplete responders (Grade C).

Side effects of medications

Medications have several side effects. Steroid-related side effects include moon face, hump, hirsutism, skin striae, and acne. More serious side effects include osteoporosis, vertebral compression, diabetes, hypertension, psychosis, pancreatitis, infection, malignancy, and avascular necrosis.^[137,138] After 2 years of treatment, 80% of AIH patients are expected to have side effects related to corticosteroid administration.^[1,4] Azathioprine-related side effects include cholestasis, pancreatitis, infection, malignancy, bone marrow suppression, and gastrointestinal complications; these side effects are observed in 10% of AIH patients.^[1,114,137] Alteration or premature discontinuation of conventional therapy (azathioprine) occurred in 13% of patients with AIH due to those side effects.^[112,139] However, a lower dosage of azathioprine can be used to maintain biochemical response in the absence of drug-related side effects. In one report of AIH from KSA, close to 55% of AIH patients had treatment side effects that varied from mild to severe, necessitating the discontinuation of AZA.^[7,9]

Treatment of special populations

Management of AIH in patients with liver cirrhosis:

Finding liver cirrhosis, with or without decompensation, at the time of diagnosis of AIH is common and has been reported in 20–40% of cases.^[100,123,140] The probability was higher in patients presenting with jaundice, reaching up to 50%.^[35] In the largest cohort from KSA, 28.8% out of 212 patients with AIH had cirrhosis at the time of diagnosis.^[9] Cirrhosis is a poor prognostic factor in the long-term outcome of AIH. Although some reports showed comparable biochemical response rate between patients with and without cirrhosis, most of the studies have shown a shorter survival, higher need for LT, and more cirrhosis-related complications.^[140,141] Treatment of cirrhotic AIH is not different from that of AIH without cirrhosis. AIH patients with liver cirrhosis should be considered for vaccination for HAV and HBV before immune suppression treatment, but that should not delay the initiation of therapy.^[142,143] Prednisolone with steroid sparing agents (azathioprine and MMF) has been used successfully for treating AIH with cirrhosis with a response rate reaching up to 70%.^[9,100,140,144] Budesonide is not recommended in patients with cirrhosis due to the expected high serum level secondary to reduced hepatic metabolism.^[103,145] These patients need closer monitoring for side effects, particularly cytopenia secondary to azathioprine and MMF.^[146] Like all compensated cirrhotic patients, AIH patients with compensated cirrhosis should be screened for the presence of esophageal varices and HCC.^[147] Patients with decompensation should be evaluated for LT.^[148] There are limited reports about the safety and

efficacy of immunosuppressive treatment in the presence of decompensation. Therefore, treatment should be initiated by experts in the field and in centers where LT facility is available.^[149] The lack of early treatment response defined as >50% decline from pre-treatment transaminases was found to predict the need for LT.^[131]

Recommendations:

- Cirrhosis is common in patients with AIH and should be considered when investigating patients suspected of having AIH (Grade B)
- Cirrhotic AIH can be treated with immunosuppressive agents (Grade B)
- Cirrhotic AIH on immunosuppressive treatment should be monitored for side effects of treatment, particularly cytopenia (Grade C)
- Budesonide should be avoided in patients with cirrhosis (Grade C)
- Patients with decompensation should be evaluated for LT. However, treatment can be initiated under close monitoring in centers where transplant facility is available (Grade C).

Treatment in co-morbid patients and old age

Systemic corticosteroids are a cornerstone in the management of AIH. Those medications are well known to have numerous side effects including and not limited to poor control of diabetes, osteoporosis, aseptic necrosis of the hip joint, and hypertension.^[150] All these complications are common in the older age group. One study evaluated the phenotype of AIH in patients who are above the age of 60 years and found that they are more prone to have cirrhosis at presentation and more frequently associated with HLA*DR4 when compared to younger patients.^[151] On the other hand, patients who are older than 60 years had a better response to corticosteroids.^[151] Local data, however, did not suggest that age is a significant contributing factor in predicting cirrhosis, although patients in this cohort were relatively young.^[8] The presence of multiple co-morbid conditions in elderly patients who have mild disease activity on liver biopsy with no evidence of cirrhosis present a clinical challenge to the healthcare providers. In the European guidelines for AIH, the decision not to treat older patients with co-morbidities and mild disease activity was left for the physician to decide on an individualized basis.^[1] The guidelines also gave the recommendation to consider budesonide rather than prednisolone when feasible.^[1] The prevalence of osteoporosis in KSA from the largest available study is 1.2–4.7%.^[152] The use of corticosteroids impacts the bone density through multiple mechanisms, including the suppression of osteoblasts, increased bone

resorption, and decreased new bone production within the natural remodeling cycle.^[153] The recently published guidelines from the Saudi Osteoporosis Society addressed the use of steroid and its impact on bone health.^[154] All patients who are planned for long-term corticosteroids must have measurement of bone density and receive prophylaxis for bone health using vitamin D and calcium. The patients who are diagnosed with steroid-induced osteoporosis should be treated with bisphosphonates.^[154]

Treatment of AIH in pregnancy

Conception in patients with AIH is a challenge to the patients and healthcare providers. Without decompensated cirrhosis, pregnancy is usually achievable and successful, albeit with a modest increase in poor outcomes.^[155] In one large series, 81 pregnancies in 53 women with AIH, the live birth rate was 73%. Prematurity occurred in 20% of the cases, and in 11% cases, an admission to the special care baby unit was necessary.^[156] About 41% of these pregnancies occurred in cirrhotic patients. Adverse event rate in the mothers was 38%. Serious adverse events (defined as death or the need for LT) occurred in 11% of the patients, mostly in patients with cirrhosis. These outcomes are clearly inferior to pregnancies in the general population.^[156] Another retrospective analysis on 7 patients with AIH with 9 pregnancies reported a miscarriage rate of 33%, but no maternal or neonatal mortality was reported.^[157] The course of AIH during pregnancy is unpredictable. Like other autoimmune diseases, pregnancy may ameliorate the course of the disease as the immune system in the mother undergoes changes to adopt a tolerance to the circulating fetal antigens with improvement in liver profile, especially in the second trimester.^[158,159] However, this is not always the case as some autoimmune diseases induce worsening of the disease course and both fetal and maternal outcomes.^[158] Flare-up of the AIH in pregnancy was reported to be 22–33%.^[156,157] Flares of AIH can also occur after delivery, with the return of the immune system to the baseline and the “loss of tolerance” that occurs after delivery. In one cohort of AIH, the reported rate of flare-ups was 30% in the post-partum period.^[160] This was even higher in another cohort from Germany (52%).^[161] Local data on pregnancy in AIH are scarce. In one report of single-center experience of AIH, pregnancy was encountered in 3 patients. Two of them had flares during gestation, and one was diagnosed with AIH during pregnancy; all of them had good response to corticosteroid therapy.^[7] They also reported one mortality during pregnancy, which was attributed to pregnancy-related complications.^[7] Although azathioprine was labeled as Category D in pregnancy and the United States food and drug administration has recently changed the labeling system of medications, this category

system is still widely used.^[162] The safety of azathioprine has been well established in different cohorts of patients. A recent meta-analysis of the birth outcome after exposure to azathioprine in inflammatory bowel disease patients revealed no effect on the fetal outcomes in terms of birth weight or malformations, although it was associated with increased preterm births.^[163] Moreover, in AIH, one study on 42 pregnancies included 14 pregnancies with exposure to azathioprine, but the outcomes of the patients who were exposed to azathioprine were not different to those who were not exposed.^[161] On the other hand, the discontinuation of azathioprine during pregnancy may lead to rapid flare-up of the disease in up to 85% of the patients.^[159]

Treatment of acute severe and fulminant AIH

Acute severe/fulminant presentation of AIH, defined by marked elevation in transaminases, significant derangement of synthetic liver function, and presence of encephalopathy within 26 weeks of onset, is reported in 3–10% of AIH patients.^[164,165] Lower rate (2.8%) has been reported in a large cohort of adult AIH patients in KSA.^[9] Fulminant AIH predicts poor prognosis with a transplant-free survival of 20% or less.^[166,129] Five out of six patients (83%) in Aljumah’s series died, and the sixth patient required LT.^[9] The presentation can be precipitated by several factors including medication (interferon, minocycline, and nitrofurantoin), infections, or pre-existing genetic condition.^[167-170] Diagnosis of fulminant AIH is challenging since the scoring systems, particularly the simplified system, are less sensitive and many patients lack the classical features of AIH.^[171] Since acute-type AIH (including fulminant) frequently lacks typical features of AIH, such as positivity of autoantibodies and/or elevation of serum IgG, AIH should always be suspected in acute hepatitis cases without identifiable etiologies. Histological assessment usually shows less fibrosis, greater interface hepatitis, hepatocyte necrosis, zone III necrosis, and sub-massive necrosis.^[172] It is difficult to draw a solid conclusion and provide a clear recommendation on the use of immunosuppressive medication in patients with fulminant AIH due to the paucity of data, which mostly came from case reports and small case series. Although some series reported a favorable outcome with steroid therapy, others showed no benefit compared to control with a higher incidence of infection in the steroids-treated group.^[130,166,173] However, experts support a trial of steroid for 2 weeks in patients with acute liver failure, where AIH is suspected with careful monitoring for clinical deterioration and infection.^[174] This decision should not delay LT evaluation. LT work-up should be initiated early in the management of fulminant AIH, particularly in those with treatment failure predicted

by rising MELD-Na at day 7 and patients with rapid clinical deterioration.^[128] Ten-year survival after LT for AIH exceeds 70%, and one-third of patients may experience a recurrence of the disease.^[175]

Recommendations:

- An expert physician in an advanced tertiary center should be involved in the management of AIH patients who had initial treatment failure or partial response, patients who relapsed after initial response, patients who are difficult to be weaned off steroids, and in special conditions like elderly or pregnant patients and post LT AIH (Grade B)
- Treatment of AIH should be continued during pregnancy and medication can be adjusted in case of development of flare during pregnancy (Grade C)
- AIH should be considered in the differential diagnosis of acute liver failure when other causes are excluded. The biochemical, serological, and histological results should be interpreted carefully (Grade C)
- Urgent transplant evaluation should be initiated in patients with fulminant AIH (Grade C)
- A trial of steroids for 2 weeks can be attempted in patients with suspected AIH with close monitoring for clinical worsening and sepsis (Grade C).

Treatment of AIH and overlap syndromes

The treatment of overlap syndromes should include the treatment of both overlapping conditions.^[24] The treatment of AIH–PBC overlap includes both the conventional treatments for AIH, in addition to ursodeoxycholic acid.^[24] The treatment doses have to be adjusted according to the predominant clinical and laboratory features in addition to the monitored treatment response.^[25,26] For AIH–PSC overlap, similar treatment regimens are commonly used, but the initial treatment response was shown to be better compared to AIH–PBC overlap. However, AIH–PSC patients were more likely to have LT or die from liver disease.^[24]

In our experience, only a few patients with AIH–PBC or AIH–PSC overlap have incomplete treatment response, and they have more advanced disease compared to patients with isolated AIH.

Treatment of drugs and toxin-induced autoimmune liver injury

The management of drug-induced autoimmune-like hepatitis includes steroids in addition to withdrawal of the causative agent.^[83,87] Resolution is characteristic,

and recurrence (which favors AIH) or a lack thereof (which favors DILI) after steroid withdrawal can support the final diagnosis. Bjornsson *et al.* have shown that in a minority of patients with AIH triggered by DILI (7%), AIH progressed to cirrhosis.^[83] In cases involving uncertainty, the recommended approach is a trial of steroid therapy (prednisone 0.5–1.0 mg/kg/day) with close observation during steroid tapering and stopping over several months, followed by long-term follow-up (for up to 3 years) to monitor for late relapse of AIH.

AIH and liver transplantation

Indications and outcomes

Globally, AIH is considered an infrequent indication for LT and accounts for only 2–6% of LT procedures.^[1,176,177] In KSA it is considered the fifth leading indication for LT based on the primary liver disease in adults and accounting for about 6% of all LTs.^[178] The outcomes of LT for AIH are excellent with 1- and 5-year survival rates of 90% and 80%, respectively.^[179] Khalaf *et al.* evaluated the outcomes of LT for 16 patients transplanted for AIH. After a median follow-up period of 530 days (range 11–2016), the overall patient and graft survival rates were 93.8%. Only one patient died following living donor LT due to primary graft non-function. Histopathological recurrence was seen in three patients (18.7%) and was successfully treated by optimizing immunosuppression.^[16] Disease recurrence is common and ranges from 15% to 42%. This wide range of reported recurrence can be related to different diagnostic criteria for reporting recurrence, the effect of immunosuppressive medications, and the possible interaction with other LT-related complications, particularly rejection. Recurrence has been shown to negatively impact LT outcomes affecting both graft and patient survival.^[180] Risk factors for disease recurrence post LT include discontinuation of corticosteroids. A recent study from the UK reported that long-term low-dose steroids were safe and associated with a lower rate of post-LT disease recurrence.^[181] The presence of pre-LT biochemical activity (elevated aminotransferases and serum IgG) or histological activity (lymphoplasmacytic infiltration associated with inflammation) was also linked to disease recurrence post LT. HLA phenotype, younger patients, and duration of follow-up were other factors associated with disease recurrence.^[182]

Treatment of recurrent AIH in allografts

Treatment of AIH recurrence depends on the overall clinical picture and severity of recurrence. Asymptomatic patients with mild elevation in liver biochemistry may only require immunosuppressive dose adjustment. Resuming treatment with corticosteroids and azathioprine in

conventional or increasing dosage is usually effective in controlling the disease.^[183] In cases of inadequate response of recurrent AIH, post-LT tacrolimus should be replaced with cyclosporine or the calcineurin inhibitors should be replaced with sirolimus. Patients with cirrhosis and graft loss will require re-transplantation.^[184]

De novo AIH after liver transplantation

The term de novo is used to describe the development of AIH in LT recipients whose indication for LT was non-immune-related liver disease. It is diagnosed by typical histological changes and hypergammaglobulinemia. It has been reported in 2.1–6.6% of LT patients.^[183] Its treatment includes adding or increasing the dose of corticosteroids, adding azathioprine or MMF, and adjusting the dose of calcineurin inhibitor. Other agents that have been successfully used in treating de novo AIH include rapamycin and everolimus.^[180] Some reports have shown a reduced risk of de novo AIH with the use of cyclosporine compared to tacrolimus or MMF. Other potential risk factors include recipients of female or older donor grafts.^[185]

Recommendations:

- LT is considered in patients with AIH who presented with acute liver failure or decompensated cirrhosis with or without HCC provided they meet the liver transplant criteria (Grade C)
- If treatment response continues to be inadequate in recurrent disease, tacrolimus should be replaced with cyclosporine or the calcineurin inhibitors should be replaced with sirolimus (Grade C)
- Re-transplantation must be considered for patients with refractory recurrent AIH that is progressing to allograft loss (Grade C)
- Consider de novo AIH in all patients with allograft dysfunction after LT regardless of whether the original indication for LT was AIH or another disease (Grade C)
- Treatment for de novo AIH should be instituted with dose adjustments of immunosuppressive drugs (Grade C)
- Re-transplantation should be considered for patients with refractory de novo AIH that is progressing to allograft failure (Grade C).

CONCLUSION

Regional studies on AIH are limited, and the precise epidemiology of AIH in KSA is not well known. The diagnosis is typically made based on clinical and laboratory criteria. Liver histology is very important in the diagnosis

not only for its value in grading and staging of the disease but also because it helps in the exclusion of other causes of hepatitis. The treatment with corticosteroids alone or in combination with azathioprine remains the mainstay to control the disease. Other immunosuppressive medications may provide a substitute for patients with incomplete response. Unfortunately, many patients in KSA still experience substantial morbidity and mortality due to the lack of experienced physicians, unclear diagnosis, delayed or missed diagnosis, side effects or intolerance to medications, and inadequate treatment response; these may result in suboptimal management and inadequate compliance. However, the diagnosis and treatment of AIH can be improved, and the majority of affected patients can be treated successfully with a high potential for improvement and better quality of life and eventual elimination of AIH as an indication for LT in the future. In these new SASLT guidelines, we endeavored to provide a concise, simplified, and evidence-based review of the diagnosis and management of AIH in KSA. The goals of these clinical practice guidelines are to improve identification, diagnosis, and management of AIH in the country. This may help to initiate plans to diagnose AIH early and accurately enough in all of the Saudi community. We anticipate it will expedite appropriate and timely referrals among primary, secondary, and tertiary healthcare providers and identify the gaps in knowledge and understanding of the status of AIH in KSA. We acknowledge that there are areas that need to be addressed in future research on AIH in KSA. These include genetic risk factors and association, the prevalence of AIH in the general population and among patients with chronic liver disease, the potential toxins and drug-inducing AIH that may be underestimated and under-reported, and the national clinical trials on the treatment of refractory and acute onset AIH and AIH post LT. Finally, medicine is an evolving science; hence, these guidelines need to be updated frequently.

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Conflicts of interest

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