



Autoimmune hepatitis in children: Guidelines of the Indian Society of Pediatric Gastroenterology, Hepatology, and Nutrition (ISPGHAN)

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Abstract

Autoimmune hepatitis (AIH) in children presents significant diagnostic and therapeutic challenges requiring a multidisciplinary and evidence-based approach. The Indian Society of Pediatric Gastroenterology, Hepatology, and Nutrition (ISPGHAN) convened a consensus meeting on February 23, 2025, bringing together national and international experts to address key clinical and research questions. The deliberations spanned epidemiology, clinical presentation, diagnosis including autoantibodies, immunoglobulin G (IgG), histology and diagnostic scores, therapeutic strategies, management of difficult-to-treat AIH, long-term monitoring, and special scenarios, such as seronegative AIH (SN-AIH), autoimmune sclerosing cholangitis/overlap syndromes and post-transplant complications like recurrence and de novo-AIH. Recommendations were formulated using standard GRADE system and finalized through structured consensus. These guidelines aim to standardize care, assist clinicians in decision-making, and improve outcomes in children with AIH across diverse healthcare settings.

Keywords Chronic liver disease · Children · Autoimmune acute liver failure · Immunoglobulin · Autoantibodies · Liver transplantation

Abbreviations

6-TG	6-Thioguanine	ASMA	Anti-smooth muscle antibody
6-MMP	6-Methylmercaptopurine	CBR	Complete biochemical remission
AASLD	American Association for the Study of Liver Diseases	CEAID	Concurrent extrahepatic autoimmune disorders
AI-ALF	Autoimmune-induced acute liver failure	DSA	Donor specific antibodies
AIH	Autoimmune hepatitis	dn-AIH	De novo autoimmune hepatitis
ALT	Alanine aminotransferase	DTT-AIH	Difficult-to-treat autoimmune hepatitis
AS-AIH	Acute severe autoimmune hepatitis	ESPGHAN	European Society for Pediatric Gastroenterology, Hepatology and Nutrition
ASC	Autoimmune sclerosing cholangitis	GGT	Gamma-glutamyl transferase
AST	Aspartate aminotransferase	HE	Hepatic encephalopathy
ANA	Anti-nuclear antibody	HLA	Human leukocyte antigen
		IAIHG	International autoimmune hepatitis group
		IBD	Inflammatory bowel disease

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IFA	Indirect immunofluorescence assay
IgG	Immunoglobulin G
IL	Interleukin
ISPGHAN	Indian Society of Pediatric Gastroenterology, Hepatology and Nutrition
LC-1	Liver cytosol type-1 antibody
LKM-1	Liver kidney microsomal antibody type-1
LOE	Level of evidence
LSM	Liver stiffness measurement
LT	Liver transplantation
MMF	Mycophenolate mofetil
NUDT15	Nudix hydrolase 15
p-ANCA	Perinuclear anti-neutrophil cytoplasmic antibody
PD-1	Programmed cell death protein-1
PSC	Primary sclerosing cholangitis
SLA	Soluble liver antigen
SNL	Survival with native liver
SN-AIH	Seronegative autoimmune hepatitis
TPMT	Thiopurine methyltransferase

Introduction

Autoimmune hepatitis (AIH) is a chronic inflammatory liver disease that presents more severely in children than in adults. Globally, the prevalence of AIH per 100,000 person-years is 15.65 and 2.34 in the overall population and children, respectively [1]. Over the past few decades, there has been a 50% increase in incidence in some parts of Europe, suggesting the introduction of new etiological triggers or a change in susceptible population [2]. In the United States, presentations have varied depending upon the ethnicity: Alaskan Natives have acute presentation of AIH, Hispanics present with cirrhosis, and African Americans have rapidly progressive disease with a higher rate of recurrence after liver transplantation (LT) [3]. Similar epidemiological data from the eastern hemisphere are limited [4, 5]. Delay in diagnosis is largely due to lack of awareness of the presentation especially in the eastern world, where the diagnosis of AIH can be mistaken for the more prevalent acute viral hepatitis among children. The aggressive course of the disease among children, along with delay in diagnosis and treatment, impacts the long-term prognosis. Moreover, the majority of the diagnostic scores are adult-centric and have not been validated in children. Timely identification of AIH and institution of first-line therapies can control liver inflammation, improve symptoms, and achieve biochemical remission. And this, in turn, would prevent disease progression and promote fibrosis regression. Then, there are special situations where first-line treatment may not be successful, as seen in difficult-to-treat AIH (DTT-AIH), AIH associated with cirrhosis and overlap syndrome. There is a discrepancy in the definition of DTT-AIH used in different

centers. DTT-AIH needs to be identified early and monitored closely with active decision-making to shift to second-line agents to ensure complete biochemical remission (CBR) and survival with native liver (SNL). Moreover, the clarity on indications and the timing of LT among children with AIH is challenged by lack of data and adult-centric prognostic scores. Finally, recurrence of AIH and de novo-AIH (dn-AIH) after LT in children need lucid diagnostic features and distinct protocols for the management. In all, the diagnosis and management of this pediatric liver disease are riddled with challenges which need clarity through a consensus among experts working in this subject area.

Department of Pediatric Hepatology, Institute of Liver and Biliary Sciences, under the aegis of ISPGHAN proposed a consensus meeting on February 23, 2025. The proposal was approved by the subcommittee of ISPGHAN on consensus guidelines. The agenda of the meeting was to develop evidence statements, recommendations and agreement on the diagnosis, and management of pediatric AIH with special reference to India and Asia Pacific region. The scientific committee invited international and national experts to participate in a consensus meeting. Before the meeting, questions were identified by a sub-group of experts and allotted to participants to review and analyze the published literature. Literature search, level of evidence (LOE), and grade of recommendations for each question were reviewed by a sub-group of experts based on the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system (Supplementary Table 1) [6]. A single day meeting held on February 23, 2025, in New Delhi, India, discussed and finalized the consensus statements, recommendations, and guidelines. A large group of experts deliberated on each question, reviewed the literature, discussed the contentious issues, and deliberated to prepare the consensus statement of evidence deciding the LOE and grade of recommendations on the particular question. The consensus agreement percentage was also noted for each statement and recommendation. The final statements and recommendations were approved and later circulated to all experts for their suggestions. The manuscript with consensus recommendations was prepared by a sub-group of experts, and the final manuscript was re-circulated for comments. The experts' suggestions were used to revise and finalize the recommendations. A brief background of each question has been included, providing recommendations and evidence from the published literature.

Epidemiology

The incidence and prevalence of AIH differ based on age, gender, ethnicity, and geographical location. These variations are influenced by environmental, infectious and genetic

factors, as well as differing diagnostic criteria used worldwide. A recent systematic review of adult and pediatric AIH cases revealed a threefold increase in incidence and prevalence over the past two decades. The estimated annual incidence of AIH in children was 0.35 (0.24–0.52) per 100,000 inhabitant-years, whereas the prevalence of AIH in children was 2.04 (1.01–4.14) per 100,000 inhabitants [1]. Average annual incidence of AIH reported from South Korea was 0.08 and 0.48 per 100,000 in the children and adolescents, respectively, with females being twice as often affected [7]. Autoimmune hepatitis is two-to-three times more common in females, with a median age of presentation in children of around 10 years [8–14]. AIH types are differentiated based on types of detectable autoantibodies: type 1 AIH with the presence of anti-nuclear antibody (ANA) or anti-smooth muscle antibody (ASMA), while type 2 AIH has the presence of anti-liver-kidney microsomal type 1 (LKM-1) or anti-liver cytosol (LC-1) antibody [9]. Type 1 AIH is three times more common than Type 2. Type 2 AIH can present earlier, even in infancy, and shows less gender disparity than Type 1 [4, 15–18]. The Asia Pacific data show no significant difference in the age of presentation between AIH types 1 and 2; however, females are more affected in both the types [13, 14]. Specific human leukocyte antigen (HLA) DRB1 alleles associated with pediatric AIH are HLA DRB1*03:01, 13:01, and 07:01 in Caucasian children [19], HLA DRB1*13:01, 03:01, and 07:01 in Latin American children [20], HLA DRB1*13:01 in Middle Eastern children [21], and HLA DRB1*03 in Indian children [22]. HLA DRB1*04:05 allele has been seen in patients with type 1 AIH in Japan, China, South Korea, and Taiwan [23–26]. A north Indian study has also shown that AIH types 1 and 2 have different HLA predispositions [27].

Clinical presentation

Autoimmune hepatitis occurs worldwide across all ethnic groups, but the clinical phenotype and outcomes vary with ethnic background, influenced by multiple factors, including geographical, genetic, environmental, immune, and diagnostic factors [28]. It can present with a broad spectrum of symptoms, ranging from asymptomatic cases to decompensated chronic liver disease and even acute liver failure. Pediatric AIH more often presents acutely and with an aggressive course [29].

AIH presentation in children includes acute hepatitis-like presentation (16–67%) with constitutional symptoms, followed by jaundice, dark urine, and pale stools, mimicking acute viral hepatitis [4, 5, 9, 13–15, 30–32]. The next common presentation is insidious/chronic onset (13–64%), which is usually characterized by recurrent jaundice, and other symptoms persisting from months to several years

before diagnosis [4, 5, 9, 13–15, 30]. Portal hypertension and variceal bleed along with ascites and/or hepatic encephalopathy (HE) can be another presentation with no prior history [29]. Autoimmune hepatitis-induced acute liver failure (AI-ALF) (7–21%) presents with HE and uncorrectable coagulopathy [4, 5, 9, 13, 15, 30]. Around 5–20% may be asymptomatic and detected on routine screening [13, 15, 30] (Table 1).

Although the current literature on the clinical presentation and outcomes of pediatric AIH comes from studies on Caucasian children, data from the Asia-Pacific region, including Malaysia, Turkey, and India, have been explored recently in the last decade. While the overall symptoms of AIH are similar across regions, notable differences exist in clinical presentation at diagnosis [4, 5, 9, 13–15, 30–33]. In Western populations, pediatric AIH often presents as an acute hepatitis-like illness resembling viral hepatitis. As highlighted in Table 1, acute hepatitis-like presentation is seen in 40–67% patients in the series from these populations [15, 30–32]. Similar data from Japan reported acute/chronic hepatitis as the commonest presentation with cirrhosis present in only 4/31 patients at baseline [12]. In contrast, up to 50–90% of Asia-Pacific children with AIH present with symptoms of cirrhotic liver disease and its complications, including decompensation [4, 5, 13, 14, 33]. Malaysian study on pan-ethnic Asian population reported 56% prevalence of cirrhosis at presentation [13]. This highlights a regional difference, but a closer look at the histological data from the Western studies shows the presence of cirrhosis in 28–68%, suggesting variation in the interpretation of clinical presentation [9, 15, 30–32]. The expert group opined that the diagnosis of cirrhosis can be suspected clinically or radiologically but has to be confirmed on liver histology.

Autoimmune sclerosing cholangitis/overlap syndrome (ASC/overlap) is characterized by the concurrent presence of features of both AIH and primary sclerosing cholangitis (PSC), the details of which will be dealt with in a separate section. ASC/overlap can be differentiated from typical AIH by a lesser female predisposition, high serum alkaline phosphatase to aspartate aminotransferase (AST) ratio, presence of peri-nuclear anti-neutrophil cytoplasmic antibodies (p-ANCA), stronger association with inflammatory bowel disease (IBD), and a worse prognosis than typical AIH. Type 2 AIH differs clinically from type 1 in terms of younger age of presentation, higher risk for ALF, and higher risk of relapse on withdrawal of immunosuppression [9, 15]. Supplementary Table 2 highlights important differences in clinical presentations of AIH types 1, 2 and ASC/overlap.

1.1 Consensus statement

1.1.1 The mode of presentation of autoimmune hepatitis in childhood varies from asymptomatic, acute to chronic hepatitis, cirrhosis, and acute liver failure (LOE 3).

1.2 Consensus recommendation

Table 1 Studies on pediatric autoimmune hepatitis highlighting the various clinical presentations

Authors (year) Country	Western literature				Asia-Pacific studies						
	Gregorio et al. (1997) UK [9]	Jimenez-Rivera et al. (2015) Canada [31]	Rodrigues et al. (2016) Brazil [30]	Di Giorgio et al. (2020) UK [15]	Maggiore et al. (2023) Italy [32]	Dehghani Iran [18]	Lee et al. (2015) Malaysia [13]	Karakoyun et al. (2016) Turkey [14]	Jain et al. (2017) India [5]	Sood et al. (2018) India [4]	Sogo et al. (2018) Japan [12]
Number	52	159	106	54	117	87	23	47	70	70	35
Age (years)	7.5–10.5	11.5	10.5	7.8–13.7	0.9–15	10.1	7.9	10	8.8	9.6	10
Female	75%	60%	77.3%	55%	74%	64.4%	69.6%	55.3%	63%	55%	60%
Presentation^a											
Acute hepatitis	–	–	39.6%	58%	66.7%	16.1%	52%	23.4%	19%	16%	23%
Chronic liver disease	–	–	35.8%	13%	–	70.1%	30.4%	61.7%	60%	64%	68%
ALF	11.5%	–	17%	9%	–	3.4%	8.7%	14.8%	21%	7%	11.4%
Silent	–	–	4.7%	20%	–	10.3%	8.7%	30%	–	–	37%
Type of AIH											
Type 1	62%	70%	67%	76%	55.6%	41%	78%	85.1%	67%	45.7%	77%
Type 2	38%	11%	4.7%	20%	44.4%	7%	22%	14.9%	25%	18.6%	0
Seronegative	–	6%	–	–	–	30%	0	0	6.5%	22.9%	23%
Unknown	–	13%	–	Anti-SLA 4%	–	22%	0	0	–	12.9%	0
Other features											
CEAIDs	21.1%	32%	17.7%	35%	19.7%	–	21.7%	–	42%	44.3%	11%
CEAIDs in family	40.4%	25%	36.8%	17%	37.6%	10.3%	13%	–	16.1%	12.9%	5.7%
Advanced fibrosis (> F3) at baseline	100% (59% cirrhosis)	20% (cirrhosis)	67% (cirrhosis)	27.8% (cirrhosis)	68.3% (cirrhosis)	25.3% (cirrhosis)	52% (cirrhosis)	–	26%	73%	11% (cirrhosis)
Treatment response	85%	90%	70.8%	96%	75.2%	71.2%	74%	86.4%	63.6%	79%	84%
Relapse on immunosuppression	–	3.2%	38.7%	31%	57%	–	43%	9.4%	–	20%	25%

ALF acute liver failure, CEAIDs concurrent extrahepatic autoimmune disorders, CLD chronic liver disease, F3 metavir stage 3 fibrosis on histology, SLA anti-soluble liver antigen antibody

^aPercentages of some of the parameters do not add up to make 100 as the presentations overlap

1.2.1 Any child presenting with acute hepatitis, chronic hepatitis, cirrhosis, or acute liver failure (negative for viral etiologies) should be screened for autoimmune hepatitis (LOE 3, Strong recommendation).

Extra-hepatic involvement

Pediatric AIH is frequently associated with concurrent extrahepatic autoimmune disorders (CEAID), with prevalence ranging from 21 to 48% across various studies [4, 9, 34–38]. Indian and Egyptian studies have reported CEAID in 40–44% of AIH children, whereas a report from Malaysia found 25% association with the same [4, 13, 34, 37]. A South Korean study reported hypothyroidism in 5/228 AIH cases in the age group between 0 and 29 years [7]. Table 2 describes the frequency of various CEAIDs in pediatric studies. Gastrointestinal (celiac disease, IBD), endocrinal (hypothyroidism, hypoparathyroidism, type 1 diabetes mellitus), hematological (autoimmune hemolytic anemia), and dermatological (early onset acne, vitiligo, and psoriasis) are among the most prevalent CEAIDs in children with AIH [4, 9, 34–38]. Regional and geographic variations also influence the prevalence and spectrum of CEAIDs, necessitating tailored screening strategies. Many of these

conditions remain asymptomatic for prolonged periods, necessitating a high index of suspicion for early detection throughout lifetime [34]. Screening for CEAID is important as it can aid in diagnosis while also having prognostic implications. The presence of CEAID aids in diagnosis of AIH by allotting a score of ‘1’ additional point in the newly proposed European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) scoring system [29]. The presence of CEAID did not affect the response to treatment or the long-term outcomes in a large study including adult patients with AIH [39]. However, the evidence of the impact of CEAID on clinical outcomes in pediatric AIH is equivocal, cannot be extrapolated, and needs further studies [40, 41]. Several pediatric studies have demonstrated that concomitant celiac disease in children with AIH is associated with a milder liver disease course, better response to treatment, and higher chances of immunosuppression withdrawal [38, 40, 41]. There have been suggestions of poor outcomes in pediatric AIH with associated hematological or dermatological CEAIDs, although the sample of each CEAID sub-group was small [34]. Given the impact of certain CEAIDs on outcomes, structured screening protocols need to be developed and validated in larger pediatric studies.

2.1. Consensus statements

Table 2 Studies on concurrent extrahepatic autoimmune disorders (CEAIDs) in children with autoimmune hepatitis

Study	Gregorio et al. [9] 1997	Nastasio et al. [38] 2013	Vajro et al. [36] 2013	Lee et al. [13] 2015	Jain et al. [5] 2017	Sood et al. [4] 2018	Paolletta et al. [35] 2019	Mogahed et al. [37] 2024
Country	UK	Italy	Italy	Malaysia	India	India	Italy	Egypt
Sample size	52	79	206	32	62	85	48	58
Prevalence of CEAIDs	21%	–	–	25%	42%	44.7%	46%	48.3%
Gastrointestinal disorders								
Celiac disease	–	19%	6.3%	–	9.6%	10.6%	10.4%	1.7%
Inflammatory bowel disease	5.7%	–	–	9.4%	–	1.1%	18.8%	5.1%
Endocrinal disorders								
Thyroid	5.7%	–	–	3.1%	–	1.1%	10.4%	17.2%
Parathyroid	1.9%	–	–	–	3.2%	–	–	–
Type 1 diabetes	3.8%	–	–	3.1%	–	2.2%	2.1%	1.7%
Hematological disorders								
Autoimmune hemolytic anemia	–	–	–	–	6.5%	24.7%	–	–
Autoimmune thrombocytopenia	–	–	–	–	1.6%	–	2.1%	–
Rheumatological disorders								
Rheumatoid arthritis	–	–	–	–	–	1.1%	6.3%	–
Behcet disease	1.9%	–	–	–	–	–	–	–
Systemic lupus erythematosus	–	–	–	9.4%	–	–	4.2%	8.6%
Others								
Vitiligo/skin disorders ^a	1.9%	–	–	–	16.1%	3.3%	6.3%	5.1%
Nephrotic Syndrome	1.9%	–	–	–	–	–	–	–

^aEarly onset acne, psoriasis and lichen planus

2.1.1 The prevalence of concurrent extrahepatic autoimmune disorders in pediatric autoimmune liver disease varies between 21 and 48%. Celiac disease, hypothyroidism, autoimmune hemolytic anemia, and vitiligo are among the common concurrent extrahepatic autoimmune disorders (LOE 3).

2.1.2 Autoimmune sclerosing cholangitis/overlap syndrome has a strong association with inflammatory bowel disease (LOE 3).

2.1.3 Pediatric autoimmune liver disease with concurrent celiac disease may have a milder course, better response to immunosuppression, and higher chances of treatment withdrawal (LOE 3).

2.2. Consensus recommendations

2.2.1 All children diagnosed with autoimmune liver disease should be screened for thyroid and celiac disease (LOE 3, Strong recommendation).

2.2.2 Other concurrent extrahepatic autoimmune diseases should be screened based on clinical suspicion (LOE 3, Strong recommendation).

Diagnosis

How to suspect

Pediatric AIH should be considered in any child presenting with acute or recurrent hepatitis or chronic liver disease in the absence of a clear infectious, metabolic, or drug-induced etiology. The wide variability in clinical presentation of pediatric AIH often results in diagnostic delays, especially in the absence of classic features. Pediatricians should maintain a high index of suspicion in these children, especially in presence of systemic autoimmune manifestations in the child or family. Early referral to a pediatric hepatologist is essential when AIH is suspected, as delays in diagnosis and treatment can lead to disease progression and cirrhosis. While the definitive diagnosis typically rests with the pediatric hepatologist, the onus of early suspicion and timely referral lies with the primary care provider. A standardized step-wise evaluation, including IgG levels, autoantibodies serology, exclusion of viral etiologies, and liver biopsy, is recommended to ensure diagnostic accuracy and avoid unnecessary delays or misclassification. Hence, all children who present with a suggestive clinical profile and abnormal liver function tests should undergo work-up for exclusion of other liver diseases before diagnosing AIH [29, 42]. Figure 1 mentions the algorithm for diagnosing a child with suspected AIH.

Immunoglobulin G

Following birth, exposure to diverse microbial antigens stimulates the developing immune system, leading to a progressive increase in endogenous IgG production. IgG concentrations rise rapidly during infancy, reaching adult levels by approximately 6–7 years of age. These levels peak and stabilize, maintaining a plateau during much of adulthood. Pediatric AIH is typically characterized by hypergammaglobulinemia (raised IgG levels), indicating ongoing histological activity, although up to 15% of children with AIH-1 and 25% of AIH-2 may have normal IgG levels, particularly in acute fulminant presentations [9, 29, 43]. IgG elevation ranges from 64 to 100% in pediatric ASC/overlap [44, 45]. Hennes et al. showed a very close correlation between IgG and serum globulin levels (Pearson coefficient: $r=0.87$) in the original study describing the ‘Simplified Diagnostic Score 2008’; however, IgG was preferred due to many missing values for serum globulin [46]. Subsequently, Mileti et al. evaluated and found that serum globulin levels correlated very closely with IgG levels and a modified ‘simplified score 2008’ using globulin instead of IgG had an excellent agreement with the ‘simplified score’ using IgG [47]. Serum IgG levels have prognostic significance, as persistently elevated IgG correlates with disease severity, treatment response, and risk of relapse. Although elevated IgG is a hallmark of AIH, but can be falsely elevated in acute liver failure and ACLF due to non-specific immune response to liver injury, infection, and systemic inflammation [48, 49]. Elevated IgG, although diagnostic for AIH, but may remain elevated even after complete biochemical and histological remission in patients with advanced fibrosis [42, 50–52].

Autoantibodies

Autoantibodies are antibodies produced by the immune system that mistakenly target the body’s own cells, tissues or proteins. The presence of autoantibodies is a hallmark of AIH; however, the titers fluctuate during the disease course and with treatment [9, 42, 50]. Autoantibodies may be present in very low titers or even be undetectable at disease onset, more frequently in children and in those with fulminant presentation [42, 50]. Such cases are labeled as SN-AIH and diagnosis is usually based on clinical profile and histopathological findings. Antibody titers may become detectable later in the disease course [42, 50]. Detection of some autoantibodies correlates with disease activity, particularly anti-soluble liver antigen (SLA) and liver cytosol type-1 (LC-1) antibodies [9, 42, 50]. Seropositive AIH is usually classified based on the autoantibody profile: type 1 AIH is labeled in the presence of ANA or ASMA antibodies, while type 2 AIH is diagnosed in the presence of LKM-1 or anti-LC-1 antibodies [9, 42, 50].

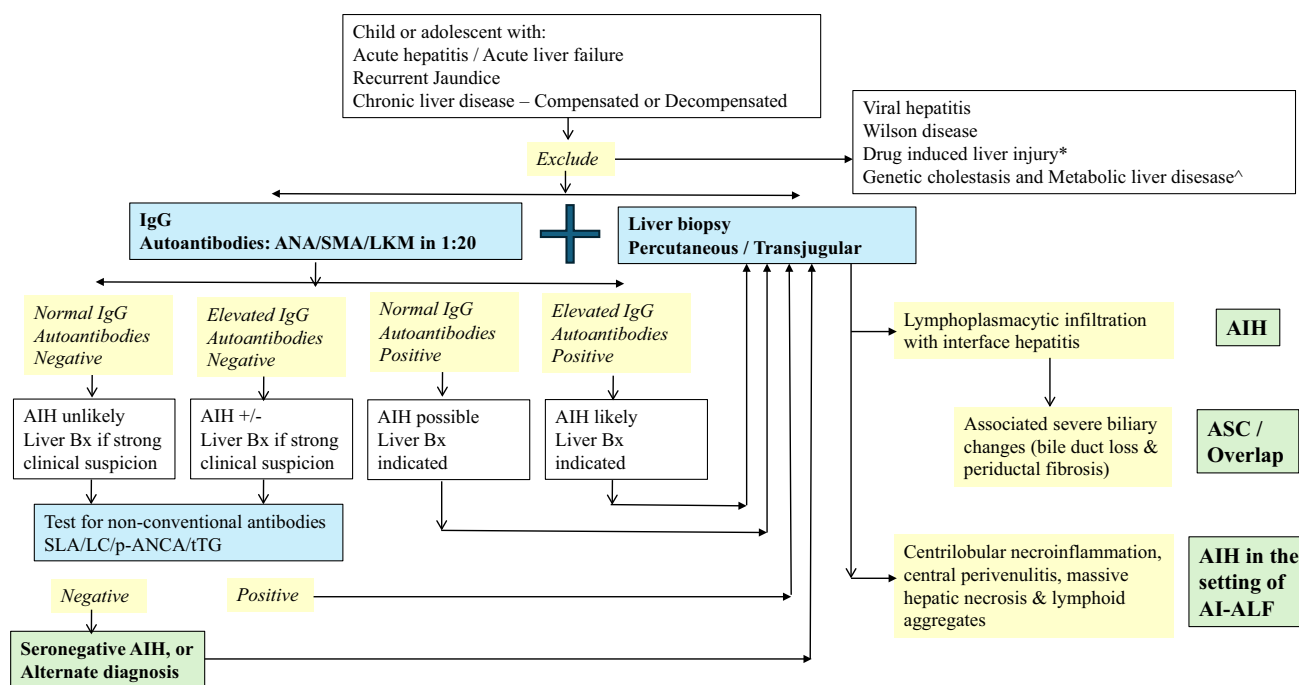


Figure 1 Diagnosis of autoimmune hepatitis in children. Diagnosis of autoimmune hepatitis should always be considered in a child presenting with acute hepatitis, acute liver failure or chronic liver disease in the absence of known etiologies. Evaluation comprises IgG, conventional autoantibodies, and liver biopsy. In presence of normal IgG and/or absent autoantibodies, liver biopsy should be performed if the index of suspicion is strong. Non-conventional autoantibodies should be tested when conventional autoantibodies are negative. *Drug-induced liver injury (DILI) should be excluded after a careful history of drug intake and in those with suspicion, revised electronic causality assessment method (RECAM) criteria may be used to diagnose DILI. ^Genetic cholestasis and metabolic liver disease

should be suspected in an appropriate setting in the presence of clinical and biochemical evidence of cholestasis (genetic cholestasis) and presence of red flag signs like young age, family history, growth failure, hepatosplenomegaly, multisystem involvement, and a positive metabolic screen (metabolic liver disease). *AI-ALF* autoimmune hepatitis-induced acute liver failure, *AIH* autoimmune hepatitis, *ANA* anti-nuclear antibody, *ASC* autoimmune sclerosing cholangitis, *Bx* biopsy, *IgG* immunoglobulin G, *LC* anti-liver cytosol antibody, *LKM* anti-liver kidney microsomal antibody, *p-ANCA* peri-nuclear anti-neutrophil cytoplasmic antibody, *SLA* anti-soluble liver antigen antibody, *SMA* anti-smooth muscle antibody, *tTG* anti-tissue transglutaminase antibody

53]. AIH type 2 constituted 14–15% in the various studies from the Asia–Pacific region, whereas another study from India reported 31.4% of AIH as Type 2 [4, 5, 13, 14]. Typically, serological patterns of type 1 and 2 AIH are mutually exclusive, but can co-exist in a proportion of pediatric cases making it difficult to classify the patient as type 1 or 2 [4]. There is a paucity of published literature on unconventional antibodies like anti-SLA and LC-1 in pediatric and adult AIH from Indian subcontinent. Table 3 describes the prevalence of various autoantibodies in adult and pediatric studies on AIH and ASC/overlap.

Autoantibody testing—techniques and interpretation: The International Autoimmune Hepatitis Group (IAIHG) recommends indirect immunofluorescence assay (IFA) for detecting ANA, ASMA, LKM-1, LC-1, and p-ANCA. IFA on fresh, multi-organ (liver, kidney, stomach) rodent slices allows simultaneous detection of ANA, ASMA, anti-LKM-1, and anti-LC-1. Enzyme-linked immunosorbent assay (ELISA) remains the preferred method for anti-SLA detection [54].

ANA and ASMA: Serological hallmarks of AIH-1, though not specific, can be found in primary biliary cholangitis, PSC, viral hepatitis, and systemic autoimmune diseases. ANA can be positive in up to 30% of the healthy population [55, 56]. On the rodents' renal substrate, ASMA can show three distinct patterns: 'V' (vessels), 'G' (glomeruli), and 'T' (tubules). 'VG' and 'VGT' patterns are indicative of AIH [54]. In the pediatric population, ANA and ASMA are considered positive at a dilution of 1:20 [29]. A meta-analysis of adult studies on AIH showed poor sensitivity (ANA: 65%, ASMA: 59.3%) and reasonably good specificity (ANA: 75.1%, ASMA: 92.6%) of ANA and ASMA for the diagnosis of AIH [57].

Anti-LKM-1: Highly specific for AIH-2, though occasionally detected in Hepatitis-C virus infection [56]. It gives a bright stain on the hepatocyte cytoplasm and on the P3 portion of the proximal renal tubules of rodents. The molecular target of anti LKM-1 is CYP2D6, a member of the hepatic P450 enzyme. Anti LKM-1 is considered positive in a dilution > 1:10.

Table 3 Prevalence of autoantibodies in adult and pediatric patients with autoimmune hepatitis and autoimmune sclerosing cholangitis/overlap syndrome [4, 9, 29, 42, 43, 50, 53, 54, 56, 57, 59, 69, 184, 188, 194]

	AIH type 1		AIH type 2		ASC/overlap	
	Pediatric	Adult	Pediatric	Adult	Pediatric	Adult
ANA	41–87%	13–80%	11–50%	31–40%	29–85%	13–39%
ASMA	46–96%	24–90%	21–50%	26%	14–82%	6–16%
SLA	40–58%	2–58%	44–58%	58%	41%	0
LKM1	0%	0%	95–100%	78–100%	3%	0
LC1	0%	0%	14.2–60%	21–51%	NA	0
p-ANCA	31–54%	42–92%	NA	NA	60–80%	60–70%

AIH autoimmune hepatitis, ANA antinuclear antibody, ASC autoimmune sclerosing cholangitis, ASMA anti-smooth muscle antibody, LC-1 anti-liver cytosol-1 antibody, LKM1 anti-liver kidney microsomal antibody-1, NA not available, p-ANCA peri-nuclear anti-neutrophilic cytoplasmic antibody, SLA anti-soluble liver antigen antibody

Anti-LC-1: Formimino-transferase cyclodeaminase, a liver enzyme related to metabolism of folates, is the target of anti LC-1. Anti-Formimino-transferase cyclodeaminase antibody can be detected by commercial ELISA and it correlates with severe inflammation and rapid progression to cirrhosis, serving as a prognostic marker in type 2 AIH [53, 58].

p-ANCA: ANCA is detected by IFA on fixed human neutrophilic granulocytes. It is frequently detected in type 1 AIH, PSC, and IBD. The detection of aberrant p-ANCA can operate as an additional signpost toward AIH diagnosis, particularly in the absence of other autoantibodies [50, 54, 55].

Anti-SLA: This antibody is highly specific for AIH-1 but may be detected in children with type 2 AIH. Its detection is usually associated with severe disease and a younger age at diagnosis [59].

3.1 Consensus statements

3.1.1 Immunoglobulin G measurement is integral to the diagnosis and monitoring of autoimmune hepatitis. Persistent elevation more than the upper limit of normal correlates with disease severity and risk of relapse, necessitating optimization of immunosuppression (LOE 3).

3.1.2 Autoantibody profiling is crucial for autoimmune hepatitis sub-classification, but seronegativity does not exclude autoimmune hepatitis, particularly in fulminant cases (LOE 4).

3.2 Consensus recommendations

3.2.1 Immunoglobulin G levels should be measured in all cases of suspected autoimmune hepatitis, but normal levels do not preclude the diagnosis of autoimmune hepatitis, especially in acute fulminant presentation (LOE 3, Strong recommendation).

3.2.2 Initial serological tests should include anti-nuclear, anti-smooth muscle, and anti-liver kidney microsomal type-1 antibodies (LOE 3, Strong recommendation).

3.2.3 Testing for additional autoantibodies (anti-soluble liver antigen, anti-liver cytosol-1, and peri-nuclear anti-neutrophilic cytoplasmic antibodies) may be considered if initial

autoantibodies are not detected and there is a strong clinical suspicion (LOE 3, Weak recommendation).

3.2.4 Indirect immunofluorescence is the method of choice for the detection of anti-nuclear, anti-smooth muscle, anti-liver kidney microsomal type-1, liver cytosol-1, and peri-nuclear anti-neutrophilic cytoplasmic antibodies. Solid-phase immunoassays may be used when indirect immunofluorescence is not available (LOE 3, Strong recommendation).

3.2.5 Autoantibody titer cut-offs for the diagnosis of pediatric autoimmune hepatitis are: anti-nuclear and anti-smooth muscle antibodies $\geq 1:20$ and anti-liver kidney microsomal type-1 antibody $\geq 1:10$. Positive results are considered for anti-soluble liver antigen, anti-liver cytosol-1, and peri-nuclear anti-neutrophil cytoplasmic antibodies (LOE 3, Strong recommendation).

Histology

Diagnosing pediatric AIH is particularly challenging due to the wide spectrum of clinical presentations and the absence of highly sensitive or specific biochemical or serological markers. Histological examination of liver tissue plays a crucial role in confirming the diagnosis, excluding alternate or comorbid etiologies, distinguishing AIH from ASC/overlap syndrome, and assessing fibrosis stage for prognostication. Liver biopsy is essential in the diagnostic work-up of AIH and is recommended by various international guidelines [29, 42]. It also serves as an important tool for follow-up, aiding in the evaluation of disease remission or progression.

Liver histology is a key component of almost all diagnostic scoring systems for AIH. However, no single histological feature is pathognomonic for AIH. Therefore, diagnosis relies on a combination of suggestive histological findings. According to the 2008 simplified scoring system [46], histological features considered 'typical' for AIH include portal inflammatory lymphocytic/lymphoplasmacytic infiltrate extending into the lobules (interface hepatitis), emperipolesis, and hepatocyte rosetting. A dense plasma-lymphocytic infiltrate in the portal tracts with

interface hepatitis is a hallmark of chronic AIH, observed in 80–90% of cases in both adult and pediatric cohorts [4, 60–63]. However, this feature is not exclusive to AIH and can be seen in other liver diseases, such as acute and chronic viral hepatitis or drug-induced liver injury. Similarly, emperipolesis (presence of intact lymphocyte within the cytoplasm of hepatocyte) and hepatocyte rosetting, once considered highly specific for AIH, are now recognized as markers of severe inflammation or liver injury and regenerative response rather than being unique to AIH [60, 62, 64] (Fig. 2).

Older diagnostic criteria, including the simplified scoring system, primarily focused on portal-based inflammation characteristic of chronic AIH but did not adequately account for histological changes seen in acute AIH presentations, leading to misclassification or underdiagnosis. Recently, a consensus statement from the International AIH Pathology Group addressed this issue by incorporating both portal and lobular hepatitis into the diagnostic criteria. Based on these recommendations, AIH can now be classified as “likely,” “possible,” or “unlikely” based on distinct histological findings [65]. However, validation and implementation of these criteria in pediatric AIH diagnosis remain pending.

In contrast to chronic AIH, AI-ALF often exhibits distinct histological features, such as centrilobular necroinflammation, perivenulitis of the central zone, lymphoid follicles, and massive hepatic necrosis. Massive hepatic necrosis types 4 or 5 has been reported in 40–60% of fulminant AIH cases [66, 67] (Fig. 2). However, a pediatric study found that its ability to differentiate AI-ALF from indeterminate ALF is limited [68].

Distinguishing AIH from ASC/overlap syndrome histologically is complex and requires a careful histological examination by an experienced pathologist. Nondestructive lymphocytic cholangitis, characterized by bile duct injury and lymphocytic infiltration of bile ducts, has been reported in up to 12–20% of AIH cases [4]. More pronounced biliary involvement, such as bile duct loss (ductopenia) with periductal fibrosis, suggests an underlying ASC/overlap syndrome. However, the classic onion-skin fibrosis characteristic of sclerosing cholangitis is rarely observed in pediatric cases of ASC/overlap syndrome [4, 69, 70]. Supplementary Table 3 describes the various studies highlighting the histological differentials of AIH.

4.1 Consensus statements

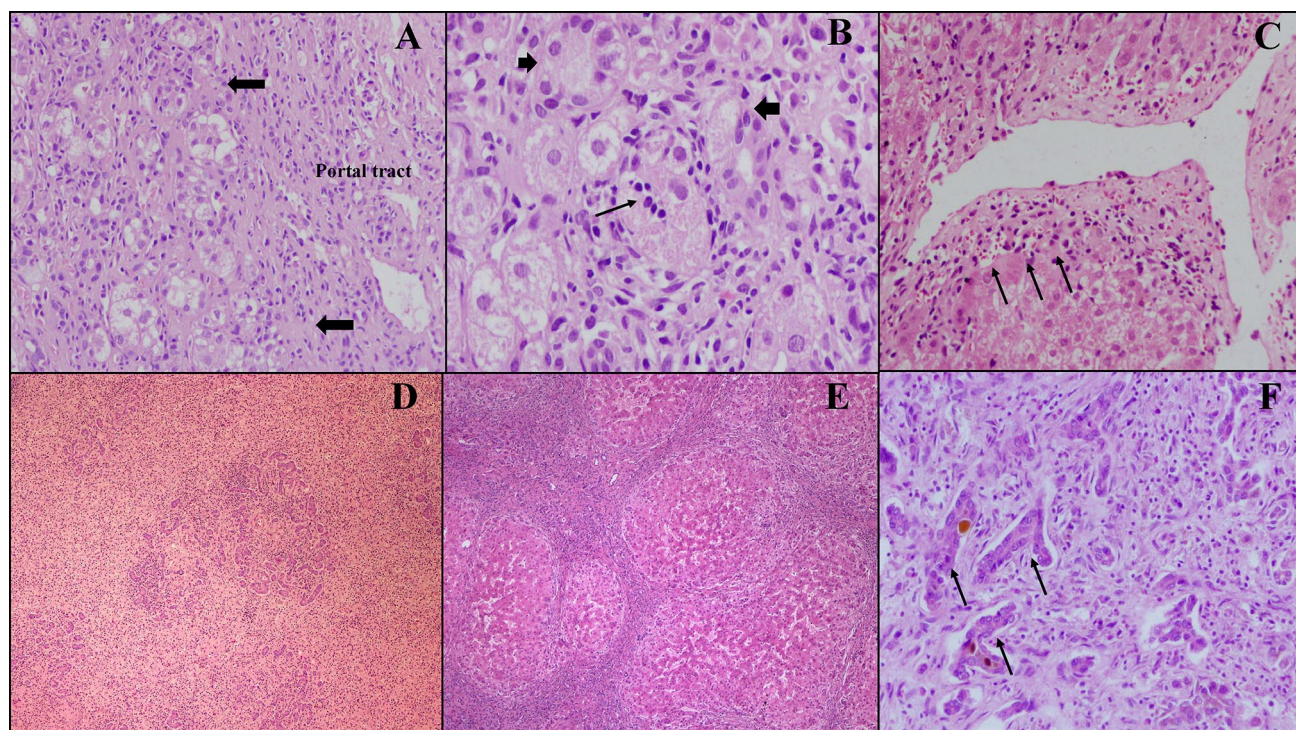


Figure 2 Histology of autoimmune hepatitis in children. Liver histology of a child presenting with acute hepatitis showing dense lymphoplasmacytic infiltrate in the portal tract extending into the adjacent liver parenchyma (interface hepatitis) [black arrow, **A**, hematoxylin and eosin (H&E) stain], emperipolesis (thin black arrow, **B**, H&E stain) and pseudorosettes (thick black arrows, **B**, H&E stain). Liver histology of children with autoimmune acute liver failure show-

ing zone 3 (central) perivenulitis with hepatocyte loss, (black arrows, **C**, H&E stain) and multiacinar necrosis (**D**, H&E stain). Liver histology of a child presenting with chronic liver disease showing cirrhotic liver with regenerative nodules and moderate interface hepatitis (Panel **E**, H&E stain) and evidence of ductular proliferation (black arrows, **F**, H&E stain)

4.1.1 Lymphoplasmacytic infiltration with interface hepatitis is the hallmark of autoimmune hepatitis, but not exclusive to it (LOE 3).

4.1.2 Centrilobular necroinflammation, central perivulinitis, and massive hepatic necrosis are characteristics of severe acute presentation of autoimmune hepatitis, including autoimmune-induced acute liver failure (LOE 3).

4.1.3 Mild bile duct injury could be seen in autoimmune hepatitis. Severe biliary changes in the form of bile duct loss and peribiliary fibrosis is suggestive of autoimmune sclerosing cholangitis/overlap syndrome (LOE 4).

4.2 Consensus recommendations

4.2.1 Liver biopsy is necessary to establish the diagnosis of autoimmune hepatitis, for the staging of fibrosis, and to rule out any comorbid condition or alternate etiologies (LOE 3, Strong recommendation).

4.2.2 Liver biopsy can be avoided in cases with autoimmune-induced acute liver failure or decompensated cirrhosis with coagulopathy where the index of suspicion is high (LOE 4, Strong recommendation).

Diagnostic scores

Various scoring systems have been developed and refined for the timely and accurate diagnosis of pediatric autoimmune liver diseases (Table 4). The original IAIHG score was introduced in 1993 which incorporated clinical, laboratory, serological and histological parameters, genetic predisposition with absence of hepatotropic viruses, and alcohol or drug intake [71]. This scoring system had a sub-optimal performance in pediatric patients [72]. The score was subsequently revised in 1999 to exclude non-hepatotropic viral testing and emphasize lower autoantibody titers and inclusion of HLA-DR3/DR4 positivity [73]. In the context of children from the Indian subcontinent and various parts of Asia, exclusion of Hepatitis-A viral (HAV) infection is mandatory before confirming the diagnosis of AIH.

In 2008, the simplified score was introduced with 4 key parameters of autoantibodies (ANA, ASMA, LKM-1 $\geq 1:40$, and SLA positivity), IgG levels, liver histology findings, and the exclusion of viral markers. This score (cut-off of ≥ 6 or 7) demonstrated high diagnostic accuracy, with an area under the receiver-operating characteristic curve (AUROC) of 0.946 in its training set and 0.91 in the validation set [46]. Since healthy children rarely have these autoantibodies, it has been suggested

Table 4 Scoring systems for the diagnosis of autoimmune hepatitis and autoimmune sclerosing cholangitis/overlap syndrome

Revised IAIHG 1999 criteria [73]	Simplified score 2008 [46]	ESPGHAN 2018 criteria [29]
Gender	Autoantibodies	Autoantibodies
ALP/AST (or ALT) ratio	ANA or ASMA	ANA and/or ASMA
Serum globulin or IgG level above ULN	Anti-LKM1	Anti-LKM-1
ANA, ASMA, or anti-LKM1	Anti-SLA	Anti-LC-1
AMA	IgG	Anti-SLA
Viral hepatitis markers	Liver histology	p-ANNA
Hepatotoxic drug exposure	Absence of viral hepatitis	IgG
Average alcohol intake (g/day)		Liver histology
Histologic findings		Absence of viral hepatitis (A, B, E, EBV), nonalcoholic steatohepatitis, Wilson disease, and drug exposure
Interface hepatitis		Presence of extrahepatic autoimmunity
Lymphoplasmacytic infiltrate		Family history of autoimmune disease
Rosette formation		Cholangiography
Biliary changes		
Other atypical changes		
Concurrent other immune disease		
Other autoantibodies		
HLA DRB1*03 or DRB1*04		
Treatment response		
Score interpretation	Score interpretation	Score interpretation
Pre-treatment	≥ 6 : probable AIH	≥ 7 : probable AIH/ASC-overlap
Definite AIH > 15	≥ 7 : definite AIH	≥ 8 : definite AIH/ASC-overlap
Probable AIH 10–15		
Post-treatment:		
Definite AIH > 17		
Probable AIH 12–17		

AIH autoimmune hepatitis, ALP alkaline phosphatase, ALT alanine aminotransferase, AMA anti-mitochondrial antibody, ANA anti-nuclear antibody, ASC autoimmune sclerosing cholangitis, ASMA anti-smooth muscle antibody, AST aspartate aminotransferase, EBV Epstein-Barr virus, HLA human leukocyte antigen, IgG immunoglobulin G, LC-1 anti-liver cytosol-1 antibody, LKM1 anti-liver kidney microsomal antibody-1, p-ANNA peripheral anti-nuclear neutrophil antibody, SLA anti-soluble liver antigen antibody, ULN upper limit of normal

to use a lower cut-off of $\geq 1:20$ for ANA and ASMA, and $\geq 1:10$ for LKM-1 antibodies [54]. Mileti et al. validated the utility of simplified score in children but also demonstrated its limited sensitivity in acute severe AIH (AS-AIH) or AIH induced ALF. Usage of revised IAIHG 1999 criteria was found helpful in diagnosing AS-AIH or autoimmune-ALF patients [47]. A systematic review and decision analysis reinforced the same results that the simplified score has moderate sensitivity but high specificity for diagnosing AIH in children, while also highlighting its limitations in AS-AIH [74].

To address certain limitations in pediatric populations, the ESPGHAN introduced a score in 2018 specifically tailored for children. This score uniquely integrates cholangiographic findings which are crucial for distinguishing PSC from AIH—with a family or personal history of autoimmunity. This approach aids in diagnosing AIH in rare cases where liver biopsy is not feasible due to coagulopathy and the absence of transjugular liver biopsy facilities [29]. However, there is a concern raised by some researchers that this score might lead to overdiagnosis of AIH without a liver biopsy. To date, two studies have validated all three diagnostic scores in pediatric populations, demonstrating a good agreement and underscoring their complementary roles in clinical practice [4, 15]. However, the ESPGHAN score needs to be validated in various populations. Pediatric-specific studies remain crucial for refining the diagnostic accuracy and distinguishing between AIH subtypes and ASC/overlap. Further, genetics can be incorporated in the diagnostic scores to rule out Wilson disease and multidrug resistance protein-3 (MDR3) deficiency in those with diagnostic uncertainty.

5.1. Consensus recommendations

5.1.1 Simplified score 2008 score should be used for the diagnosis of pediatric autoimmune hepatitis (LOE 3, Strong recommendation).

5.1.2 Revised International Autoimmune Hepatitis Group 1999 criteria may be used for diagnosis of suspected pediatric autoimmune hepatitis presenting with severe acute presentation, including acute liver failure (LOE 3, Weak recommendation).

5.1.3 Cut-off values of $\geq 1:20$ for anti-nuclear antibody and anti-smooth muscle antibody, and $\geq 1:10$ for anti-liver kidney microsomal antibody type 1 should be used (LOE 4, Strong recommendation).

5.1.4 Diagnostic scores may be used with caution for the diagnosis of autoimmune sclerosing cholangitis/overlap syndrome (LOE 3, Weak recommendation).

Management

The management of AIH in children aims to achieve symptom control, biochemical remission, reduction of hepatic inflammation, and prevention of fibrosis progression.

Treatment typically involves induction with corticosteroids, followed by long-term immunosuppression to maintain remission and prevent disease relapse.

Pre-treatment evaluation

It is important to check vaccination status and perform additional tests while initiating therapy with corticosteroids and other immunosuppressives.

Vaccination: Vaccination status should be reviewed, and pending vaccines administered at the time of initiating immunosuppression. Live vaccines should be avoided during high-dose immunosuppression. With the changing epidemiology of hepatitis-A infection, vaccination to prevent the infection should be given to all children. Hepatitis B vaccination should be given if not previously received. Testing for total (IgG) anti-Hepatitis-A and anti-Hepatitis-B antibodies before vaccination is not cost-effective in developing countries [75].

Thiopurine methyltransferase (TPMT) activity: TPMT activity testing before azathioprine initiation aims to identify those at risk of severe myelosuppression. However, 94% of children with AIH have normal TPMT activity, and 5.5% have intermediate activity. Intolerance to azathioprine and leukopenia do not significantly differ between those with low or normal TPMT activity compared to those untested [76, 77]. In view of low prevalence of TPMT polymorphism in Indian and Asian populations, high cost and unavailability of the test, and absence of clear correlation between the polymorphism and azathioprine intolerance, TPMT testing is not routinely recommended in Indian children [78].

Nudix hydrolase 15 (NUDT15) activity: NUDT15 is an enzyme that plays a crucial role in the metabolism of thiopurine drugs, like azathioprine and 6-mercaptopurine. Specifically, NUDT15 reduces the toxic effects of thiopurines by breaking down their active metabolites into less harmful forms. Mutations in the NUDT15 gene can lead to reduced enzyme activity, causing increased levels of toxic thiopurine metabolites and potentially severe side effects like leukopenia. Among Asian patients with IBD on azathioprine, 66% of those with leukopenia had NUDT15 variants, compared to 9.4% without leukopenia. Heterozygous and homozygous variants had a 19-fold higher risk of leukopenia [79]. In adult AIH patients, leukopenia occurred in 100% of homozygous and 27% of heterozygous patients [80]. Further studies are needed to establish the prevalence and impact of NUDT15 variants in Indian children with AIH.

Screening for tuberculosis: As per World Health Organization operational handbook on diagnosis of tuberculosis 2025, screening for latent tuberculosis in children living in areas with high endemicity for tuberculosis should be done using symptom screen, recent contact with active tuberculosis, and chest X-ray. In areas with low endemicity for

of prednisolone (1 mg/kg/day, maximum 60 mg) have a higher remission rate and also have more steroid-related side effects than those which used a lower dose (0.5 mg/kg/day). However, there is no single study directly comparing the effect of high versus low dose steroids. [82]. Some international bodies recommend a starting dose of 1 mg/kg/day of prednisolone in children, especially if starting in conjunction with another immunosuppressive like azathioprine [42]. Budesonide, with high first-pass metabolism, has been tried as an induction agent instead of prednisolone to minimize steroid-related side effects. There are conflicting data on the efficacy of budesonide compared to prednisolone in achieving biochemical remission in adults with AIH [83, 84]. In pediatric population, a clinical trial has found similar remission rates between budesonide (32%) and prednisolone (33%) arms at 6 months. Except for weight gain and cushingoid facies (which were more frequent with prednisolone), other adverse effects were not different in the two groups. However, the low remission rate in the prednisolone arm is difficult to explain that could be related to rapid tapering schedule followed in a sub-group of patients. Moreover, the proportion of patients with ASC/overlap syndrome was also not defined [85]. Thus, the results from these studies cannot be generalized until robust RCTs are available. Budesonide can be recommended for induction only in a select subset of non-cirrhotic AIH as the presence of advanced liver fibrosis and portosystemic shunting affect budesonide metabolism and cause comparable side effects to oral prednisolone [42]. A small pediatric study reported normalization of alanine transaminase (ALT) by 5.5 months in children with mild AIH (elevated liver enzymes with no portal hypertension) using azathioprine alone for induction [86]. However, long-term outcomes and flare rates are unknown, so steroid-free induction cannot be recommended until further evidence is available.

Maintenance therapy

Prednisolone monotherapy can maintain remission in only a small subset of patients [15]. Adding azathioprine (1–2 mg/kg/day) with low-dose prednisolone (2.5–5 mg/day) maintains remission in up to 79%, with a 28–35% relapse rate [9, 87]. Most flares on azathioprine maintenance are mild to moderate, and easily managed with short courses of steroids [10]. Bone marrow suppression occurs in 2.5–6.3% of children receiving azathioprine [88]. Monitoring 6-thioguanine (6-TG) levels do not reliably predict remission or relapse in AIH, unlike in IBD. In one study, only 32% of patients in remission had 6-TG levels within the IBD therapeutic range ($250\text{--}450\text{ pmol}/8\times 10^8\text{ RBCs}$) [89]. While another pediatric study found that 87% of those in remission had sub-optimal therapeutic 6-TG levels between 50 and $250\text{ pmol}/8\times 10^8\text{ RBCs}$ [76]. On the other hand, a recent meta-analysis showed significantly higher 6-TG levels among AIH in remission than those who failed to achieve remission [90]. Hence, more studies are needed to establish the role of

6-TG in therapeutic drug monitoring strategy and to establish the target drug level before it can be implemented in routine clinical practice. Significant hepatotoxicity with azathioprine has not been reported in any major adult and pediatric studies. Azathioprine monotherapy could maintain remission in 79% of children. Of the 35% who experienced flares, half were successfully treated by simply increasing the azathioprine dose [76]. Another study found overall relapse rates of 19% (12% on azathioprine monotherapy vs. 2% on combination therapy) [88]. In a study of adults on maintenance therapy, 36% relapsed after prednisolone withdrawal and required reintroduction of steroids [91]. A recent systematic review of studies done in adults showed that azathioprine monotherapy maintained prolonged remission in 83% of patients after achieving remission on a combination of prednisolone and azathioprine for a period of more than 1 year [92]. However, two real-world studies from 22 countries reported that none used azathioprine monotherapy for maintenance [93, 94]. Considering the results of systematic review, azathioprine monotherapy can be recommended for those who have sustained biochemical remission for more than 1 year on a combination of prednisolone and azathioprine [92]. Mycophenolate mofetil (MMF) in combination with steroids as inducing agents in a recent randomized-controlled trial in adults showed a higher proportion of CBR by 3 months (56% vs 29%) and 6 months (72% vs 32%) in comparison to azathioprine with steroids, with lesser number of serious adverse events (0% vs 13%) [95]. There is no such comparative trial in the pediatric age group. Administration of MMF in females of the reproductive age group should be avoided because of its teratogenic effects. Hence, MMF should be reserved for patients with poor response to steroids and azathioprine. A recent North European retrospective study in 157 children with AIH showed comparable efficacy but delayed response with tacrolimus (with or without steroids) versus azathioprine with steroids [96]. Table 5 mentions various drugs in the management of pediatric AIH. Declining IgG levels suggest successful immunosuppression, while persistently high levels may indicate sub-optimal therapy or ongoing inflammation, necessitating treatment adjustments [50]. However, it may be prudent to note that IgG levels may remain elevated even after a patient has achieved biochemical and histological remission, if the patient has advanced fibrosis [42, 51, 52].

7.1. Consensus recommendations

7.1.1 Prednisolone (1–2 mg/kg/day, maximum 40–60 mg/day) is recommended for induction therapy of AIH in children. Lower dose (1 mg/kg/day) is preferred in combination with other immunosuppressants (LOE 2, Strong recommendation).

7.1.2 Gradual tapering of prednisolone should be started from 2 to 4 weeks to bring down to a minimum dose of 0.1–0.2 mg/kg/day (2.5–5 mg/day) by 3–6 months based on decrease in transaminases (LOE 2, Strong recommendation).

Table 5 Common immunosuppressive medications used in treatment of autoimmune hepatitis and their adverse effects [10, 17, 29, 42, 44, 52, 76, 79, 82–88, 91–96, 104–115, 136–141]

Drug	Dosages	Adverse effects	Incidence of adverse effects	Management options for adverse effects
Prednisolone	Induction dose of 1–2 mg/kg/day for 2–4 weeks followed by gradual tapering to a maintenance dose of 2.5–5 mg/day or 0.05–0.1 mg/kg/day	Cosmetic: facial rounding, hirsutism, striae, acne Weight gain and increased appetite Glucose intolerance/diabetes, hypertension Quality of life: emotional instability, psychosis, depression, anxiety Cataracts, glaucoma Osteoporosis Opportunistic infections Effect on linear growth Pancreatitis	11–44% 17.2% 3.4% NA NA 50% NA 0–10.5% 0–1.5%	Taper to the lowest steroid dose Attempt withdrawal after remission Consider Budesonide in non-cirrhotic patients Proactive screening and management for quality of life and mental health symptoms Yearly eye examination for cataract and glaucoma Bone density monitoring (baseline assessment and follow-up every 3–5 years), Vitamin D3 and calcium administration, bisphosphonates Use antimicrobial prophylaxis when using high-dose steroid Regular monitoring and taper steroids to lowest possible dose Switch to MMF/tacrolimus
Azathioprine	Start at 1 mg/kg/day—Increase slowly at 1–2 weekly intervals to maximum of 1.5–2 mg/kg/day (up to 150 mg/day)	Gastrointestinal disturbances Hematological toxicity Lymphopenia, leucopenia Thrombocytopenia Flu like illness Hepatotoxicity Invasive Infections Leukopenia and neutropenia Gastrointestinal symptoms: Abdominal pain and diarrhea Headache/dizziness Hair loss Invasive infections Neurotoxicity	5–20% 1.6–39.3% 5% 15–28% Not applicable 16.6–27% 7.7–16.6% 3.8–7.7%	Split dosing, switch to 6-mercaptopurine, and use of low-dose azathioprine in combination with allopurinol TPMT (thiopurine methyltransferase) and nudix hydrolase 15 (NUDT15) testing Monitoring of drug metabolites: 6-thioguanine, 6-methylmercaptopurine Reduce dose or shift to alternate immunosuppression (MMF/Tacrolimus) Split dosing, switch to 6-mercaptopurine, and use of low-dose azathioprine in combination with allopurinol Delayed introduction in presence of high bilirubin, Switch to MMF Symptomatic treatment of infections and temporary discontinuation Temporary discontinuation or dose reduction
Mycophenolate mofetil (MMF)	Start at 20 mg/kg/day—Increase slowly at 1–2 weekly intervals to a maximum of 40 mg/kg/day (maximum up to 2 g/day)			
Tacrolimus	Target trough levels: 3–8 ng/ml		Around 5% 5–20%	Symptomatic treatment of infections and temporary discontinuation Temporary discontinuation and/or switch to alternative immunosuppression

Table 5 (continued)

Drug	Dosages	Adverse effects	Incidence of adverse effects	Management options for adverse effects
Cyclosporine	Target trough levels: 200–250 ng/ml (induction); 50–100 ng/ml (maintenance)	Gastrointestinal disturbances	–	Reduce dose or switch to alternate immunosuppression
		Diabetes mellitus	–	
		Nephrotoxicity	5%	
		Hypertrichosis	45–80%	Dose reduction
		Gingival hyperplasia	33–55%	Dose reduction
		Nephrotoxicity	9.5–20%	Dose reduction and/or switch to alternative immunosuppression
Sirolimus	Target trough levels: 4–8 ng/ml	Hypertension	3.5–6.6%	
		Tremor, headache	6.6%	
		Hypercholesterolemia dyslipidemia	Variable	Dose reduction and/or switch to alternate drug
		Stomatitis, delayed wound healing, edema, respiratory infections, cytopenia		
Rituximab	375 mg/m ² /dose	Hypogammaglobulinemia	Around 16%	Intravenous Immunoglobulin
		Lymphopenia		
		Recurrent infections	Variable	Appropriate treatment of infections

7.1.3 Azathioprine in combination with prednisolone is recommended for induction and maintenance at a dose of 1–2 mg/kg/day with close monitoring for side effects (LOE 1, Strong recommendation).

7.1.4 Response to treatment should be assessed after exclusion of sub-optimal dosing, non-adherence, alternative etiologies, co-morbidities, and autoimmune sclerosing cholangitis/overlap syndrome (LOE 5, Strong recommendation).

Difficult-to-treat autoimmune hepatitis

Definition: Most of the children with AIH respond well to first-line conventional treatment. Difficult-to-treat AIH (DTT-AIH) refers to cases where the standard first-line treatment is ineffective, poorly tolerated, or leads to frequent relapses. These cases pose significant challenges for clinicians and often necessitate personalized or advanced treatment strategies.

Various studies and society guidelines report that approximately 5–27% of patients do not respond to or cannot tolerate first-line treatment [4, 15, 22, 29, 30, 32, 42, 97–102]. Table 6 defines and Fig. 3 outlines the algorithmic management of treating DTT-AIH. Following the initiation of standard therapy, patients may experience treatment failure with or without immediate severity or exhibit only a partial response. The criteria for remission or treatment response have varied across national and societal guidelines (Table 6). Observational studies indicate that in most patients, an 80% reduction in aminotransferase levels occurs within the first two months, although complete normalization may take several months [98]. Institution or laboratory-specific normal standard values of transaminases should be defined beforehand. In 2022, the IAIHG initiated a consensus process to establish standardized definitions for treatment response. The term “complete biochemical response” was defined as the normalization of serum transaminases and IgG levels below the upper limit of normal within 6 months of treatment initiation. An insufficient response was a lack of complete biochemical response by 6 months of treatment. Non-response was defined as a less than 50% decrease in serum transaminases within 4 weeks of starting treatment. Treatment intolerance was defined as any adverse event potentially linked to the therapy, leading to the need for drug discontinuation [99].

Treatment: Almost 10–20% of children with AIH may not respond to a combination of prednisolone and azathioprine and require second-line agents to achieve remission [103]. Before escalating to second- or third-line therapies, clinicians should first evaluate for potential confounding factors such as non-adherence, sub-optimal drug dosing, azathioprine hypermethylation, alternative etiologies, and co-existing conditions like celiac disease, metabolic dysfunction-associated steatotic liver disease, or ASC/overlap

Table 6 Definitions used in various guidelines for difficult-to-treat autoimmune hepatitis

Society, year	Defining criteria	Prevalence
EASL, 2015 [97]	1. Non-response: < 25% decrease in AST/ALT in 2 weeks with or without immediate severity 2. Incomplete response 3. Treatment intolerance due to drug side effects	10–15%
ESPGHAN, 2018 [29]	1. Treatment intolerance 2. Unresponsiveness to standard immunosuppression	13%
AASLD, 2019 [42]	1. Treatment failure: worsening laboratory or histological findings despite compliance with standard therapy 2. Incomplete response: improvement of laboratory and histological findings that are insufficient to satisfy criteria for remission 3. Treatment-ending side effects	7–9% 15% 13%
APASL, 2021 [98]	1. Non-response: < 25% decrease in AST/ALT in 2 weeks, or increase in bilirubin or worsening of coagulation 2. Incomplete response 3. Treatment intolerance 4. Relapse after withdrawal	10–15%
IAIHG Consensus, 2022 [99]	1. Non-response: < 50% decrease in AST/ALT in 4 weeks 2. Insufficient response: lack of complete biochemical response after 6 months of treatment initiation 3. Treatment intolerance	–

AASLD American Association for the Study of Liver Diseases, ALT alanine aminotransferase, APASL Asian Pacific Association for the Study of the Liver, AST aspartate aminotransferase, EASL European Association for the Study of the Liver, ESPGHAN European Society for Pediatric Gastroenterology, Hepatology, and Nutrition, IAIHG International Autoimmune Hepatitis Group

syndromes [29, 104]. Assessing thiopurine metabolites such as 6-TG and 6-methylmercaptopurine (6-MMP) can be instrumental in tailoring therapy and monitoring treatment adherence in AIH. Maintaining 6-TG nucleotide levels above $220 \text{ pmol}/8 \times 10^8$ red blood cells has been associated with sustained biochemical remission in adults with AIH [105–107] (Table 5). A systematic review and meta-analysis of four adult and three pediatric studies showed that 6-TG nucleotide levels were higher in patients achieving biochemical remission, with no difference in 6-MMP levels or the 6-MMP/6-TGN ratio [90]. Testing for 6-TG can identify patients who might benefit from allopurinol, a xanthine oxidase inhibitor that diverts the metabolism toward 6-TG. Introduction of allopurinol guided by thiopurine metabolites led to long-term remission in 75% of the adult AIH cohort [106]. Supplementary Fig. 1 describes the metabolism of azathioprine and 6-mercaptopurine with key enzymatic steps, and role of allopurinol.

Mycophenolate mofetil is recommended as the preferred second-line therapy by both the American Association for the Study of Liver Diseases (AASLD) and ESPGHAN [29, 42]. In adults, MMF achieves remission in 50–60% of patients who are intolerant or non-responsive to azathioprine [108–110]. As mentioned before, MMF has been reported to be superior to azathioprine in a recent RCT in adults [95]. Calcineurin inhibitors, such as tacrolimus and cyclosporine, have remission rates of 63–87% in azathioprine-intolerant patients and 41–53% in non-responders [111–113]. No direct comparative trials between MMF and tacrolimus

exist, but retrospective analyses in pediatric patients indicate a potential advantage of tacrolimus in non-responders [114]. According to a pediatric meta-analysis involving 76 AIH patients, response rates at 6 months were 36% for MMF, 50% for tacrolimus, and 78% for cyclosporine; however, the small sample size does not provide any definite conclusion [115]. Although tacrolimus is apparently more efficacious in azathioprine non-responders than MMF, it is seldom used as a second-line agent considering the need for drug-level monitoring, higher cost, and associated toxicity [94, 113, 114].

8.1 Consensus recommendations

8.1.1 Difficult-to-treat autoimmune hepatitis should be defined as requiring second-line therapy due to the following conditions:

1. Treatment intolerance: Presence of adverse effects preventing the continuation or escalation to an adequate therapeutic dose of the immunosuppressive drug.
2. Incomplete or insufficient response: Failure to achieve remission characterized by the lack of normalization of transaminases and immunoglobulin G levels within 6 months despite adherence to therapy.
3. Treatment failure or non-response: Defined as a less than a 50% decline in transaminases levels within 4 weeks, or worsening serum bilirubin levels and/or coagulopathy, or frequent relapses upon tapering treatment (LOE 5, Strong recommendation).

8.1.2 Before initiating second-line immunosuppressive therapy, it is essential to exclude sub-optimal dosing, non-adherence, alternative etiologies, co-morbidities and autoimmune sclerosing cholangitis/overlap syndrome (LOE 5, Strong recommendation).

8.1.3 Measurement of thiopurine metabolites may be considered to optimize therapeutic efficacy of azathioprine and to evaluate the benefit of adding allopurinol (LOE 3, Weak recommendation).

8.1.4 Mycophenolate mofetil is recommended as the preferred agent for second-line therapy (LOE 2, Strong recommendation).

8.1.5 Calcineurin inhibitors may be considered as an alternative second- or third-line therapy (LOE 3, Weak recommendation).

Salvage treatment

Salvage therapy, also known as rescue therapy, is a treatment given after AIH has failed to respond to standard or first-line treatments. Salvage therapy is considered for children with AIH refractory to first and second-line treatments. Salvage treatment strategies involve drugs that inhibit the mammalian target of rapamycin (sirolimus, everolimus), inhibit B-cell activation and proliferation (rituximab, VAY736), block tumor necrosis factor (infliximab), and enhance regulatory T cells (low-dose interleukin-2, IL-2) among others [94, 116]. However, there are limited data on various salvage treatment options. Hence, usage of salvage treatment options should be individualized based upon clinician's decision. A recent survey conducted in 36 European centers reported that drugs like sirolimus and rituximab were preferred in only 2 (5.1%) of these centers [94]. Figure 3 provides a structured algorithm for management of pediatric AIH patients who need salvage therapy.

Sirolimus has shown response rates of 80–100% in adults with refractory AIH patients, while one pediatric study has reported a response rate of 50% [117–119]. Similarly, everolimus has shown response in 5 out of 6 children after a median follow-up of 28 months [120]. Rituximab usage has shown a response rate of up to 89% in adults with refractory AIH [121–123]. Two pediatric case series have also shown comparably good response rates to rituximab [124, 125]. Infliximab in refractory AIH has shown a response rate of 78% in a multicentric adult study with similar results in a pediatric case series [126–128]. Methotrexate and cyclophosphamide have been rarely used in AIH [129–131]. These salvage treatment options have a narrow therapeutic index in comparison to first- and second-line therapeutic agents and need close monitoring for adverse effects and therapeutic levels (Table 5). Several new therapeutic agents are currently under investigation for AIH, including B-cell activating

factor (BAFF) inhibitors, low-dose IL-2, Toll-like receptor-4 antagonists, pre-implantation factor, and inflammatory inhibitors among others [132].

9.1 Consensus recommendation

9.1.1 In the presence of limited data in pediatric refractory autoimmune hepatitis, usage of salvage treatment options should be individualized based upon clinician's decision (LOE 5, Weak recommendation).

Monitoring a child with autoimmune hepatitis

Currently, no standardized monitoring protocols are available for patients with AIH. The recommendations provided in various guidelines are primarily based on expert opinions and center-specific practices. Several guidelines, both pediatric and adult, outline monitoring protocols for the initial treatment period [29, 42, 97]. The frequency and extent of monitoring depend on clinical severity and the type of immunosuppressive therapy used. Essential components include monitoring for disease activity, disease progression, growth, and drug side effects (Tables 5 and 7) [29, 42, 50, 97, 133–135]. Baseline parameters should be assessed before initiating treatment. Any modifications in medication or dosage should prompt more frequent monitoring until remission is achieved. Vaccinations for vaccine-preventable diseases, including influenza, should be administered regularly. Ensuring vaccination against hepatitis-A and B will help in preventing acute-on-chronic liver failure and its related morbidity and mortality in these children with underlying chronic liver disease. As mentioned in Table 5, these children should be given special attention for psychological counseling and help.

10.1 Consensus recommendation

10.1.1 Children with autoimmune hepatitis on immunosuppression should be regularly monitored (weekly or biweekly for the first 6–8 weeks, then monthly for the first 6 months, followed by every 3–6 months) for disease activity, disease progression, treatment-related adverse effects, and for growth and development (LOE 5, Strong recommendation).

Managing adverse effects of immunosuppression

Adverse effects of immunosuppressive therapy may lead to treatment discontinuation in up to one-sixth of patients [136]. A structured approach is necessary to mitigate these effects while maintaining therapeutic efficacy.

Steroids: Steroid-associated adverse effects are common, affecting nearly half of the patients, with treatment discontinuation in one-sixth, particularly among adolescents. Cushingoid features, increased appetite, rapid weight gain (due to water retention and increased appetite), abdominal pain from gastritis, hirsutism, cutaneous striae, acne,

Table 7 Protocol for monitoring of children with autoimmune hepatitis and autoimmune sclerosing cholangitis [29, 42, 69, 133–135, 137–139, 188]

Parameter	Test	Frequency
Monitoring disease activity		
Liver inflammation	Liver biochemistry including serum gamma-glutamyl transpeptidase levels	Intensity based on clinical setting; weekly or biweekly for the first 6–8 weeks, then 1–2 months for the first 6 months, followed by every 3–6 months
Autoimmunity	Serum IgG levels	Every 6–12 months
Histopathology	Liver Biopsy	Not routinely required; indicated if transaminases remain persistently high or if an alternative diagnosis is suspected
Biliary ductal changes already present (ASC/overlap phenotype)	MRCP	Annually
Monitoring disease progression		
Portal hypertension	Upper gastrointestinal endoscopy	Variceal screening as per standard guidelines
Fibrosis	Liver stiffness measurement using transient elastography	Recommended after 6 months of treatment initiation; Consider annually
Biliary ductal changes	MRCP	Performed in presence of clinical or biochemical evidence of cholestasis (pruritus, elevation of serum GGT levels)
Liver biopsy	Histology	Not routinely required
Hepatocellular carcinoma (in presence of cirrhosis)	Ultrasonography ± Serum alpha-fetoprotein levels	Every 6–12 months
Monitoring growth and development		
Growth	Anthropometry	At every clinical visit
Development	Sexual maturity rating (tanner staging)	Baseline assessment and periodic follow-up during adolescence
Monitoring drug effects	Refer to Table 5	

AASLD American Association for the Study of Liver Diseases, ASC autoimmune sclerosing cholangitis, GGT gamma-glutamyl transpeptidase, IgG immunoglobulin G, MRCP magnetic resonance cholangiopancreatography

and cataract are frequent adverse effects [44, 85]. Steroid-induced hypertension and hyperglycemia require regular monitoring, symptomatic management, prompt tapering of steroids, and alternate immunosuppression. Steroid-induced gastritis can be treated using gastric acid suppressants. Steroid therapy suppresses the adrenal axis, potentially impacting linear growth and development [137]. Morning administration of steroids is advised to minimize this effect. There is evidence that systemic corticosteroids given to children with decompensated cirrhosis and AIH can cause significant increase in intraocular pressure [138]. Long-term data suggest that low-dose steroids used for maintenance of remission do not significantly impact growth in pediatric AIH [139]. Prolonged low-dose steroid therapy has been seen to increase the risk of osteopenia, osteoporosis, and fractures in adults, while high-dose steroid therapy causes cataract and diabetes [140]. Calcium (50 mg/kg/day) and vitamin D supplementation (800 IU/day) are routinely indicated, while the data on bisphosphonate use in children are limited. Dual-energy X-ray absorptiometry (DEXA) may be considered for monitoring bone density in adolescents every 3–5 years. If steroid-induced osteopenia is a concern, switching to

azathioprine or MMF monotherapy may be considered [114]. Budesonide, in combination with azathioprine, may be considered in steroid responders with intolerable steroid-related adverse effects [85].

Azathioprine: Adverse effects to azathioprine occur in approximately 25% of patients, requiring drug withdrawal in 10% [141]. Pancreatitis seen in up to 7% of adults within the first few weeks of treatment necessitates azathioprine discontinuation [142]. Hematological toxicity occurs in approximately 10% of patients which could be due to NUDT15 variants (more common in Asians) or TPMT polymorphism [79, 141]. Azathioprine-induced and hypersplenism-induced cytopenia may co-exist and should be differentiated on a bone marrow aspiration and/or biopsy. Therapeutic drug monitoring of azathioprine metabolites (6-TG, 6-MMP) may aid in dose titration, compliance to treatment, and evaluation of sub-optimal response, but ideal therapeutic levels in the pediatric age group are not yet defined [76]. Azathioprine-related hepatotoxicity may necessitate discontinuation and thiopurine metabolite assessment. This selected group of patients may benefit from addition of allopurinol [143].

Given potential hepatotoxicity, azathioprine is avoided in the setting of high bilirubin and acute liver failure. MMF is a preferred alternative in patients with azathioprine related serious adverse events [114].

Mycophenolate mofetil: Gastrointestinal symptoms (abdominal pain, diarrhea) occur in 8–17% of patients and improve with temporary discontinuation or dose reduction [114, 144]. Bone marrow suppression leads to cytopenia in 17–27% of cases, while headache and hair loss may also necessitate drug withdrawal [114, 144]. Incremental dosing with monitoring is recommended. Teratogenicity is an important adverse effect; hence, it is customary to prescribe contraception in the childbearing age group.

Tacrolimus: Neurotoxicity, including headaches and seizures, occurs in 5–30% of patients requiring dose reduction or temporary discontinuation. Other adverse effects include nephrotoxicity and gastrointestinal symptoms, which usually resolve with dose reduction or discontinuation [114, 115].

Table 5 provides an overview of common adverse effects associated with various immunosuppressive agents used in the treatment of pediatric AIH, along with strategies for their management.

11.1 Consensus recommendations

11.1.1 Careful monitoring of treatment-related adverse effects should be done in children with autoimmune hepatitis. Management is based on reducing dose with or without switching to alternate immunosuppression (LOE 4, Strong recommendation).

11.1.2 Calcium and vitamin D supplementation is recommended to prevent and treat osteopenia/osteoporosis in children on long-term steroid therapy (LOE 4, Strong recommendation).

11.1.3 Monitoring of bone density by dual-energy X-ray absorptiometry may be considered in older children on long-term steroid therapy (LOE 5, Weak recommendation).

Withdrawal of immunosuppression

Withdrawal of immunosuppressive therapy has been explored in a select subset of AIH, albeit with variable success rates [145–152]. While most studies including those in children attempted treatment withdrawal in patients having sustained biochemical remission (normalization of transaminases for more than 2 years); majority of them also preferred to document normal IgG and absence of histological activity prior to attempting withdrawal [15, 32, 145–153]. Although ESPGHAN recommends documenting the absence of autoantibodies prior to immunosuppression withdrawal in children, there is limited evidence to support the clinical utility of such retesting [29]. In children on combination therapy, a step-wise withdrawal (steroid followed by azathioprine) has been suggested by a

recent pediatric study [32]. As patients with cirrhosis may continue to have elevated IgG despite complete biochemical and histological remission, treatment withdrawal may still be considered in such patients on a case-to-case basis [42]. After immunosuppression withdrawal, frequent monitoring is essential, particularly in the first two years, when the risk of relapse is highest [32, 147, 148]. Most experts recommend ALT monitoring every 3–4 weeks for the first three months and then at 3- to 6-month intervals [32, 42, 146, 152, 154]. Others suggest monitoring transaminases every 3–6 months [29, 149, 150]. Studies in adults indicate high relapse rates after withdrawal (25%–88%), even in those with prolonged biochemical remission [145–152]. In pediatric AIH, reported relapse rates on stopping therapy have been lower, ranging between 12.5 and 55% [15, 32, 153]. A stable transaminase level (< 0.5 times the upper limit of normal) for 6 months to 2 years has been independently associated with a lower relapse risk in both adult and pediatric studies [32, 148]. Higher IgG levels at the time of treatment initiation and withdrawal have also been linked to higher relapse risk [146, 148]. While most studies require histological remission (histological activity index < 4) before stopping immunosuppression, a single pediatric study has suggested that liver biopsy before withdrawal may not always be necessary [32]. Certain histological markers, such as portal plasma cell infiltration, may indicate a high risk of relapse, but fibrosis scores have not consistently predicted relapse [32, 149, 154]. Age, gender, AIH type, treatment duration, presence of other autoimmune diseases, and HLA type have not been universally identified as predictors of relapse [15, 32, 145–153]. While some studies suggest no difference in relapse rates between pediatric AIH type 1 and type 2 [32], others report a higher risk in AIH type 2 [9]. Overall, predictors of relapse in pediatric AIH remain poorly defined, necessitating further research. Relapses are generally manageable, with most patients responding well to reintroduction of prior immunosuppressive therapy [32, 147, 148, 152]. A high incidence of relapse has been reported in patients where a second attempt at immunosuppression withdrawal was made [32]. Table 8 describes the various studies evaluating outcomes following treatment withdrawal in adults and children with AIH. Figure 4 shows a suggested protocol for treatment withdrawal in pediatric AIH and monitoring thereafter.

12. Consensus recommendations

12.1.1 Withdrawal of immunosuppression may be considered in a carefully selected cohort of pediatric autoimmune hepatitis with prolonged (> 2 years) biochemical remission followed by histological remission and after a detailed explanation of the risk of relapse (LOE 4, Weak recommendation).

Table 8 Studies describing treatment withdrawal in adults and children with autoimmune hepatitis

Study	Criteria for withdrawal	No of patients	Median follow-up post withdrawal	Relapse rates after withdrawal	Predictors of relapse
Studies in adults					
Verma et al. (2004) [149]	As per treating hepatologist's discretion—most had normal AST/ALT for 2 years	40	52 months	75% relapse within 2 months	Failure to maintain consistently normal transaminases ($p=0.02$) Time to remission > 5 months ($p=0.01$) Portal plasma cell score > 3 ($p=0.04$)
Montano-Loza et al. (2007) [146]	Absence of symptoms AND AST < 2 times the upper limit of normal AND histological remission	132	71 months	77% (median duration to relapse: 3 months)	Abnormal IgG (> 1500 mg/dL), AST (> 31 IU/L) and Gamma globulin (> 1.7 g/dL) at the time of withdrawal associated with a higher risk of relapse
van Gerven NMF et al. (2013) [147]	Complete clinical remission and normalization of ALT levels for at least 2 years	131	8.8 years	89% had either relapse or loss of remission 1y, 2y, 3y, 5y: 59%, 73%, 81%, 88%	Concomitant autoimmune disease ($p=0.04$) Age less than 45y ($p=0.03$)
Hartl et al. (2015) [148]	Remission (normal ALT and IgG) on immunosuppressive monotherapy for at least 2y	28	45 months (24–111 months)	46% relapse, majority within 2 years of withdrawal	Higher ALT level at withdrawal (HR 4.35; CI 1.10–17.07; $p=0.04$) and higher IgG
Zachou et al. (2016) [145]	Normal transaminases and IgG for at least 2 years All treatment withdrawal patients were on MMF	40	24 months (2–129 months)	25%	Univariate: Shorter duration of treatment with MMF ($p=0.005$), Higher IgG at month 6 of treatment ($p=0.004$), Lower ALT levels at baseline ($p=0.01$) Multivariate: Shorter duration of treatment with MMF
Guirguis et al. 2018 [150]	Normal or near-normal AST/ALT for 2 years	34	11.5 months	25%	No role of histology including fibrosis
Ben Merabet et al. (2021) [151]	Normal transaminases and IgG for 2 years	39	64 months	At 12 months: 13.4% At 64 months: 28.9%	Higher prevalence of ASMA ($p=0.005$) Shorter duration of treatment with azathioprine ($p=0.055$)
van den Brand et al. (2021) [152]	Normal transaminases and IgG for 2 years AND Liver biopsy HAI ≤ 3/18	12	62 months (13–75 months)	33% (all asymptomatic)	No predictors of relapse were identified
Czaja et al. (2003) [154]	Absence of symptoms AND AST less than 2 times the upper limit of normal AND histological remission	88		Not explicitly mentioned, 70 out of 100 biopsies evaluated had relapse	Presence of portal plasma cells was associated with relapse (31% versus 7%, $p=0.01$)
Studies in children					

Table 8 (continued)

Study	Criteria for withdrawal	No of patients	Median follow-up post withdrawal	Relapse rates after withdrawal	Predictors of relapse
Maggiore et al. (2023) [32]	Before 1980 Normal AST/ALT/IgG for 1 year Histology—no activity After 1980 Normal AST/ALT and IgG for 1 year, no liver biopsy	Supervised withdrawal 49 Unsupervised withdrawal 16	7 years	52% (25/49) in supervised withdrawal 5 patients relapsed after > 4 years of treatment withdrawal Relapse rate 15/16 (94%) in unsupervised withdrawal	Younger age at withdrawal ($p = 0.012$) Shorter relapse-free duration on initial therapy before withdrawal ($p = 0.038$) ALT > 0.5 times the upper limit of normal No difference between incidence of relapse between Type 1 and 2 AIH No predictors of relapse were identified Extra-hepatic autoimmune disease ($p = 0.08$) and cirrhosis at baseline ($p = 0.02$)
Di Giorgio et al. (2020) [15]	Histologic and immunologic remission for at least 3 years	12	3.78 years	25% (3/12)	
Deneau et al. (2014) [153]	Normal AST/ALT and IgG for 1 year, and liver histology not showing any active inflammation	16	3.4 years	12.5% (2/16)	

AIH autoimmune hepatitis, *ALT* alanine aminotransferase, *ASMA* anti-smooth muscle antibody, *AST* aspartate aminotransferase, *CI* confidence interval, *HAI* histological activity index, *HR* hazard ratio, *IgG* immunoglobulin G, *MMF* mycophenolate mofetil, *y* years

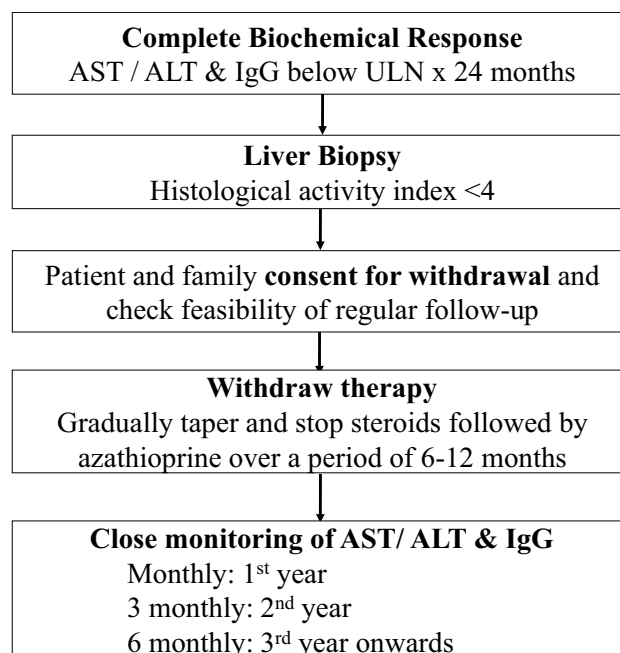


Figure 4 Protocol for withdrawal of immunosuppression in children with autoimmune hepatitis. Complete biochemical remission, i.e., normalization of transaminases and immunoglobulin G (IgG) should be ensured for 24 months. Histological remission (histological activity index <4) should then be documented on liver biopsy. After an informed decision, immunosuppression can then be withdrawn while carefully monitoring for transaminases and IgG as mentioned in the figure. *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *IgG* immunoglobulin G, *ULN* upper limit of normal

12.1.2 Withdrawal of immunosuppression should be attempted in a step-wise manner (LOE 4, Weak recommendation).

12.1.3 Frequent protocol-based monitoring should be followed after withdrawal of immunosuppression (LOE 5, Strong recommendation).

Long-term outcome

Relapse on treatment

Relapses following initiation of immunosuppression have been reported in 19–57% of children with AIH [4, 15, 30, 32]. Median of 1–2 (range 1–5) relapses occur in children while on treatment and are related to poor adherence to treatment, decrease in immunosuppression, presence or development of ASC/overlap phenotype. There is no relationship between the occurrence of relapses with baseline clinical, biochemical or histological features [4, 15, 30, 32]. A proportion of relapses (10%) may occur beyond 20 years of onset of treatment [32]. Most of the relapses while on immunosuppression are easily treatable with increase in steroids

and/or change in immunosuppression; however, few may present with liver failure with need for LT [30, 32]. Study from King's reported poor SNL in those with relapses [15], while two other pediatric studies did not find this association [30, 32].

Survival with native liver and need for liver transplant

Survival with native liver in adult patients with AIH is around 80–90% at 10 years and 70–80% at 20 years from the time of diagnosis [101, 102, 155]. Pediatric literature also mentions SNL at 5 and 10 years of above 90% and 80%, respectively, in these patients [4, 5, 15, 30–32, 156]. Only 2 European pediatric studies have reported SNL of 72–74% at 20 years and beyond [15, 32]. Poor SNL in adults is related to non-achievement of remission, cirrhosis, presence of decompensation, frequent relapses on treatment, persistently deranged INR, failure to normalize ALT within 12 months of diagnosis, presence of SLA antibodies, and concomitant IBD [101, 102, 155, 157–159]. Non-response to treatment, presence of cirrhosis, and frequent relapses reduce SNL in children [4, 15, 31, 32, 156].

Cirrhosis is present in 11–53% of adults and 20–75% of children at diagnosis and is associated with poor outcome [4, 5, 15, 30–32, 101, 102, 155–157, 160]. However, data from one adult and one pediatric study each described no effect of cirrhosis on remission or treatment failure or SNL [15, 161]. Baseline LSM value above 8.5 kPa on transient elastography predicts the development of cirrhosis, and follow-up LSM value is affected by the presence or absence of CBR [159, 160]. Up to 62% of adults with decompensated cirrhosis due to AIH recompensate over a period of time [133, 162]. A single small pediatric study reported improvement in the histological activity index and Ishak's fibrosis stage during follow-up [163]. Given this evidence, most centers and guidelines advocate initiating immunosuppression in the presence of cirrhosis with or without decompensation, and disease activity. Budesonide is contraindicated in the presence of cirrhosis, while azathioprine and MMF should be used cautiously with the risk of worsening cytopenias in the presence of hypersplenism [4, 5, 29, 42, 98, 162]. Cirrhotic complications of portal hypertension and hypersplenism are managed as per standard guidelines [134]. Table 9 summarizes key studies examining the long-term outcomes of pediatric AIH.

Risk of hepatocellular carcinoma

A systematic review and meta-analysis of 25 adult studies including 6528 patients followed for a median of 8 years showed that incidence of hepatocellular carcinoma in AIH is 3.06 per 1000 patient-years—this rate increases with

presence of cirrhosis at diagnosis of AIH (10.07 per 1000 patient-years) [164]. There is a single case report of hepatocellular carcinoma in pediatric age group in the setting of AIH [165].

13.1 Consensus statements

13.1.1 In children with autoimmune hepatitis, 10-year survival with native liver is above 80% (LOE 3).

13.1.2 Non-achievement of remission, presence of cirrhosis, and frequent relapses are associated with poor survival with native liver in children with autoimmune hepatitis (LOE 3).

Special scenarios

Severe acute presentations of autoimmune hepatitis

Severe acute presentation of AIH in adults has been classified into AS-AIH, autoimmune-induced acute liver failure (AI-ALF), and autoimmune-induced acute-on-chronic liver failure based on the clinical spectrum [42, 166–168]. However, it is difficult to segregate these presentations in the pediatric age group. Pediatric acute liver failure study group (PALFSG) definition includes both AS-AIH and AI-ALF, and gives a single, easy-to-use, familiar terminology [4, 5, 9, 15, 30]. This consensus group agreed that the usage of PALFSG definition would be more appropriate in such settings. Of the total AIH cases, the proportion that developed severe acute AIH in adults range from 3 to 33%, while the same in the pediatric age group is 7–21% [4, 5, 9, 15, 30, 169–173]. (Table 1). There are diagnostic difficulties in this set of patients—the simplified score may classify a significant proportion of these patients as probable (50–83%) [5, 169–173], IgG may be normal in up to 53% [167–173], and 0–43% of these patients are seronegative [5, 167–173]. Liver histological features include centrilobular necroinflammation, central perivenulitis, interface hepatitis, lymphoid aggregates, and massive hepatic necrosis [167–173] (Supplementary Table 3). Liver biopsy via the transjugular route is feasible and safe in children with severe acute presentation of AIH [174].

A meta-analysis of 61 studies on 335 pediatric AI-ALF patients (67% females with a median age of 10 years) showed that 60% survived with their native liver, while 35% underwent LT and 5% died without LT. Steroids plus other immunomodulators (azathioprine or cyclosporine) were received by 31% of patients and were associated with 2.5 times increased chance of SNL than usage of steroids alone (in 18.5%). Type of AIH reported in only 68 patients revealed that 63% were Type 1, which was associated with 3.3-fold increased odds of SNL in comparison to Type-2 AIH on multivariate Cox regression analysis. However, the

Table 9 Studies on long-term outcome of autoimmune hepatitis in children with autoimmune hepatitis

Study	Number of patients	FU duration	Dev of ASC in FU	Cirrhosis PHT	Relapses	SNL and its predictors
Radha-Krishnan et al. (2010) (USA) [156]	33 AIH	Median 73 months (11–344 months)	–	Cirrhosis 55% Vx 18%	–	5 and 10 years: 66% and 58% LT 9 (27%) Shorter survival related to weight loss at presentation, baseline high bilirubin, prolonged INR and LKM-1 positivity
Jiménez-Rivera et al. (2015) (Canada) [31]	159 AIH	Mean 4 ± 2 years	–	Cirrhosis 30/150 (20%)		5 years: 95% without cirrhosis and 88% with cirrhosis LT 9, Deaths 4
Rodrigues et al. (2016) (Brazil) [30]	134 AIH (28 ASC)	Median 6.1 years (2.8–10.5) years	28 (21%)	Cirrhosis 68%	39% in AIH and 52% in ASC	5 and 10 years: 94% and 80% (16 deaths, 11 LT) Cirrhosis associated with poor survival Outcome unrelated to presence of ASC
Jain et al. (2017) (India) [5]	70 ALF = 15 Non-ALF = 55)	Median: 43 months (0.5–120 months)	–	Cirrhosis in 18/48 (37.5%) Splenomegaly 40/55 (73%)	–	78.6% Poor outcome in AI-ALF Outcome unrelated to seropositivity
Sood et al. (2018) (India) [4]	85 AIH = 70 ASC = 15	Median 16 months (1–80 months)	–	Cirrhosis 75% PHT 75% Vx Bleed 7%	19%	68/80 (85%) LT = 6, deaths = 6 Outcome comparable in AIH and ASC
Di Giorgio et al. (2020) (UK) [15]	83 AIH = 54 ASC = 29 Type 1 = 68 Type 2 = 12	Median 14.5 years (10.4–16.8 years)	3 (5.5%)	Cirrhosis 29% Splenomegaly 71% Low platelets 28%	31%	5, 10, 15 and 20 years: 95%, 88%, 83% and 74% (11 LT) Predictors of LT/death: relapse on treatment, non-responders, ASC Not affected by presence of cirrhosis or cholangiolitic changes on liver biopsy
Maggiore et al. (2023) (France and Italy) [32]	117 AIH Type 1 = 65 Type 2 = 52	Median: 20 years in survivors	2 (1.7%)	Cirrhosis 68% Vx at diagnosis 21/49 (43%) Vx at last FU 32/49 (65%)	57% (1 to > 5 relapses)	10, 20 and 30 years:—88%, 72% and 61% (23 LT, 17 Deaths) Predictors of SNL: male gender, absence of ascites or cirrhosis, normal INR throughout FU Not affected by Type 1 or 2 AIH

AI-ALF autoimmune acute liver failure, AIH autoimmune hepatitis, ALF acute liver failure, ALT alanine aminotransferase, ASC autoimmune sclerosing cholangitis, Dev development, FU follow-up, INR prothrombin time international normalized ratio, LKM liver kidney microsomal antibody, LT liver transplantation, PHT portal hypertension, Vx varices, SNL survival with native liver

studies included in this meta-analysis were small and heterogeneous in terms of usage of definitions, treatment protocols, and end-points [175]. Response to steroids has been assessed in adults using various predictors and prognostic scores including SURFASA score (survival and prognostic factors for AS-AIH) [42, 167–173]. Predictors of response to steroids have not been studied in pediatric AIH. However, ISPGHAN guidelines on PALF recommend opting for LT in the presence of advanced (Grade III or IV) HE or lack of response to steroids within 7 days [176].

14.1 Consensus statements

14.1.1 Approximately 7–21% of children with autoimmune hepatitis presents as acute liver failure (LOE 4).

14.2 Consensus recommendations

14.2.1 The transjugular approach for liver biopsy can be used in children in the setting of autoimmune-induced acute liver failure (LOE 4, Weak recommendation).

14.2.2 Steroids should be administered in children and adolescents with autoimmune-induced acute liver failure under careful vigilance (LOE 3, Strong recommendation).

14.2.3 In the presence of advanced (Grade III or IV) hepatic encephalopathy or lack of response to steroids within 7 days, patients should be offered liver transplantation (LOE 4, Strong recommendation).

Seronegative autoimmune hepatitis

SN-AIH presents with symptoms, elevated transaminases, hypergammaglobulinemia, and histological features of AIH but lacks detectable autoantibodies. Data on pediatric SN-AIH, although limited, have reported a wide range of prevalence (mean 19%, range 0–29%) [4, 5, 9, 15, 18, 30, 31, 177–180]. The largest pediatric case series was reported in 2016 from two Italian pediatric liver centers over a 22-year period, showing a prevalence of 17% among 223 children diagnosed with AIH [177]. Two Indian cohorts reported proportions of SN-AIH of 20% and 23% of the overall cohort of pediatric AIH [4, 5]. A retrospective study in adults reported SN-AIH to present with a similar demographical, clinical, and biochemical presentation resembling seropositive AIH [180]. However, SN-AIH may have a predisposition for an acute presentation including acute liver failure [177, 178], though this has not been confirmed in other studies [5, 179].

Currently, there are no established diagnostic algorithms for SN-AIH, and delayed diagnosis can lead to disease progression. All studies diagnosing SN-AIH ensured negative results for conventional autoantibodies, including ANA, ASMA, and anti-LKM-1 [4, 5, 9, 15, 18, 30, 31, 177–179]. Some case series did not perform additional testing for non-conventional autoantibodies [5, 18, 178], while others conducted extensive antibody panels, including anti-LC-1, anti-SLA, myeloperoxidase-anti-neutrophil

cytoplasmic antibody, anti-mitochondrial, anti-tissue transglutaminase, and anti-platelet antibodies, though in varying order [31, 177, 179]. As with seropositive AIH especially in the scenario of non-response to standard immunosuppression, it is crucial to exclude other potential causes, such as viral hepatitis, genetic/metabolic disorders like Wilson disease, multidrug resistance protein-3 (MDR3) deficiency, etc., and drug-induced liver injury. A positive response to immunotherapy supports the diagnosis of SN-AIH. Serum total IgG levels do not reliably differentiate SN-AIH, as they may be normal [178], elevated [5, 18, 179], or decreased [177, 181].

A few studies indicate that some SN-AIH cases become autoantibody-positive over time. In an Indian cohort, 72% of the SN-AIH cases eventually became seropositive within 7 (range 2–54) months [5]. Similarly, Maggiore et al. found that 16% of their SN-AIH cases became seropositive during follow-up [177]. In adult patients, Czaja et al. reported that 50% of ASMA-negative and 60% of ANA-negative patients converted to seropositive status within 39 (range 3–83) and 60 (range 3–194) months, respectively [182]. Similarly, Wang et al. reported a seroconversion rate of 23% over 5–26 months [181]. The queries around the frequency of serial testing for autoantibodies in SN-AIH and its interpretation remain unanswered due to the scarcity of literature. SN-AIH responds well to corticosteroids in a similar manner as seropositive AIH, with comparable long-term outcomes in terms of survival with native liver [5, 177, 178].

15.1 Consensus statements

15.1.1 Among children with autoimmune hepatitis, up to 29% are seronegative and this proportion depends on the extent of autoantibodies testing (LOE 4).

15.1.2 Clinical presentation, response to treatment, and outcome of seronegative autoimmune hepatitis are similar to seropositive autoimmune hepatitis (LOE 3).

15.1.3 Seronegative cases at diagnosis can turn seropositive during the course of disease over a period of months to years (LOE 4).

15.2 Consensus recommendations

15.2.1 Seronegative autoimmune hepatitis is diagnosed based on compatible histological features and response to standard immunosuppression (LOE 4, Strong recommendation).

15.2.2 Repeat testing for extended panel of autoantibodies may be considered (LOE 4, Weak recommendation).

Autoimmune sclerosing cholangitis or overlap syndrome

Diagnosis: Autoimmune sclerosing cholangitis or overlap (ASC/overlap) syndrome is characterized by the concurrent presence of features of both AIH and PSC, the evidence

of the latter may be in the form of large duct PSC based on abnormal cholangiography on imaging (magnetic resonance or endoscopic retrograde) or small-duct PSC based on “onion skinning” periductal fibrosis on histology. It has been proposed that all children and adults with AIH and cholestatic clinical or biochemical profiles (pruritus and/or elevated gamma-glutamyl transferase), non-response to first-line treatments, and those with concurrent ulcerative colitis, should be evaluated for ASC/overlap [29, 42, 183–185]. AASLD 2019 guidelines on AIH emphasized that neither the revised nor the simplified IAIHG scoring systems should be used for assessing overlap syndromes [42]. IAIHG 1999 and simplified scores can miss 38% and 48% of ASC/overlap in children [15]. ESPGHAN score correctly diagnosed these children when additional points are given for the presence of peri-nuclear neutrophilic antibodies and cholangiographic abnormalities [29]. A score more than or equal to 7 was useful in diagnosing ASC/Overlap and has been validated in two pediatric cohorts [4, 15].

Natural history and outcome of ASC/overlap syndrome: association with inflammatory bowel disease:

Description of the natural history of pediatric ASC/overlap is limited due to its relative rarity and lack of long-term follow-up studies. ASC/overlap is more frequently reported in children than in adults [186, 187] and concurrently presents with AIH in 18–49% [4, 69, 188]. A recent long-term follow-up study from Birmingham reported that 20% of patients with AIH develop biliary features by adulthood—50% transitioned to PSC and 50% developed ASC/overlap phenotype. There was a strong association between the development of IBD with biliary progression in both these populations [188]. On the other hand, the prevalence of ASC/overlap in childhood PSC ranges from 26 to 63% [45, 184, 189–192]. This association is concurrent in 65% or sequential in a bidirectional way in 35% as reported by one large study [193] (Table 10). In contrast to AIH, most of the studies have reported a male preponderance in ASC/overlap [4, 184, 188, 192–194]. No difference in age at diagnosis between AIH and ASC/overlap has been reported [4, 69, 188].

The prevalence of IBD is highest with PSC (up to 93%) [190, 192, 193], followed by ASC/overlap (34–63%) [69, 184, 188, 192–194] and AIH in children (0–18%) 60,181 [69, 194]. A hypothesis suggests that the development of IBD leads to a dominant PSC phenotype, resulting in a loss of response to immunosuppression. This indicates the continuum spectrum rather than a distinct nature of these three entities—AIH, ASC/overlap, and PSC [186]. However, contrary to this, two studies including the multicentric data reported better SNL and event-free survival with the presence of IBD in children [184, 193].

Portal hypertension and biliary complications are seen in 2–48% and 3–31% of children with ASC/overlap,

respectively [184, 188–194]. Worse liver-related outcomes and higher need for LT have been reported in children with ASC/overlap than with AIH [69, 194]. However, on comparison of ASC/overlap with PSC in children, two studies have given conflicting evidence. The larger study among the two has reported a comparable outcome [189, 190]. Survival with native liver at 5 years ranging from 77 to 97% and event-free survival of 69% has been reported [184, 190–194]. Table 10 shows various studies mentioning the outcome of ASC/overlap from cohorts of children with AIH and PSC.

16.1 Consensus statements

16.1.1 Autoimmune sclerosing cholangitis/overlap syndrome may present concurrently or sequentially with autoimmune hepatitis in children (LOE 4).

16.1.2 Autoimmune sclerosing cholangitis/overlap syndrome has strong association with inflammatory bowel disease (LOE 3).

16.1.3 Children with autoimmune sclerosing cholangitis/overlap syndrome have poorer liver-related outcomes compared to those with autoimmune hepatitis but similar to those with primary sclerosing cholangitis (LOE 3).

16.2 Consensus recommendations

16.2.1 Diagnosis of autoimmune sclerosing cholangitis or overlap syndrome in children should be based on the coexistence of features of autoimmune hepatitis and primary sclerosing cholangitis (LOE 3, Strong recommendation).

16.2.2 Children with autoimmune hepatitis with cholestatic clinical or biochemical profile should be evaluated for concurrent or sequential autoimmune sclerosing cholangitis/overlap syndrome by magnetic resonance cholangiography (LOE 3, Strong recommendation).

16.2.3 European Society of Pediatric Gastroenterology Hepatology and Nutrition 2018 criteria may be useful in the diagnosis of autoimmune sclerosing cholangitis or overlap syndrome in children (LOE 3, Weak recommendation).

Drug and virus-induced autoimmune-like hepatitis

Drug-induced autoimmune-like hepatitis (DI-ALH) is related to several drugs, such as hydralazine, methyldopa, nitrofurantoin, and minocycline [195]. DI-ALH has been defined clinically where IgG, autoimmune markers, and histology may suggest AIH with an unequivocal response to stoppage of the drug, and complete recovery spontaneously or on corticosteroids with no relapses [42, 195]. Convincing evidence links DI-ALH with immune modulators, such as interferon, infliximab, and imatinib, while there is less evidence regarding statins, adalimumab, and diclofenac [196]. Association of DI-ALH with the herb *Tinospora cordifolia* was first reported in 2021 during the COVID pandemic [197] and later in a multicentric trial [198]. When applying the DI-AIH definition, some of the cases fulfilled the

Table 10 Studies on autoimmune sclerosing cholangitis/overlap syndrome in children

Studies	Original cohort N	Number (%) of ASC/ overlap	Age at diagnosis	M:F	IBD in ASC/overlap (%)	Follow-up duration of ASC	Progression complica- tions in ASC/overlap	Outcome of ASC/ overlap
Gregorio et al. (2001) (UK) [69]	AIH 55	27 (49%) 92% Concurrent 1 AIH to PSC, 1 PSC to AIH	11.8 (2.3–16) y	56%	44% (vs 18% in AIH)	6 (2–16) years	Lower bilirubin & AST, higher ALP/ AST ratio than AIH, higher p-ANCA+, less inflammation, more cholangitis on biopsy	Remission in 56% (vs 86% in AIH) 10-year SNL 65% for ASC (vs 100% for AIH)
Sood et al. (2018) (India) [4]	AIH 85	15 (17.6%) All concurrent	14 (9.5, 16.3) y	33%	–	9 (3.5, 24) mo	–	Remission in 60%; overall outcome com- parable to AIH cohort (80%)
Warner et al. (2024) (UK) [188]	AIH 159	41 (26%) 51% concurrent 49% Sequential	11.7 y	43%	34% (0% in type 2 AIH)	16.7 y	67% progressed to PSC (related to high GGT & development of IBD); PHT 48%, decompensation 10%, cholangitis 3%	4 (20%) with progres- sive biliary changes need LT
Curci et al. (2025) (Italy) [194]	AIH 32 + PSC 13	22 (40%)	11.3 (3–16.1) y	27%	55% ^a	6.2 (3.2–11.4) y	PHT 38% & Biliary complications 6% (comparable to PSC); Biliary disease progressed in 41%	LT 6% (0% with AIH, 15% with PSC)
Feldstein et al. (2003) (USA) [45]	PSC 52	14 (35%)	–	–	81% in overall cohort	6.6 ± 4.4 y	–	SNL comparable between ASC & iso- lated PSC
Valentino et al. (2016) (USA) [193]	PSC 120	31/113 (26%) 65% Concurrent 7 PSC to AIH 4 AIH to PSC	14.7 (11–16.5) y	29%	68%	3.7 (1.5–6.9) years	Liver-related outcome (cirrhosis, variceal bleed, and need of ERCP) comparable to PSC Varices 13%, cholangi- tis 3.5%	5-y SNL 97% compara- ble to PSC (94%) Presence of IBD associ- ated with less cirrho- sis, LT & liver-related outcomes
Deneau et al. (2017) (USA) Multicentric [184]	PSC 781	260 (33%) Large duct 83% Small duct 17%	11.3 y	45%	63%\$	5-y follow-up	PHT 25% and biliary complications in 12% (comparable to iso- lated PSC)	5-y SNL 90% (similar to isolated PSC) 5-y event-free survival 69%, was better with small-duct involve- ment and presence of IBD

Table 10 (continued)

Studies	Original cohort N	Number (%) of ASC/ overlap	Age at diagnosis	M:F	IBD in ASC/overlap (%)	Follow-up duration of ASC	Progression complica- tions in ASC/overlap	Outcome of ASC/ overlap
Umetsu et al. (2019) (Japan) [189]	PSC 39	13 (33%)	–	–	–	12 mo	Varices 69%, LT 54%, HPS 23%, Recurrent cholangitis 15%,	Outcome unrelated to presence of IBD, but less SNL in those with ASC/overlap, high Bilirubin & APRI
Joosse et al. (2019) (Dutch) [192]	PSC 86	54 (63%)	11.4 (8.2–14.3) y	39%	76% ^b	5.5 (0.7–14.5) years	PHT and biliary com- plications in 17% each (22% had both)	LT 4%, Death 2% (Com- parable to isolated PSC)
Hensel et al. (2021) (UK) [191]	PSC + IBD 82	59 (72%) ^c Large duct 72% Small duct 28%	–	–	100%	9 (3.3–13.8) y	PHT 2% & biliary complications 5% (comparable to isolated PSC)	LT 3% at 5-y (compara- ble to isolated PSC)
Skarby et al. (2024) (Sweden) [190]	PSC 124	39 (31%) All Type 1 Large duct 95% Small duct 5%	14.4 (6.2–17.8) y	51%	93% IBD in overall cohort	13 (5.7–21.6) y	PHT 19% and biliary complications in 31% (similar to isolated PSC) Less biliary complica- tions in girls and with IBD	LT 23% (higher than isolated PSC 8%; HR 2.85) Need for LT related to SCOPE index (0–3.4%; 4–5: 18%; 6–11: 28%; HR 2.35)

AIH autoimmune hepatitis, *ALP* Alkaline phosphatase, *ALT* alanine aminotransferase, *GGT* gamma-glutamyl transferase, *p-ANCA* peri-nuclear anti-neutrophilic cytoplasmic antibody, *ASC* autoimmune sclerosing cholangitis, *AST* aspartate aminotransferase, *ERCP* endoscopic retrograde cholangio-pancreatography, *IBD* inflammatory bowel disease, *LT* liver transplantation, *M:F* males:females, *mo* months, *PHT* portal hypertension, *PSC* primary sclerosing cholangitis, *SCOPE* sclerosing cholangitis outcomes in pediatrics, *SNL* survival with native liver, *y* years

^aIBD diagnosis was concurrent, before and after the diagnosis of ASC in 58%, 33% and 9%; ^bIBD incidence lower than isolated PSC (82% vs 63%)

^bASC diagnosis was 73% concurrent, 15% before and 12% after the diagnosis of IBD; incidence similar to isolated PSC (76% vs 84%)

^cASC more prevalent in large duct than small-duct PSC (97% vs 9%)

criteria. Further studies on the purity and safety of untested herbals in the market are an urgent need [199].

Hepatitis A (HAV) and Epstein–Barr virus (EBV) infections can act as potential triggers for immune-mediated hepatic damage akin to DI-ALH [200]. In Indian children, HAV-induced autoimmune-like hepatitis has been reported with higher AST levels, presence of autoantibodies, and histological evidence in the form of severe zone 3 perivenulitis and marked pseudorosetting [201].

17.1 Consensus statement

17.1.1 Drug and virus-induced autoimmune-like hepatitis resemble typical autoimmune hepatitis clinically, biochemically, and serologically, with the majority resolving spontaneously following discontinuation of incriminating drug or with a short course of steroids (LOE 4).

De novo autoimmune hepatitis

De novo-AIH (dn-AIH) was first reported by Kerkar et al. in 1998 in 4% of children following LT for indications other than AIH. De novo-AIH is a diagnosis of exclusion, characterized by elevated transaminases, presence of autoantibodies, raised IgG, and response to the immunosuppression used to treat AIH in children transplanted for non-AIH causes [202]. Subsequently, various centers have reported dn-AIH in 1–7% of recipients with a median time to development ranging from 1 to 15 years [203–211]. The liver histology of these patients had dense lymphoplasmacytic portal tract infiltrate, periportal hepatitis, and bridging collapse, similar to AIH. Diagnosis of dn-AIH is made following exclusion of all other causes of graft dysfunction, including cellular and antibody-mediated rejection. The proposed pathogenesis of dn-AIH is related to the re-stimulation and re-expansion of the pool of memory T cells in the transplant recipient. In 2016, the Banff working group proposed the term “Plasma cell rich rejection” to replace dn-AIH [212]. This term was used in adults, and it would be inappropriate to use this nomenclature for very carefully categorized pediatric LT recipients who fulfill criteria of AIH based on IAIHG scoring [213]. Risk predictive factors for dn-AIH are non-adherence to immunosuppression (leading to erratic levels), usage of calcineurin inhibitors [208], anti-Glutathione-S-transferase T1 (GSST1) antibodies (alloantigen) [214], and presence of non-tolerant DQ donor-specific antibodies [215]. The presence of DQ donor-specific antibodies was associated with dn-AIH with an odds ratio of 12.5 [215]. Recurrent episodes of rejection and viruses like Epstein–Barr virus, cytomegalovirus, and Parvovirus B19 have also been mentioned as potential triggers for dn-AIH [210].

Graft loss secondary to dn-AIH can reach up to 50% necessitating a re-transplant. For the treatment of dn-AIH, prednisolone along with azathioprine are recommended as the first line of therapy. Low-dose steroids should be continued on a long-term basis [216]. If there is absence of response, then azathioprine can be replaced with MMF or

tacrolimus. It is advisable to target a lower than conventional trough levels of tacrolimus, in the setting of a dn-AIH. Nearly 60% of non-responders develop progressive fibrosis and 25% require re-transplantation [217]. Recently, researchers have proposed that newer biomarkers could lead to advances in personalized management of these children [218].

18.1 Consensus statements

18.1.1 De novo autoimmune hepatitis can occur in 2–7% of pediatric liver transplant recipients after 1–15 years of liver transplantation (LOE 5).

18.1.2 Usage of tacrolimus, recurrent episodes of rejection, and viral infections have been proposed as potential risk factors for the development of de novo autoimmune hepatitis (LOE 5).

18.2 Consensus recommendations

18.2.1 De novo autoimmune hepatitis should be diagnosed on the basis of suggestive liver histology, corroborated with raised immunoglobulin G and autoantibody positivity, along with exclusion of other known causes of graft dysfunction including cellular and antibody-mediated rejection (LOE 5, Strong recommendation).

18.2.2 Treatment of de novo autoimmune hepatitis is like conventional autoimmune hepatitis. Lower tacrolimus trough levels should be targeted (LOE 5, Strong recommendation).

Recurrence of autoimmune hepatitis after liver transplant

Disease recurrence after LT is a challenge and affects graft and overall survival. Recurrence of AIH after LT reportedly ranges from 16 to 28% in adults [219–224] and 0–39% in children [33, 225–228]. The time of recurrence of AIH varies from as early as 1 month to as late as 20 years after LT. Risk factors for AIH recurrence include high grade necro-inflammatory activity in the explant, higher levels of IgG before LT, younger age at LT (≤ 42 years), usage of MMF, and donor-recipient gender mismatch (particularly female-to-male donation) [220, 221, 223]. Other risk factors with conflicting or insufficient evidence are presence of HLA-DR3/DR4 in the recipient, first-degree living donor, acute cellular rejection episodes, stoppage of steroids after LT, and presence of overlap syndrome [33, 219, 221–224, 227, 228]. Performing annual protocol liver biopsies has been shown to reduce the incidence of recurrent AIH, but is not a standard practice at most of the centers [219, 223]. The diagnosis of recurrent AIH is based on excluding other causes of graft dysfunction, such as rejection, vascular, biliary, and infective causes, along with suggestive histology, which includes the presence of lymphoplasmacytic infiltrate in the lobule and portal tracts along with interface hepatitis; acidophil bodies may also be observed [219, 220]. Serological markers and IgG

levels are less reliable in post-LT setting [223]. Natural course of recurrent AIH is variable from slow [219, 220] to rapid progression to cirrhosis and need for re-transplantation [223–225, 227, 228]. Treatment of recurrent AIH includes reintroduction or increase in the dose of steroids and modification of immunosuppression [220, 225, 227, 228].

After LT for ASC/overlap syndrome, one should be careful about the recurrence of sclerosing cholangitis in the graft. Data comes from studies on PSC where the reported recurrence rates are 10–37% of adults and 26% of children 18–36 months after LT [221, 229, 230]. Diagnosis of ASC/overlap recurrence should be based on a compatible histology of AIH along with biliary changes on imaging in the absence of vascular, immunological and biliary causes [229]. There is limited data on outcome of recurrent ASC/overlap, however extrapolation of data from recurrent PSC (graft survival rates of 90%, 81%, and 63% at 1, 2, and 5 years) suggests poor outcome [230].

19.1 Consensus recommendations

19.1.1 Pediatric liver transplant recipients transplanted for autoimmune hepatitis and presenting with graft dysfunction should be monitored for autoantibodies and immunoglobulin G levels keeping a high index of suspicion for recurrent autoimmune hepatitis (LOE 4, Strong recommendation).

19.1.2 Liver histology is essential to make a diagnosis of recurrent autoimmune hepatitis. (LOE 4, Strong recommendation).

19.1.3 Treatment of recurrent autoimmune hepatitis warrants an increase and/or modification of immunosuppression (LOE 4, Strong Recommendation).

Conclusion

This comprehensive document, crafted by the members of the Indian Society of Pediatric Gastroenterology, Hepatology, and Nutrition alongside international experts, synthesizes extensive data research and critical evaluations. It categorizes statements and recommendations based on the quality of evidence available in the literature, ensuring that healthcare professionals have access to reliable information tailored to specific clinical scenarios in AIH. A simplified, algorithmic approach to managing these children is presented, encompassing induction and maintenance therapy, as well as strategies for difficult-to-treat cases and salvage treatments. Guidance on the timing and process of immunosuppression withdrawal is also included. This guidance offers detailed recommendations for challenging cases, including severe acute presentations of AIH, SN-AIH, and ASC/overlap syndromes, with brief coverage of post-transplant de novo and recurrent AIH.

Future directions

It is necessary to identify areas in AIH that need to be addressed to improve the overall outcomes of both AIH and ASC/overlap syndrome, enhance quality of life, and prevent post-LT recurrence of AIH and dn-AIH [231]. As recently reported, molecular chaperones can facilitate the processing of environmental antigens that could trigger AIH, affecting the occurrence, severity, and outcome of AIH [232]. Certain molecular chaperones can modulate the immune response by favoring the development of regulatory T cells (Tregs) or down-regulating the transcription of pro-inflammatory cytokines via the nuclear factor kappa B pathway [233, 234]. Clarification of their contributions to the immune mechanisms could have therapeutic implications.

AIH lacks a quantifiable biomarker that closely reflects its pathogenic mechanisms and that can be used to monitor treatment response. As reviewed recently, the various biomarkers showing potential are adenosine deaminase, cytokeratin-18 death marker m 65, transforming growth factor (TGF beta-1), B-cell activating factor, anti-asialoglycoprotein receptor, ratio of Forkhead Box P3 (FOXP3, biomarker of regulatory T cells) and Retinoic acid-related orphan receptor gamma t (ROR gamma t, transcription factor for the development/function of TH17 cells), deoxyribonuclease I, ferritin, ratio of CD74 and macrophage migration inhibitor factor (MIF), and the vitamin D receptors [235]. As in adults, the programmed cell death protein-1 (PD-1) pathway is associated with pediatric AIH activity. At diagnosis, children with AIH had significantly higher levels of soluble PD-1 compared to other liver diseases, and this positively correlated with liver fibrosis stage [236]. Furthermore, soluble PD-1 levels were significantly higher in pediatric patients with AIH with active disease compared to those in remission [237]. Proteomic profile of pediatric AIH compared to controls revealed 16 proteins which can be considered as potential biomarkers of AIH. Future studies in larger cohorts of newly diagnosed patients are warranted to validate the findings [238].

Gut dysbiosis leads to a decrease in secondary bile acids, short-chain fatty acids, and polyamines, while increasing lipopolysaccharide, branched-chain amino acids, tryptophan metabolites, amino acids, and bile acids. This imbalance can disrupt immune homeostasis, resulting in abnormal activation of the immune system [239]. Exploring this can have clinical implications for treating AIH with drugs that target intestinal dysbiosis and related signaling pathways. One such Chinese drug (Yinchenhao decoction) decreased the transaminase activity (AST and ALT), autoantibodies (LC-1 and LKM-1), and tumor necrosis factor-alpha, IL-12, and IL-17 levels in AIH mice by reversing the dysbiosis,

affecting the release of short-chain fatty acids (especially butyric acid) and could also decline the ratio of T-helper 1 and Tregs [240]. New therapeutic modalities like IL-2 and increasing Tregs can improve the prognosis of AIH [241]. Mesenchymal stem cell endoplasmic vesicles therapy decreases activation of CD4 + T cells and increases mitochondrial phosphorylation by transferring mitochondrial proteins in mice [242].

A study treating AIH mice with a mix of Bifidobacterium and Lactobacillus probiotics found that the higher differentiation of Tregs for immune tolerance improved the intestinal barrier function [243]. Significant reduction in Bifidobacterium in the gut microbiota of AIH patients was noted to be associated with a failure to achieve remission [244]. Studies are also needed to explore the role of bacteriophages as they can also regulate the immune system by interacting with host cells, promote immune tolerance, and reduce autoimmune responses. Therapeutic fecal microbiota transplantation in AIH mouse models exhibited reduced liver injury, improved follicular Tregs and T-helper cells in the spleen, decreased serum AST, ALT, and bilirubin levels, and effectively restored gut microbiota dysbiosis [245].

Future studies are needed that re-strengthen and expand the above-mentioned observations in AIH. There is a need for the incorporation of genetics into diagnostic scores to overcome diagnostic ambiguity. Multi-center randomized-controlled trials are needed to compare various therapeutic modalities for induction as well as maintenance of AIH and to identify interventions that can reduce risk, severity, and relapse. The management and outcome of AIH and the overall well-being of patients with AIH will continue to improve as understanding of its pathogenic mechanisms, therapeutic molecular interventions, and adjunctive measures advances.

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