

# EASL Clinical Practice Guidelines: Autoimmune hepatitis<sup>☆</sup>

European Association for the Study of the Liver\*

## Introduction

Autoimmune hepatitis (AIH) was the first liver disease for which an effective therapeutic intervention, corticosteroid treatment, was convincingly demonstrated in controlled clinical trials. However, 50 years later AIH still remains a major diagnostic and therapeutic challenge. There are two major reasons for this apparent contradiction: Firstly, AIH is a relatively rare disease. Secondly, AIH is a very heterogeneous disease.

Like other rare diseases, clinical studies are hampered by the limited number of patients that can be included in trials. Possibly and more importantly, the interest of the pharmaceutical industry to develop effective specific therapies for rare diseases is limited due to the very restricted market for such products. The wide heterogeneity of affected patients and clinical manifestations of the disease limits both diagnostic and further therapeutic studies. AIH's age spectrum is extremely wide, it can affect small infants and can manifest for the first time in octogenarians. AIH can run a very mild subclinical course or be very acute, rarely leading to fulminant hepatic failure. AIH sometimes demonstrates quite dramatic disease fluctuations with periods of apparent spontaneous remissions, acute flares and/or smouldering disease. AIH can be associated with a number of other hepatic conditions, in particular the cholestatic liver diseases; primary biliary cirrhosis (PBC) or primary sclerosing cholangitis (PSC), but also with drug-induced liver injury (DILI), alcoholic or non-alcoholic steatohepatitis (NASH) or viral hepatitis. Each condition provides special diagnostic and therapeutic challenges. Despite these challenges and complexities, diagnosis and treatment of AIH has seen

striking progress, and now patients in specialised centres have an excellent prognosis, both in respect to survival and to quality of life.

The aim of the present Clinical Practice Guideline (CPG) is to provide guidance to hepatologists and general physicians in the diagnosis and treatment of AIH in order to improve care for affected patients. In view of the limited data from large controlled studies and trials, many recommendations are based on expert consensus. This is to some extent a limitation of this EASL-CPG, but at the same time it is its special strength: consensus in this guideline is based on intensive discussions of experts from large treatment centres. The core consensus group has experience of over one thousand AIH patients managed personally, and the recommendations have been reviewed by both the EASL Governing Board as well as external experts, who have a similarly wide personal experience. Therefore, the guidelines are a resource of information and recommendations based on the largest experience available thus far. At the same time, we formulate key scientific questions that result from the consensus discussions on the limitations of our knowledge. All recommendations of this CPG were agreed upon unanimously (100%) consensus. Grading of the recommendations is based on the GRADE system for evidence (Table 1) [1].

## Epidemiology of AIH

AIH is a non-resolving chronic liver disease that affects mainly women and is characterized by hypergammaglobulinaemia even in the absence of cirrhosis, circulating autoantibodies, association with human leukocyte antigens (HLA) DR3 or DR4, interface hepatitis on liver histology, and a favourable response to immunosuppression [2–5]. The disease, if untreated, often leads to cirrhosis, liver failure and death.

AIH is considered relatively rare, as its prevalence ranges from 16 to 18 cases per 100,000 inhabitants in Europe [6–11]. Until recently, the incidence and prevalence of AIH on a population-based level was assessed in only two studies [6,9]. Interestingly however, higher prevalence rates have been reported in areas with quite stable populations. For instance, prevalence rates of 42.9 cases per 100,000 and 24.5 cases per 100,000 inhabitants have been reported in Alaska natives [12] and New Zealand [9], respectively. In addition, a large Danish nationwide population-based study assessed the incidence and prevalence of AIH in Denmark during a nearly 20 year time period ranging from 1994 to 2012 including 1721 AIH patients [13]. The most striking observation in that study was the marked increase in AIH incidence over time, which could not be attributed to a relative

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**Abbreviations:** ACG, American College of Gastroenterology; AGA, American Gastroenterological Association; ANCA, Antineutrophil cytoplasmic antibodies; APECED, Autoimmune polyendocrinopathy-candidiasis ectodermal dystrophy; AS, acute severe autoimmune; CNI, Calcineurin inhibitor; CPG, Clinical Practice Guideline; DEXA, Dual energy x-ray absorptiometry; DILI, Drug-induced liver injury; HAI, Hepatitis activity index; HBV, Hepatitis B virus; HLA, Human leukocyte antigens; HRQoL, Health related quality of life; IBD, Inflammatory bowel disease; IgG, Immunoglobulin G; LBR, Live birth rate; LT, Liver transplantation; MMF, Mycophenolate mofetil; MRCP, Magnetic resonance cholangiopancreatography; NAFLD, Non-alcoholic fatty liver disease; NASH, Non-alcoholic steatohepatitis; PBC, Primary biliary cirrhosis; PROM, Patient reported Outcome Measures; PSC, Primary sclerosing cholangitis; SCBU, Special care baby unit; SMA, Smooth muscle antibodies; TPMT, Thiopurine methyltransferase.



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**Table 1. Grading of recommendations.**

I	Randomised controlled trials
II-1	Controlled trials without randomisation
II-2	Cohort or case-control analytic studies
II-3	Multiple time series, dramatic uncontrolled experiments
III	Opinions of respected authorities, descriptive epidemiology

Adapted from: [1].

change in case ascertainment rates. Actually, the incidence rate of AIH in Denmark has nearly doubled between 1994 to 2012, reaching a point prevalence in 2012 of 24/100,000 (35/100,000 for females) [13].

AIH prevalence and clinical expression seem to vary according to ethnicity. Alaskan natives appear to have a high frequency of acute icteric disease at the disease onset [12], and the disease is more common and more severe in North American Aboriginal/First Nations populations compared with predominantly Caucasian, non-First Nations populations [14]. African-American patients more commonly have cirrhosis, a higher frequency of treatment failure and higher mortality than white American patients [15,16]. Mexican Mestizos commonly show cirrhosis at initial evaluation [17] and patients of Hispanic origin are characterized by an aggressive presentation both biochemically and histologically with a very high prevalence of cirrhosis and cholestatic features [18,19], whereas patients of Asian or other non-European Caucasoid background have very poor outcomes [18,20]. Although most of the above mentioned studies are retrospective and have been performed in tertiary centres, these observations have led to the assumption that AIH has diverse clinical phenotypes and outcomes in different ethnic groups within a country and between countries. These differences may reflect genetic predispositions, indigenous etiological agents, and/or pharmacogenomic mechanisms, but they might also be primarily due to complex socioeconomic reasons such as variations in the delivery of health care, delayed diagnosis as well as competing risk factors [21].

1. Prevalence of AIH ranges from 15 to 25 cases per 100,000 inhabitants in Europe and is increasing in both women and men (II-2)  
AIH can affect all populations and all age groups (II-2)

## Clinical spectrum

### Clinical features of AIH

In the early 1950s, a novel type of chronic hepatitis with several particular features, such as a predilection for young women, a progressive and usually fatal outcome accompanied by arthralgia, endocrine dysfunction, cutaneous striae and acne, and very high levels of immunoglobulins in the serum that correlated with an excess of plasma cells in the liver, was reported firstly by the Swedish physician Jan Waldenström [22] and later by Kunkel *et al.* [23]. In 1955, the lupus erythematosus cell phenomenon

was demonstrated in these patients and therefore, the term “lupoid hepatitis” was introduced by the group of Ian Mackay in 1956 [24], but ten years later this term was replaced by ‘Autoimmune hepatitis’ [25], which after a variety of different terms was accepted in the 1990s by the International AIH Group (IAIHG) as the final one [26].

It is now well established that AIH is a clinically distinct syndrome characterized by a large heterogeneity of clinical, laboratory and histological manifestations (Table 2). Therefore, AIH should be considered in any patient with acute or chronic liver disease, particularly if hypergammaglobulinemia is present, and if the patient has features of other autoimmune diseases (Table 3) [2–4,26–28]. The disease can also affect males (ca. 25–30% of all AIH patients) and may present at any age and in all ethnic groups [8–13,29–33]. In most studies, a bimodal age pattern at presentation has been reported with one peak during childhood/teenage years and another in middle age between the 4th and 6th decade of life [8,11,13,33,34]. Recent studies have shown that an increasing number of patients are diagnosed also at older ages (above 65 years) [30–32,35]. Recently it has been shown that appropriate attention should also be paid to the health related quality of life (HRQoL) parameters, since a high rate of previously unrecognised mental impairment with depression and anxiety symptoms are present in patients with AIH [36].

The spectrum of clinical manifestations is variable, ranging from no obvious signs or symptoms of liver disease to a severe and almost identical form of an acute or even fulminant episode of viral hepatitis (Table 2) [3,4,37]. Indeed, approximately 25% of patients present with an acute onset of AIH, which is phenotypically similar to acute hepatitis cases of other causes [33,38]. However, acute presentation of AIH actually may contain two different clinical entities. One is the acute exacerbation of chronic AIH (acute exacerbation form of undiagnosed or misdiagnosed AIH cases) and the other is the genuine acute AIH without chronic histological changes (acute form of AIH; Table 2) [33,37–39]. Of note, in some patients with acute presentation of AIH, immunoglobulin G (IgG) levels may be within the normal range and antinuclear (ANA) and/or smooth muscle antibodies (SMA) as first screening may be negative and thus, the clinician may not consider AIH [3,4,34,40,41]. A more extensive and sensitive autoimmune liver serology testing could be helpful in such cases. Furthermore, in some patients autoantibodies may only become positive some months later in the disease course. Some of these acute cases of AIH may rarely progress to acute liver failure and this should be kept in mind. The identification of AIH as the aetiology of acute hepatitis and/or fulminant hepatic failure is very important because a delay of the diagnosis and thus delay of initiation of therapy results in poorer prognosis of AIH, whereas administration of immunosuppression with steroids might avoid the need for liver transplantation (LT) [33,37–39,41–43].

Commonly (about one third of patients), the clinical presentation is characterized by the presence of one or more of several non-specific symptoms listed in Table 2 [8,11,13,18,21,29,33,44,45]. Amenorrhoea is also common whereas maculopapular skin rash and unexplained low-grade fever are rare features. Physical findings may be normal, but sometimes hepatomegaly, occasionally painful, splenomegaly and, when frank cirrhosis has developed, signs and symptoms of chronic liver disease like palmar erythema and spider naevi may be found. In advanced stages, the clinical picture of portal hypertension dominates including

**Table 2. Clinical spectrum of autoimmune hepatitis.**

Characteristic	
Patients affected	<ul style="list-style-type: none"> <li>Any age (with a bimodal distribution usually with peaks around puberty and between 4th and 6th decade although a significant proportion of patients are even older (above 65 years of age))</li> <li>Both sexes (♀: ♂ ≈ 3:1)</li> <li>All ethnic groups</li> </ul>
Presentation of disease at onset	<ul style="list-style-type: none"> <li>Broad range from asymptomatic to acute/severe or even fulminant</li> <li>Most common clinical phenotype of the disease (two thirds of patients) is characterized by an insidious onset either without any apparent symptom or with one or more of the following non-specific symptoms: fatigue, general ill health, right upper quadrant pain, lethargy, malaise, anorexia, weight loss, nausea, pruritus, fluctuating jaundice and polyarthralgia involving the small joints without arthritis, sometimes dating back years</li> <li>Acute onset of AIH does exist (about 25% of patients); there are two different clinical entities (the acute exacerbation of chronic AIH and the true acute AIH without histological findings of chronic liver disease); centrilobular zone 3 necrosis (central perivenulitis) usually present in patients with acute presentation; autoantibodies or other classical features can be absent; not always responsiveness to corticosteroids</li> <li>One third of patients at diagnosis have already developed cirrhosis irrespective of the presence of symptoms due to delay in diagnosis</li> </ul>
Subclassification	<ul style="list-style-type: none"> <li>AIH-1: the more frequent type of AIH (accounts almost for 90% of AIH cases); detection of ANA, SMA or anti-SLA/LP; association with HLA DR3, DR4 and DR13; any age at onset of variable clinical and histopathological severity; rare failure of treatment but variable relapse rates after drug withdrawal and variable need for long-term maintenance therapy</li> <li>AIH-2: accounts for up to 10% of AIH cases; detection of anti-LKM1, anti-LC1 and rarely anti-LKM3; association with HLA DR3 and DR7; onset usually in childhood and young adulthood; clinical and histopathological severity commonly acute and advanced; frequent failure of treatment and frequent relapse rates after drug withdrawal; need for long-term maintenance therapy very common</li> <li>AIH-3: SLA/LP positive, otherwise very similar to AIH-1; often Ro52-antibody positive. Possibly more severe</li> </ul>
Physical findings	<ul style="list-style-type: none"> <li>Depend on the clinical status of the disease ranging from completely normal to signs and symptoms of chronic liver disease and/or portal hypertension</li> </ul>
Complications	<ul style="list-style-type: none"> <li>HCC development in AIH is less common than in other liver diseases, but it does occur; is strictly associated with cirrhosis suggesting surveillance in all cirrhotic patients with AIH</li> <li>Drug-related complications are also significant in up to 25% of patients; these are most commonly related to long-term corticosteroids use or azathioprine toxicity and/or drug intolerance</li> </ul>

AIH, autoimmune hepatitis; HCC, hepatocellular carcinoma; HLA, human leukocyte antigens; ANA, antinuclear antibodies; SMA, smooth muscle antibodies; anti-SLA/LP, soluble liver antigen/liver pancreas antibodies; anti-LKM1, liver/kidney microsomal antibody type 1; anti-LKM3, liver/kidney microsomal antibody type 3; anti-LC1, antibodies against liver cytosol type 1 antigen.

**Table 3. Differential diagnosis of autoimmune hepatitis.**

Other autoimmune liver diseases
- Primary biliary cirrhosis
- Primary sclerosing cholangitis (including small duct primary sclerosing cholangitis)
- IgG4-associated cholangitis
Chronic viral hepatitis
- Chronic hepatitis B with or without hepatitis delta
- Chronic hepatitis C
Cholangiopathy due to human immunodeficiency virus infection
Alcoholic liver disease
Drug-induced liver injury
Granulomatous hepatitis
Hemochromatosis
Non-alcoholic steatohepatitis
α1-antitrypsin deficiency
Wilson's disease
Systemic lupus erythematosus
Celiac disease

ascites, oesophageal varices and portal hypertensive gastropathy, cytopenias due to hypersplenism as well as hepatic encephalopathy.

Up to a third of patients have an insidious onset and gradual progression without apparent symptoms at diagnosis (asymptomatic) and the final diagnosis is usually established during investigation for unexplained elevation of serum aminotransferases on routine testing or testing performed for other reasons [8,11,13,29,31,32,44,45]. However, approximately one third of adult patients and about half of children at diagnosis have already developed advanced disease with the presence of cirrhosis, which in most studies is associated with lower overall survival irrespective of the presence of symptoms or not [8,13,29,44–47]. The latter finding along with the presence of histological evidence of chronic disease on liver biopsy in a proportion of patients with acute presentation imply that they probably have had subclinical disease for a long time [37,38,42]. Actually, this is one important diagnostic challenge, because subclinical disease often precedes the onset of the disease symptoms, whereas long periods of subclinical disease may also occur after presentation.

According to the pattern of autoantibodies detected, a sub-classification of the disease into two or three subtypes has been

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proposed. Initially, two major types, AIH-1 and AIH-2, have been proposed (Table 2). AIH-1 is characterized by the presence of ANA and/or SMA [3,4,27,28,34,40]. AIH-2 is characterized by the detection of specific anti-liver/kidney microsomal antibody type 1 (anti-LKM1) or infrequently anti-LKM type 3 (anti-LKM3) and/or antibodies against liver cytosol type 1 antigen (anti-LC1) [3,4,27,28,34,40]. This distinction was initially based on circulating autoantibodies alone but thereafter other differences have been reported (Table 2). Similarly, the discovery of antibodies against soluble liver antigens (anti-SLA), later found to be identical with previously described antibodies against liver pancreas (anti-LP) and therefore called anti-SLA/LP antibodies, lead to the definition of a third subtype, AIH-3 (Table 2) [48]. Differences between AIH-1 and AIH-3 seemed less pronounced than between AIH-1 and AIH-2, but some authors postulated more severe disease and the need for lifelong immunosuppression in most if not all AIH-3 patients [48–50]. The validity of these sub-classifications, however, is questionable and subject of an ongoing debate [3].

### Specific clinical features and presentations of AIH

#### Variant forms of AIH and cholestatic liver disease

Some patients within the spectrum of AIH present either simultaneously or consecutively, with clinical, biochemical, serological, and/or histological characteristics of PBC or PSC [51]. Vice versa, some patients with a diagnosis of PBC or PSC show or develop features of AIH. So far, several terms have been used to describe these phenomena, in particular “overlap syndromes”, but also “the hepatitic forms of PBC”, “secondary autoimmune hepatitis”,

“autoimmune cholangitis”, “autoimmune sclerosing cholangitis” or “combined hepatitic/cholestatic syndromes” to describe patients with features of both AIH and PBC or PSC [51–54]. A descriptive terminology of these variant forms (e.g. PBC with features of AIH) is probably the most appropriate terminology in the absence of a clear pathogenetic understanding of these variants.

Internationally agreed criteria defining these variant conditions are lacking, and therefore the characteristics of these entities vary between studies making it difficult to give standardised recommendations. Recently, on behalf of the IAIHG, an international working party critically reviewed “overlap syndromes” and found a low sensitivity of the scoring systems for AIH diagnosis (either revised or simplified) in clinically defined “overlap” patients [51], which is in keeping with results of previous studies (Table 4) [55]. As a consequence, use of these AIH scoring systems is not generally recommended for the distinction of these particular patients. Interface hepatitis is a fundamental component of hepatitis and histology is therefore vital in evaluating patients with overlap presentation. The degree of interface hepatitis can be considered a measure of AIH-like disease activity irrespective of co-existence or underlying cholestatic liver disease [51].

The pathogenesis of these “variant forms” is debated and it remains unclear whether this syndrome forms a distinct entity or a variant of PBC, PSC or AIH. It has been suggested that features of AIH develop in patients with immune-mediated cholestatic liver disease and a genetic susceptibility for AIH as shown by the high prevalence of the AIH-susceptibility HLA-genes DR3 or DR4 in PBC patients with features of AIH, leading to the term “secondary AIH” in patients with PBC and overlapping features

**Table 4. Specific characteristics and features of autoimmune hepatitis.**

Characteristic	
Clinical features in special conditions	<ul style="list-style-type: none"> <li>Some patients within AIH spectrum have characteristics of either PBC or PSC (overlap or variant forms); though these conditions really do exist, diagnosis is usually difficult and problematic as internationally agreed criteria are lacking; concurrent cholestatic findings require investigation for AMA and cholangiography (particularly in children - <i>autoimmune sclerosing cholangitis</i>)</li> <li>Presentation of AIH in pregnant women or more frequently after delivery can occur; the disease usually subsides during pregnancy but post-partum exacerbations are common; maternal and fetal complications are similar to general population</li> <li>AIH-like disease can arise after liver transplantation for other liver diseases (<i>de novo</i> AIH)</li> </ul>
Specific characteristics	<ul style="list-style-type: none"> <li>Onset of disease after viral infections (e.g. hepatitis A, Epstein-Barr, human herpes 6, measles) has been described; AIH should be considered as an alternate “emerging” diagnosis in cases with previous viral infections followed by unexplained and prolonged hepatitis</li> <li>Development after administration of drugs, supplements or herbals (drug-induced AIH — difficult to differentiate from DILI); nitrofurantoin and minocycline implicated in most cases; treatment with biological agents has been implicated (TNF-<math>\alpha</math> blockade) as well as after interferon-<math>\alpha</math> for HCV</li> <li>Concurrent autoimmune or immune-mediated diseases in the patient or first-degree relatives are common (Hashimoto thyroiditis - the strongest association, Grave’s disease, vitiligo, alopecia, rheumatoid arthritis, diabetes mellitus type-1, inflammatory bowel disease, psoriasis, systemic lupus erythematosus, Sjögren’s syndrome, celiac disease, panniculitis, mononeuritis, urticaria pigmentosa, Sweet’s syndrome, idiopathic thrombocytopenic purpura, polymyositis, hemolytic anemia, uveitis)</li> <li>An unusual form of AIH occurs in 10-18% of patients with APECED - also known as APS-1</li> </ul>

AIH, autoimmune hepatitis; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; AMA, antimitochondrial antibodies; IAIHG, International AIH Group; DILI, drug-induced liver injury; TNF, tumour necrosis factor; HCV, hepatitis C virus; APECED, autoimmune polyendocrinopathy candidiasis ectodermal dystrophy; APS-1, autoimmune polyglandular syndrome type 1.



of AIH [56]. In this regard, the name “*overlap*” that strongly suggests the presence of two distinct diseases could be a misnomer. It should be kept in mind that “*variant forms*” of AIH should not be over-diagnosed in order not to expose PBC or PSC patients unnecessarily to the risk of steroid side effects.

**Features of both AIH and PBC.** With no codified diagnostic approach, reported prevalence figures are variable, but it is generally assumed that the prevalence of AIH-PBC variant is approximately 8–10% of adult patients with either PBC or AIH [57,58]. The “Paris criteria” are currently the most commonly used tool for diagnosing AIH-PBC variant form as attested by the presence of at least two of the three accepted key criteria of each disease namely, for PBC: 1) alkaline phosphatase (ALP)  $\geq 2 \times$  upper normal limit (ULN) or  $\gamma$ -glutamyl-transpeptidase ( $\gamma$ -GT)  $\geq 5 \times$  ULN; 2) presence of antimitochondrial antibodies (AMA); 3) a liver biopsy specimen showing florid bile duct lesions; and for AIH: 1) alanine aminotransferase (ALT)  $\geq 5 \times$  ULN; 2) serum IgG levels  $\geq 2 \times$  ULN or presence of SMA, 3) a liver biopsy showing moderate or severe periportal or periseptal lymphocytic piecemeal necrosis [57]. Indeed, a recent study [59], has shown that the criteria strictly defined previously by Chazouilleres *et al.* [57] could identify patients with a clinical diagnosis of AIH-PBC “*variant*” with high sensitivity (92%) and specificity (97%). In addition, the 2009 EASL guidelines on the management of cholestatic liver diseases endorsed these diagnostic criteria, but specified that histologic evidence of moderate to severe lymphocytic piecemeal necrosis (interface hepatitis) was mandatory. It was stated that these “*variants*” should always be considered once PBC has been diagnosed and the patient responds poorly to ursodeoxycholic acid (UDCA) because of potential therapeutic implications (i.e. the need of immunosuppression) [60]. Simultaneous presence of features of both diseases is the usual presentation, but it should be noted that occasionally the onset of AIH and PBC is temporally dissociated, usually with PBC presenting first. Interestingly, in most cases, it is possible to define one primary disorder (“*dominant*” disease), usually PBC [51].

**Features of both AIH and PSC.** The co-existence of features of AIH and features of PSC variant has been described both in children and adults and is assumed to exist in a considerable part of mainly young patients with autoimmune liver disease [51–54,61]. Unfortunately, diagnostic criteria for these conditions are even less well-defined than in AIH-PBC variant cases. As a result, reported prevalence figures vary greatly but an approximate prevalence of 7–14% is generally assumed [51]. The diagnosis of large duct PSC should always be established on typical cholangiographic findings, keeping in mind that an intrahepatic biliary tree which simulates a sclerosing pattern can also be observed in any liver disease with extensive fibrosis and nodular regeneration or in cirrhosis [62]. In addition, magnetic resonance cholangiopancreatography (MRCP) may lead to false positive diagnosis due to its limited specificity. Some cases of small duct PSC (normal cholangiogram)-AIH variant forms have also been reported, but it can be argued that approximately 10% of patients with typical AIH, with or without ulcerative colitis, may have histological features of bile duct injury, thus making this diagnosis particularly uncertain [63]. In clinical practice, the diagnosis of AIH-PSC “*variants*” is made in a patient with overt

cholangiographic or histological features of PSC, alongside robust biochemical, serological and histological features of AIH. It appears that patients with features of AIH and PSC also require immunosuppression [64,65].

It should be noted that in children with AIH a specific entity has been described in almost half of patients characterized by lesions of both AIH and sclerosing cholangitis. Thus, the term “*autoimmune sclerosing cholangitis (AISC)*” was introduced by Mieli-Vergani’s group [52] suggesting also the need of an investigation of the biliary tree at least with MRCP in all children with a diagnosis of AIH (Table 4) [52,54]. At present, this variant seems unique for children, as a prospective study in adults with AIH was negative and thus, in the absence of cholestatic indices, MRCP screening does not seem justified in adult-onset AIH [62]. However, particularly in young adults with AIH and cholestatic features, and in AIH patients with remaining cholestasis despite adequate immunosuppression, MRCP for the detection of possible underlying or co-existent PSC is recommended.

**IgG4-related AIH.** In the emerging era of IgG4-related diseases, the role of IgG4 response has been investigated in AIH patients [66,67]. Typically IgG4 disease in the liver manifests as a differential diagnosis of PSC with features of cholangiopathy and jaundice. Despite anecdotal reports from Japan, confirmation is lacking. Therefore it is difficult to judge, if an entity of AIH-like IgG4 disease exists and presents a separate disease entity.

In summary, based on the current, very limited knowledge about the aetiopathogenesis of AIH, PBC, and PSC, definition of diagnostic criteria for these “*variant forms*” of AIH are very difficult to be established and can only be arbitrary. Consequently, patients with autoimmune liver diseases should rather be categorized according to the primary clinical and histological manifestation of the disease as AIH, PBC, or PSC, and additional features of the respective other immune-mediated liver disease should be listed as such (e.g. PBC with features of AIH). In addition, the low prevalence of these variants has made it impractical to perform randomised controlled trials for their management. However, as these variant conditions do occur quite frequently, specific therapeutic considerations may be required in patients with PBC or PSC with features of AIH [68]. In general, features of AIH should be managed like AIH, as untreated AIH has a poor prognosis, but response to therapy is generally very good.

#### DILI and AIH

The relationship between DILI and AIH is complex and not fully understood. In principle, three scenarios are possible [69,70]:

1. DILI with a strong immunoallergic component mimicking AIH
2. AIH mimicking as DILI due to drug exposure in recent weeks and spontaneous improvement after cessation of drug exposure
3. AIH triggered by an offending drug (DILI-induced AIH)

It appears that all three scenarios occur. As both immunoallergic DILI and AIH are presumably mediated by specific immune reactions to antigens in hepatocytes, clinical and histological overlap between these conditions is not surprising. Nonetheless, the differential diagnosis between these conditions

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and the implications for the pathogenesis of AIH are both important.

Drug-induced AIH has been particularly well described for drugs no longer in use such as tienilic acid and dihydralazine [71,72]. Reactive metabolites created through hepatic metabolism of drugs have been shown to bind to cellular proteins such as components of CYP450, i.e. CYP2C9 in the case of tienilic acid and CYP1A2 in the case of dihydralazine. These can then be recognized by the immune system as neoantigens [71,72]. Among drugs still widely used, drug-induced AIH has been well documented for nitrofurantoin and minocycline [73]. When comparing patients with drug-induced AIH to those with genuine AIH, the two groups were found to have quite similar clinical and histological patterns, although the former has lower histological activity and does not seem to require long-term immunosuppression [74].

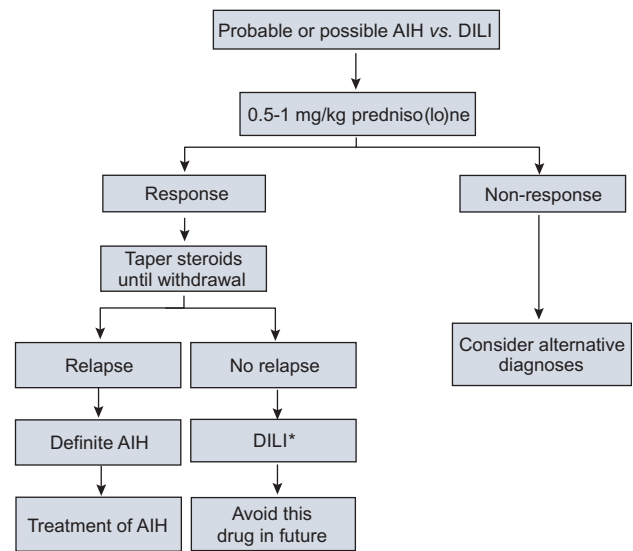
Histologically distinguishing DILI from AIH remains a challenge. A recent study has suggested that sufficient differences exist so that pathologists can use the pattern of injury to suggest a correct diagnosis in many cases [75]. Nevertheless, the differentiation is often very difficult, because DILI lacks a reliable diagnostic test and, like AIH, the diagnosis is mainly based on clinical and serological grounds [76]. Although the frequency of drug-induced AIH-like syndrome is difficult to be assessed, it can account for approximately 9–12% of cases with classical features of AIH [74,77]. An important element in the identification of this syndrome is the patient's history that should focus on recent exposure to drugs that can induce AIH-DILI [74]. In 30% of cases it can be associated with features of hypersensitivity such as fever, rash and eosinophilia [78]. The absence of cirrhosis at presentation can also be an element in favour of AIH-DILI [78]. Severe AIH-DILI usually responds to high doses of steroids in the same way as severe AIH, if treatment is started without delay. Sometimes only the follow-up can differentiate between AIH and DILI: steroid treatment can be discontinued without relapse in DILI, whereas in genuine AIH relapse will occur universally, if immunosuppression is stopped within a few months. A trial of steroid treatment and close observation upon steroid tapering and possible withdrawal is therefore recommended for uncertain cases (see treatment algorithm Fig. 1).

### AIH and pregnancy

The disease is very rarely diagnosed during pregnancy, but, like other autoimmune diseases, may notably manifest in the post-partum period. In patients with known AIH, improvement or even spontaneous remissions during pregnancy can be observed, while flares after delivery are frequently observed [79–84]. This is presumably due to immune reconstitution following delivery. Therefore, the possibility of AIH should be strongly considered in the differential diagnosis of liver dysfunction, particularly accompanied by hypergammaglobulinemia with selective IgG elevation, in the post-partum period, but even during pregnancy, as flares can also occur anytime during pregnancy. Effective immunosuppression has enabled the occurrence of pregnancy in young females with AIH presenting initially with amenorrhea, and immunosuppression should almost always be continued during pregnancy with generally good pregnancy outcome.

### Viral hepatitis and AIH

It has been suggested, that in susceptible individuals, AIH may be induced by viral infections, and a number of possible cases have



**Fig. 1. Suggested diagnostic algorithm for autoimmune hepatitis using routine autoantibody testing by indirect immunofluorescence (IFL) and enzyme linked immunosorbent assay (ELISA) testing with a set of four autoantibodies.** A liver biopsy is always required for the demonstration of inflammatory hepatitis, as well as for staging and grading of the liver disease. \*Long-term follow-up is advised in order not to miss a late relapse of AIH (e.g. 6 monthly for 3 years).

been reported [3,4,85,86]. Molecular mimicry between viral epitopes and epitopes of autoantigens have supported the concept of virally induced AIH. On the other hand, the few cases reported might also represent a diagnostic bias in two forms: firstly, patients with subclinical AIH previously overlooked may become diagnosed when suffering from an acute incidental viral hepatitis; secondly, patients with acute AIH and marked hypergammaglobulinaemia might display false positive results on serology for viral markers. On the other hand, the development of AIH, or of features of AIH, has also been reported in some patients with hepatitis C virus (HCV) after treatment with interferon-alpha [87,88] and rarely in acute HCV infection even after viral clearance [89]. The differentiation between AIH and chronic HCV was a challenge in the past, particularly because of the immunostimulatory side effects of interferon-alpha, but due to the advent of interferon-free treatment regimens, this represents no longer a difficult clinical problem: HCV infection should be treated primarily, and if inflammatory liver disease persists, the diagnosis of AIH should be considered.

### De novo AIH in liver transplant recipients

AIH, or an AIH-like syndrome, can develop after LT undertaken for other liver diseases, both in adults and children. This situation has been called “*de novo AIH*” [90,91], although it has been suggested that alternative nomenclature such as “*post-transplant immune hepatitis*” or “*graft dysfunction mimicking AIH*” or “*post-transplant plasma cell hepatitis*” may be more appropriate as the transplanted hepatocytes are not strictly “self” and thus the conditions not strictly “autoimmune” [5,92]. Nevertheless, the timely recognition of this entity appears to be helpful for avoiding graft rejection, and the need for another LT and for improving long-term survival, as these patients benefit from increased

immunosuppression including steroids and azathioprine like in genuine AIH [90].

*Associated autoimmune conditions*

AIH is associated with the presence of a wide variety of other autoimmune or immune-mediated diseases (Table 4) [8,13,29,45,93–96]. Actually, concurrent autoimmune diseases are common in patients with AIH and mirror the full range of known autoimmune diseases. Therefore, an extended diagnostic screening for other autoimmune diseases, especially autoimmune thyroiditis, seems reasonable in patients with AIH, both at diagnosis and at regular intervals during follow-up [95]. In addition to the patient being affected by immune-mediated diseases, their occurrence is also more frequent in first-degree relatives of AIH patients, and therefore a careful family history should be undertaken. A careful personal and family history may also help in identifying rare variants of AIH due to autosomal recessive genetic aberrations such as the autoimmune polyendocrinopathy-candidiasis ectodermal dystrophy syndrome (APECED) also known as autoimmune polyendocrinopathy syndrome type 1 (APS-1) which is caused by mutations in the autoimmune regulator gene (AIRE) and characterized by chronic mucocutaneous candidiasis, ectodermal dystrophy and autoimmune destruction of several endocrine organs, leading mainly to hypoparathyroidism, adrenocortical failure and gonadal failure in females (Table 4) [8,13,29,45,93–96].

*Complications of AIH*

In principle the complications of AIH are the same as in any other acute or chronic progressive liver disease. In acute presentations the risk of liver failure and infectious complications are predominant and may be aggravated by immunosuppressive treatment. In chronic disease, especially in patients undiagnosed or insufficiently treated, complications of cirrhosis occur. In particular, hepatocellular carcinoma (HCC) is a known consequence of AIH-related cirrhosis although its occurrence in association with AIH is significantly less frequent compared to most other causes of liver cirrhosis (Table 2) [3,11,13,97,98]. A recent population-based study showed that the risk of hepatic and extra-hepatic malignancy was significantly increased in AIH patients [99]. Studies from Denmark, Germany, Netherlands, UK, USA and Japan identified male gender as a particular risk factor, and the presence of cirrhosis was a universal prerequisite for HCC development, which was observed in the at risk cirrhotic population at a rate of 1–2% per year [11,13,97,98,100–102]. Surveillance recommendations have not been validated in AIH and cirrhosis, but as the HCC risk appears to be significant, liver ultrasonography every six months in patients with cirrhosis appears reasonable.

In addition to complications of the liver disease, complications of long-term immunosuppression need to be considered, and the two risks may associate. Of note, extra-hepatic malignancies of diverse cell types occur in 5% of patients in an unpredictable fashion with non-melanoma skin cancers being the most common [99,103]. It is likely that this risk is primarily due to the long-term immunosuppression required in most patients. To what extent the risk for extra-hepatic malignancy is different from the normal population is poorly studied. Nonetheless, it appears sensible to apply routine health screening measures for other malignancies in AIH patients.

2. AIH should be considered in any patient with acute or chronic liver disease, particularly in the context of hypergammaglobulinemia (II-2)
3. Prompt and timely diagnosis is crucial as untreated AIH has a high mortality rate (I)
4. Approximately 1/3 of adult patients and about 1/2 of children with AIH have cirrhosis at presentation (II-2)
5. Acute presentation of AIH can occur and may manifest as acute exacerbation form of previously undiagnosed AIH or new onset acute AIH without histological changes suggestive of chronic disease (II-2)
6. AIH is associated with a broad variety of other autoimmune diseases (II-2)
7. All children with a diagnosis of AIH should undergo (MR-) cholangiography to exclude autoimmune sclerosing cholangitis (II-2)
8. AIH patients with cirrhosis should undergo liver ultrasound in six-month-intervals for HCC screening (II-2)
9. Counselling for UV-protective measures should be considered for patients on immunosuppressants. Dermatological monitoring for non-melanoma skin cancer after long-term immunosuppressant treatment may be considered (III)

**Diagnostic work-up and diagnostic criteria**

The diagnosis of AIH is usually based on the presence of the typical phenotype of the disease along with the exclusion of other causes of chronic liver diseases (Tables 2 and 4). The diagnostic criteria for AIH and a diagnostic scoring system have been codified by a group of experts in the IAHG in 1993 [26], revised in 1999 [27] and more recently proposed in a simplified manner for routine clinical use (Table 6) [28].

Obvious features raise the suspicion of AIH and the application of published criteria (Tables 5 and 6) allows a ready diagnosis [26]. Unfortunately, in a considerable proportion of cases, the diagnosis is challenging and referral to hepatologists with specific clinical expertise in AIH may be warranted. In patients with an insidious onset and gradual progression without apparent symptoms, the diagnosis relies predominantly on laboratory findings. Therefore, the diagnostic work-up rests on such central elements as circulating non-organ specific autoantibodies associated with polyclonal hypergammaglobulinemia and typical or compatible histology in the absence of viral hepatitis markers. Histology is also essential in making the diagnosis.

*Laboratory findings*

A predominantly hepatic pattern, with bilirubin concentrations and aminotransferases ranging from just above the upper limits of normal to more than 50 times these levels, with usually normal or only moderately elevated cholestatic enzymes, is the typical biochemical profile of the disease [4,26–28]. However, the

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**Table 5. Summary of the criteria for the diagnosis of autoimmune hepatitis, on which the 1999 International Autoimmune Hepatitis Group (IAIHG) diagnostic score was based [27].**

Definite AIH	Probable AIH
Normal $\alpha$ -1AT phenotype	Partial $\alpha$ -1AT deficiency
Normal ceruloplasmin level	Non-diagnostic ceruloplasmin/copper levels
Normal iron and ferritin levels	Non-diagnostic iron and/or ferritin changes
No active hepatitis A,B,C infection	No active hepatitis A,B,C infection
Daily alcohol <25 g/day	Daily alcohol <50 g/day
No recent hepatotoxic drugs	No recent hepatotoxic drugs
Predominant AST/ALT abnormality	Predominant AST/ALT abnormality
$\gamma$ -globulins or IgG level >1.5 times the upper normal limit	Hypergammaglobulinemia of any degree
ANA, SMA anti-LKM1 >1:80, in adults and >1:20 in children	ANA, SMA, anti-LKM1 >1:40 in adults
AMA negative	Other autoantibodies
Liver histology	Liver histology
Interface hepatitis moderate to severe	Interface hepatitis moderate to severe
No biliary lesions, granulomas or prominent changes suggestive of another disease	No biliary lesions, granulomas or prominent changes suggestive of another disease

**Table 6. Simplified diagnostic criteria of the International Autoimmune Hepatitis Group [28].**

Feature/parameter	Discriminator	Score
ANA or SMA+	$\geq 1:40$	+1*
ANA or SMA+	$\geq 1:80$	+2*
or LKM+	$\geq 1:40$	+2*
or SLA/LP+	Any titer	+2*
IgG or $\gamma$ -globulins level	>upper limit of normal	+1
	>1.1x upper limit	+2
Liver histology (evidence of hepatitis is a necessary condition)	Compatible with AIH	+1
	Typical of AIH	+2
	Atypical	0
Absence of viral hepatitis	No	0
	Yes	+2

Definite autoimmune hepatitis:  $\geq 7$ ; Probable autoimmune hepatitis:  $\geq 6$ . \*Addition of points achieved for all autoantibodies (maximum, two points). Typical liver histology for autoimmune hepatitis = each of the following features had to be present namely, interface hepatitis, lymphocytic/lymphoplasmacytic infiltrates in portal tracts and extending into the lobule, emperipolesis (active penetration by one cell into and through a larger cell), and hepatic rosette formation. Compatible liver histology for autoimmune hepatitis = chronic hepatitis with lymphocytic infiltration without all the features considered typical. Atypical = showing signs of another diagnosis, like steatohepatitis.

degree of ALT elevation does not reliably reflect severity of AIH at the histological level. Of interest, recent studies have shown that along with the elevations of aminotransferases,  $\gamma$ -GT levels but not ALP can also be increased in AIH and furthermore, might be used as independent predictor of treatment outcome [29,45]. In keeping with the fluctuating nature of the disease, the aminotransferases and  $\gamma$ -GT levels may even spontaneously normalise (spontaneous biochemical remission), despite histological evidence of persisting inflammatory activity, sometimes even severe inflammation. Such spontaneous apparent biochemical remissions are a critical issue that may sometimes result in delay and/or underestimation of the diagnosis, since reappearance of clinical disease may only become obvious several months or years later, or may even be completely asymptomatic. This disease behaviour may sometimes explain the presence of already established cirrhosis in almost one third of patients at the time of initial diagnosis.

Increased serum  $\gamma$ -globulin or IgG levels are found in approximately 85% of patients with AIH even in the absence of cirrhosis [29,104,105]. This prevalence tends to be lower in patients with an acute onset of the disease, in which a higher proportion of patients (25% to 39%) with normal IgG levels has been reported [106,107]. The presence of high IgG levels is a very distinctive feature (IgA and IgM levels are usually normal) [28]. Increased IgA or IgM levels suggest different diseases such as alcoholic steatohepatitis and PBC, respectively.

It is important to underline that the range within which  $\gamma$ -globulins and IgGs are considered normal is wide. This may explain why a proportion of patients may show apparently “normal” IgG levels at diagnosis. Many, if not most of these patients have IgG levels in the upper range of normal, and show a marked fall upon initiation of therapy, sometimes even to levels below the normal range. These patients have a relative increase of their IgG levels considering their very low natural IgG levels but are still within the statistical normal range hampering initial diagnosis. The drop in IgG levels observed during treatment seems to confirm this hypothesis. Indeed, the level of immunoglobulins is an important and useful marker in monitoring the response to treatment and the achievement of remission. Reaching normal levels of immunoglobulins has been shown to correlate well with the improvement of inflammatory activity, even if sometimes a mild inflammatory activity (hepatitis activity index (HAI) 5–6) may coexist with normal IgG levels [108]. Normalisation of both transaminase levels and IgG levels has therefore been agreed upon as diagnostic marker of full biochemical remission [34].

The absence of viral markers is one of the four elements included in the simplified diagnostic criteria for AIH [28], but in countries with a high prevalence of viral hepatitis co-existence of AIH and viral hepatitis may exist [109–111]. In these cases the diagnosis of AIH may be overlooked and AIH could remain untreated, if absence of viral hepatitis is considered a prerequisite for making the diagnosis AIH. Usually AIH has a more aggressive course and more severe prognosis than viral hepatitis (either B or C) and a careful evaluation of the liver biopsy along with liver autoimmune serology testing can help in identifying the co-existence of a double mechanism of liver damage. With the advent of interferon-free regimens for the treatment of HCV infection, the possibility of treating both AIH and viral hepatitis has become



much easier, and in milder cases HCV infection should be treated first and then liver disease reassessed.

Autoantibodies

Autoantibodies are the hallmark of AIH and represent an important part of the diagnostic work-up. Indirect immunofluorescence (IFL) is the preferable and main technique for routine autoantibody testing [112] for all autoantibodies except anti-SLA/LP antibodies (Fig. 2). It should be performed on freshly frozen rodent substrate that usually includes kidney, liver and stomach. This combination allows detection of ANA, SMA, anti-LKM1, as well as the rare antibodies anti-LC1 and anti-LKM3, if anti-LKM1 is absent. At the same time, AMA are also reliably detected by initial IFL screening and can thus help detect co-existent or variant forms of AIH-PBC. Positive sera should be titrated up to extinction. In adults, significant titers are  $\geq 1:40$  dilution by IFL. In children, titers of 1:20 for ANA or SMA and 1:10 for anti-LKM1 are already strongly supportive of the diagnosis of AIH when used in combination with other laboratory and clinical features suggestive of the disease [54]. Other immunochemical techniques like ELISA or immunoblotting are available for the search of autoantibodies such as anti-LKM1, anti-LKM3, anti-LC1 and the only diagnostic tests for anti-SLA/LP, whose exact target antigens have been identified on a molecular level and are used in solid phase assays [4,112,113].

ANA and SMA are markers of AIH-1, which account for about 75% of patients [8,11,29], but are not disease specific and show a wide range of heterogeneity in terms of antigenic specificity,

together with a broad spectrum of titers. The fluorescence pattern of ANA in AIH is usually homogeneous using Hep2 cells but speckled pattern is not infrequent. The antibody is found in 43% of AIH-1 patients [29], and is associated with a variety of antigenic specificities including histones, double-stranded DNA (15%), chromatin and ribonucleoprotein complexes. However, no single pattern or combination is pathognomonic of AIH, whereas investigation for different staining of ANA patterns seems to have no practical clinical implications and diagnostic relevance in routine clinical practice and, therefore, the use of Hep2 cells at the screening stage of AIH is not recommended [112–114]. SMA reacts to several cytoskeletal elements including F-actin with a reported prevalence of anti-actin antibodies in 41% of patients. When kidney sections are utilised as a substrate for IFL SMAvg (vessel/glomeruli) and SMAvgt (vessel/glomeruli/tubules) patterns can be identified, which are frequently associated with, but not pathognomonic of, AIH. They correlate with F-actin antigenicity [112]. In the diagnostic work-up for AIH, SMA/anti-actin antibody testing is appropriate and may also be done by ELISA [114,115]. However, IFL remains superior to ELISA and provides the best specificity/sensitivity compromise for testing for SMA. In fact, actin is not the only target antigen of AIH-specific SMA reactivity and thus ELISA can miss the diagnosis in about 20% of cases [4,112,113,116–118]. ANA and SMA re-activities frequently coexist in the same serum and this improves the strength of the diagnosis.

Anti-LKM1 and/or anti-LC1 are the serologic markers of AIH-2. The two antibodies often coexist and in a series of 38 AIH-2 patients, the reported prevalence was 66% for anti-LKM1 and 53% for anti-LC1, respectively [29]. Unlike the antigen

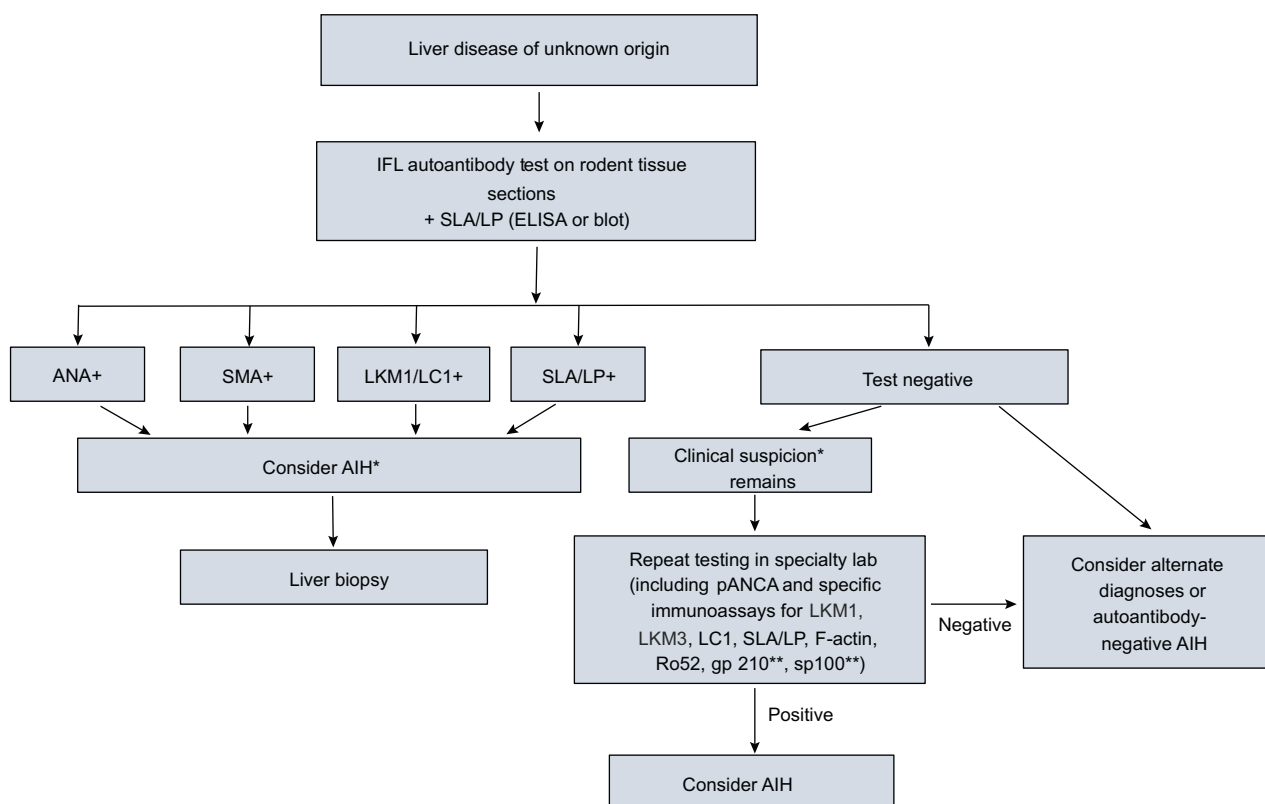


Fig. 2. A case based algorithm for patients with a suspicion of autoimmune hepatitis or drug-induced liver injury (DILI) using a response guided approach. \*Test also for elevated IgG-levels. \*\*These antibodies are highly specific for the diagnosis of PBC.

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heterogeneity seen for ANA and SMA the major target autoantigen of anti-LKM1 has been clearly identified as the cytochrome P4502D6 (CYP2D6) and the formiminotransferase cyclodeaminase (FTCD) for anti-LC1. Despite a well characterized target antigen, neither anti-LKM1 nor anti-LC1 are disease specific, as they have been described in a small proportion (5–10%) of adult and paediatric patients with chronic HCV infection [87,88,119–123]. The presence of homology sequences between CYP2D6 and HCV proteins is the basis for the appearance of anti-LKM1 antibody in HCV patients who are genetically susceptible for AIH (mainly DRB1\*07 positive) through a mechanism of molecular mimicry [124]. Homologies of the target antigen of anti-LKM1 antibodies with other viral proteins have also been observed [5]. Also, anti-LKM1 antibodies have been described in a liver transplant recipient transplanted for Wilson's disease following rejection episodes [125].

Anti-SLA/LP is the only disease specific autoantibody and therefore it has high diagnostic value. The target antigen has been identified as a synthase (S) converting *O*-phosphoseryl-tRNA (Sep) to selenocysteinyl-tRNA (Sec), whose terminological correct label is SepSecS [126,127]. This has led to the development of reliable commercial assays for anti-SLA/LP detection (ELISA and dot-blot) [126,128]. Anti-SLA/LP is detected in approximately 30% of patients with AIH more commonly associated with conventional autoantibodies, and is often associated with anti-Ro52 antibodies [128–132], but sometimes it is the only autoantibody reactivity detectable. Its presence may identify patients with more severe disease and worse outcome [49,50,133,134] though these prognostic associations are controversial [129,132].

Further autoantibody testing may be helpful, in particular for those patients testing initially negative in the above assays. Antineutrophil cytoplasmic antibodies (ANCA) are detected using ethanol-fixed human neutrophils with serum diluted 1:20. Atypical pANCA antibodies, originally considered specific of PSC and inflammatory bowel disease, are also frequently present in patients with AIH-1 [135,136]. Recent evidence indicates that the target antigen is located in the nuclear membrane and for this reason some authors describe these antibodies as perinuclear anti-neutrophil nuclear antibodies (p-ANNA) [137,138]. Their positivity can be an additional element used towards the diagnosis of AIH, particularly if other autoantibodies are negative [27,112]. AMA, the specific serologic marker of PBC diagnosis, can be occasionally detected (8–12%) [139,140] in patients with the classical phenotype of AIH without any other evidence of PBC, and may hint at co-existent or underlying PBC. Nonetheless, these patients should be classified and treated according to their clinical phenotype.

Autoimmune serology remains the Achilles' heel in the diagnostic work-up for AIH. In fact IFL using rodent tissue, which has been indicated by the committee for autoimmune serology of the IAIHG as the best technique for the detection of autoantibodies is time-consuming, requires experienced technicians and is insufficiently standardised. Indeed, in real life the development of in-house validated sections for IFL does not seem to be feasible. Commercial substrates are also available; their quality however is variable. These are treated with fixatives in order to lengthen their shelf life, but this also causes enhanced background staining which can potentially cause difficulties in the interpretation of fluorescence patterns.

Therefore, methods other than IFL, like ELISA, are gaining popularity. This shift has been supported by the introduction of

assays based on recombinant/purified target antigens (CYP2D6, FTCD, SLA/LP, and F-actin). However, the use of ELISA as the sole primary screening test for AIH-related autoantibodies is inappropriate because there is no useful combination of molecular specificities for a dependable detection of ANA and SMA, while the results are interchangeable with IFL for those autoantibodies (anti-LKM1, anti-LC1) whose target antigen has been identified at the molecular level [141]. Fig. 2 provides an algorithm for autoantibody testing in AIH.

Autoantibody titers and specificity may vary during the course of the disease, and seronegative individuals at diagnosis may express the conventional autoantibodies later in the disease course [142,143]; in fact, repeated testing may allow autoantibody detection and, thus, correct disease diagnosis and classification [27,112,113]. In adults, autoantibody titers correlate only roughly with disease activity, clinical course and treatment response [144] and, therefore, they do not need to be monitored regularly unless a significant change in the clinical phenotype does appear. However, in paediatric patients, autoantibody titers may be useful biomarkers of disease activity and can be used to monitor treatment response [145]. In particular anti-LC1 antibodies have been shown to correlate well with disease activity showing a significant decrease in titer (>50%) or disappearance during remission and flare up during relapse [146].

The detection of autoantibodies plays a pivotal role in the diagnosis of AIH. Laboratory personnel and clinicians need to increase their expertise with disease expression and the interpretation of liver autoimmune serology in order to derive maximal benefits for patients. Tests must be ordered specifically on the basis of reliable clinical data and test results must not be interpreted outside the specific clinical context. Only then, can sensible evidence-based decisions be made, and the potential of serological work-up be exploited to the benefit of the patient. Finally, complete work-up for autoimmune serology is not available in all laboratories; it is important to identify laboratories, which are able to fully characterize patients' sera, and patient sera should be sent to such reference laboratories for full evaluation especially in cases of diagnostic uncertainty.

### Histology

Liver biopsy is considered a prerequisite for the diagnosis of AIH [26–28]. Apart from diagnosis, it is used to guide treatment decisions and should be performed before starting treatment, provided there are no contraindications [27,28]. When severe coagulopathy is present the transjugular approach can be used, in particular, in acute/fulminant onset of the disease. Alternatively, biopsy under visual control by mini-laparoscopy has also been shown to be safe [147] even in cases of advanced coagulopathy [148], and may yield additional information [147,149]. Interface hepatitis (hepatitis at the portal-parenchymal interface) with dense plasma cell-rich lymphoplasmacytic infiltrates, hepatocellular rosette formation, emperipolesis (active penetration by one cell into and through a larger cell) and hepatocyte swelling and/or pycnotic necrosis are the typical hallmarks of AIH [28,150,151]. Plasma cells are typically abundant at the interface and throughout the lobule, but their paucity in the inflammatory infiltrate (34% of cases) does not preclude the diagnosis [150,152,153]. However, there is no morphological feature that is pathognomonic of AIH. Interface hepatitis is not

disease specific and patients with drug-related, viral or immune-mediated disease may show similar features.

Panlobular hepatitis, bridging necrosis and massive necrosis all of which are signs of severe inflammatory activity, are present less commonly but are part of the histological spectrum [27] and may occur in acute disease onset. The characteristic histological pattern is panacinar hepatitis (parenchymal collapse) especially in biopsies performed during an acute onset and closely resembles drug-induced hepatitis [154,155]. Alternatively pericentral (Rappaport zone 3) necrosis may be present, which also resembles acute toxic injury [107,156,157]. These histological lesions have recently been proposed by the US NIH Acute Liver Failure Study Group as a set of diagnostic criteria for AIH presented as acute liver failure [37]. Additional features in cases of acute liver failure due to AIH include the presence of portal lymphoid follicles, a plasma cell-enriched inflammatory infiltrate and central perivenulitis [37,107]. Transition from pericentral hepatitis to interface hepatitis has been demonstrated in sequential biopsies from patients with acute disease onset [158]. These observations suggest that the perivenular pattern of injury may be an early histological manifestation of AIH that is missed in biopsies obtained later in the course of the disease. Other lesions such as granulomata, cholangitis, steatosis or steatohepatitis can be seen, but if prominent they reduce the probability of the diagnosis of AIH. An inflammatory lymphocytic infiltrate of bile ducts has been described in 10% of cases but such individuals usually lack clinical, serological and immunological features of PBC, and they respond to corticosteroid therapy as patients with classical AIH [63,159]. At the time of diagnosis different stages of fibrosis are present and about one third of patients already display established cirrhosis [150,151,160]. Macroscopic assessment by minilaparoscopy increases the detection rate of cirrhosis by up to one third, as the macronodular nature of AIH cirrhosis may lead to false negative biopsy results missing the fibrous septa between regenerative nodules [147,161]. Of interest, the histological features of necroinflammatory activity and severity of AIH are often not in parallel with the biochemical activity of the disease [27,28,34,40]. Liver biopsy, therefore, provides information on prognosis and management as for instance the presence of cirrhosis may influence the choice and dose of the immunosuppressive agents prescribed while suggesting the need for regular screening for complications, such as oesophageal varices and HCC. It is highly recommended to have the histology reviewed by an experienced liver histopathologist who should discuss the most difficult cases with the clinician. The pathologist should weigh the inflammatory activity with the aid of the HAI score in order to give a quantitative evaluation of the inflammatory process to be monitored during treatment and follow-up. Despite the growing interest for non-invasive methods for the assessment of fibrosis and inflammation, most studies with these techniques have been performed in the field of viral hepatitis C and very few data are available on AIH. The limits for the clinical use of these methods in AIH, in particular Fibroscan, are related to the interference of necroinflammatory activity in the florid phase of the disease and to the overlap of adjacent stages of fibrosis [162]. A recent proposed non-invasive diagnostic score to predict inflammatory activity and severity of fibrosis based on routine laboratory parameters in AIH provides a useful tool for monitoring disease activity during treatment but cannot at present substitute the need of a biopsy, particularly at diagnosis [163].

*Diagnostic scoring criteria*

A comprehensive scoring system which grades every clinical, laboratory and histological feature of AIH, including response to corticosteroid treatment, has been published in 1999 by the IAIHG [27]. This scoring system was initially developed to define homogeneous cohorts of AIH patients for clinical trials rather than diagnosing AIH in individual patients. This scoring system has been validated in several papers [164–166] and, although developed as a research tool to provide comparability among populations in clinical trials, it has been widely used in clinical practice in assessing patients with few or atypical features of the disease not readily captured by the descriptive criteria [167]. The typical features, on which the diagnostic score is based, are summarized in Table 5. The drawbacks of this scoring system as a clinical tool are its complexity and failure to consistently distinguish AIH from cholestatic syndromes. In 2008, a simplified scoring system designed for every day clinical practice was proposed by the IAIHG [28]. It is based on four parameters: presence and titer of autoantibodies detected by IFL or ELISA (for anti-SLA/LP), serum IgG concentration, presence of typical or compatible histology, and absence of viral hepatitis markers (Table 6). Compared with the original revised score system the simplified score has somewhat lower sensitivity (95% vs. 100%) but higher specificity (90% vs. 73%) and accuracy (92% vs. 82%) [55,166,168,169] and, according to some studies, seems to work well in patients with AIH-PBC variant [168,170]. It does not grade response to corticosteroid therapy [169] whose inclusion has been advocated as an additional criterion, but is primarily meant to serve as a guide for the initiation of treatment, at which time point information on response can naturally not be available. The simplified scoring system is useful in excluding AIH in patients with other conditions and concurrent immune features [166,170], but it is more likely to result in the exclusion of atypical cases [166,169,171]. Prospective evaluation of these criteria is required to corroborate these observations.

In conclusion, the simplified criteria are user-friendly and a good tool for daily clinical practice but without a diagnostic “gold standard” the clinicians must regard any diagnostic score only as an aid to diagnosis of AIH [172] and the criteria should be used alongside clinical judgement. In this context, a subgroup of patients especially those with acute or fulminant onset of AIH may be missed by standard diagnostic criteria and therefore require special attention. Acute or fulminant AIH is characterized by an abrupt onset of symptoms and frequently with acute liver failure. The challenge in the diagnosis is related to the lack of a widely accepted definition [173] and of the phenotype characteristic of AIH. In fact, 25% to 39% of patients with acute onset AIH have normal levels of IgG [106,107] while 9% to 17% test negative for circulating autoantibodies [39,106]. The higher percentage of those patients with normal IgG in this setting can be explained by the short duration of the inflammatory process. A liver biopsy is essential although the classical lesions pathognomonic of AIH are frequently lacking and the most prominent lesion is the pericentral necrosis [37,156–158]. So far, few data are available on the use of the published scoring systems in acute onset of AIH [169,174]. In 70 patients with fulminant liver failure, the revised scoring system supported the diagnosis of AIH in 40% of cases, whereas only 24% were identified by the simplified scoring system [169]. In another series of 55 patients with acute/fulminant

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onset 91% had a score compatible with AIH with the revised scoring system vs. 40% with the simplified version [174]. The use of the diagnostic scoring systems in this setting of patients should be further evaluated prospectively.

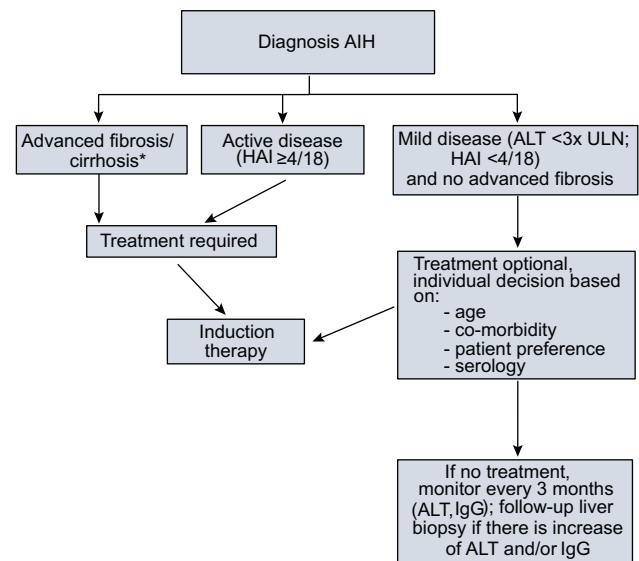
10. AIH is a clinical diagnosis. The diagnosis of AIH relies particularly on the presence of autoantibodies, hypergammaglobulinemia and typical or compatible histology (II-2)
11. The presence of elevated IgG levels, especially in the absence of cirrhosis, is a distinctive feature of AIH. A selectively elevated IgG in the absence of IgA and IgM elevation is particularly suggestive of AIH (II-3)
12. Normal IgG or  $\gamma$ -globulin levels do not preclude the diagnosis of AIH. Most of these patients demonstrate a fall of IgG levels upon treatment (III)
13. Circulating non-organ specific antibodies are present in the vast majority of AIH patients. Autoantibody profiles have been used for sub-classification of AIH.
  - AIH-1 (ANA and/or SMA positive)
  - AIH-2 (LKM1, LKM3 and/or LC-1 positive)
  - AIH-3 (SLA/LP positive).
 The clinical implications arising from this sub-classification are uncertain (II-2)
14. Indirect immunofluorescence is the test of choice for the detection of ANA, SMA, LKM and LC-1. Immunoassays (ELISA/Western blotting) are the tests of choice for the detection of SLA/LP. Methods and cut-off values should be reported by the laboratory (III)
15. Histological demonstration of hepatitis is a prerequisite for the diagnosis of AIH and needs to be part of the initial diagnostic work-up (II-2)
16. There are no morphological features that are pathognomonic of AIH, but interface hepatitis, periportal necrosis, emperipolesis and rosetting of hepatocytes are suggestive of AIH. These features should be reported by the pathologist in addition to grading (hepatitis activity index) and staging of disease (II-2)
17. Pericentral necrosis may be present in the acute onset of AIH and histologically indistinguishable from DILI (II-3)
18. The simplified scoring system (2008) of the IAIHG is a useful tool for every day clinical practice (II-2) By considering response to treatment, the revised scoring system (1999) of the IAIHG can be helpful in diagnosing difficult cases (II-2)
19. Adult patients with AIH and cholestatic lab changes should be considered for (MR) cholangiography to recognize sclerosing cholangitis (II-3)
20. Co-existence of features of AIH and cholestatic liver diseases can be observed, both at diagnosis and during follow-up. Diagnostic tests for PBC and PSC should be performed in patients showing features of cholestasis (II-2)

## Treatment of AIH

The aim of treatment in AIH is to obtain complete remission of the disease and to prevent further progression of liver disease. This requires mostly permanent maintenance therapy, or (only achievable in a minority of patients) induction of a sustained remission following treatment withdrawal.

The current immunosuppressive treatment regimens are based on studies that were mostly published in the 1970s and 80s [175–179]. These studies revealed that untreated, moderate to severe AIH (confluent necrosis on liver biopsy, AST levels  $>5$  times the ULN,  $\gamma$ -globulin levels  $>2 \times$  ULN) had a very poor prognosis and have demonstrated that immunosuppressive therapy improves liver functions tests, ameliorates symptoms and prolongs survival. As these studies were performed before discovery of the HCV they are likely to have included patients with viral hepatitis C.

The benefits of immunosuppressive treatment in asymptomatic older patients with mild necroinflammatory activity on liver biopsy are not well established in terms of clinical endpoints and their management remains controversial (Fig. 3). Treatment related side effects should be counterbalanced to the risk of sub-clinical disease progression and evolution into symptomatic disease as well as the prospect of a complete and sustained response to treatment. Ten-year survival in untreated patients with mild disease was reported to be 67–90% [180,181], and in an uncontrolled study untreated asymptomatic patients had similar survival to those receiving immunosuppression [44]. Thus, a decision not to treat might be justified, especially if there are relative contraindications to the use of steroids. In addition, spontaneous resolution of AIH may occur [182]. However, it also has to be acknowledged that untreated AIH has a fluctuating, unpredictable disease behaviour and a substantial proportion of asymptomatic patients become symptomatic during the course of their disease follow-up [44,183], and progression towards



**Fig. 3. Therapeutic algorithm with case-by-case decisions about commencing steroid therapy, informed by baseline assessments.** For example, a patient with active disease (elevated transaminases  $>3$  normal values and hepatitis activity index (HAI)  $>4/18$ ) requires treatment. \*Treatment probably no longer indicated in decompensated, burn-out cirrhosis, unless high inflammatory score on liver biopsy.



end-stage liver disease with liver failure and development of HCC is possible [181]. In addition, as AIH is a lifelong disease, and progressive fibrosis may take many years to become clinically apparent, the observational studies published may have been too short and may have included too few patients in order to demonstrate the benefit of immunosuppressive therapy in milder disease. The fluctuating course of disease and the danger of subclinical disease progression make it of critical importance, that if patients with mild disease are left untreated, they must nonetheless undergo a regular subsequent monitoring including follow-up liver biopsy, if ALT and/or IgG levels increase or fluctuate (Fig. 3). In symptomatic patients and patients with advanced fibrosis or cirrhosis, treatment should always be initiated as this represents a negative prognostic predictor [44,104,160,184]. In addition, even in advanced fibrosis and cirrhosis substantial regression of scarring after successful treatment has been reported. In view of the progressive nature of AIH and the effectiveness of immunosuppressive therapy, the consensus group recommends that all patients with active disease should receive treatment.

- 21. Treatment of AIH should be aimed to obtain complete biochemical and histological resolution of the disease in order to prevent further progression of liver disease (II-2)
- 22. The management of patients with AIH should also include early recognition of extra-hepatic manifestations and symptoms, and associated autoimmune diseases as well as surveillance for disease specific, and treatment-associated complications (III)
- 23. All patients with active AIH should be treated (I)  
Dosage of therapy should be adapted to the activity of the disease (III)  
Only patients in (spontaneous) remission may not require therapy but must be closely followed (three-six monthly) (III)

Remission induction (Fig. 4)

The survival benefit of corticosteroid therapy with or without azathioprine has been shown in a number of controlled trials performed in the 1960s and 1970s [175–179]. In 1971, Cook *et al.* demonstrated survival benefits of immunosuppressive therapy comparing prednisolone monotherapy (15 mg/day) with placebo. Mortality rates differed markedly (14% vs. 56%) [175]. The results were confirmed in a study from the Mayo Clinic one year later. This study compared prednisone monotherapy (starting with 60 mg/day and reduced to 20 mg over four weeks), azathioprine monotherapy (100 mg/day), combination therapy (prednisone starting at 30 mg/day reducing to 10 mg/day maintenance combined with azathioprine at 50 mg/day) and placebo, [176] the beneficial effect on survival was similar with prednisone monotherapy and prednisone/azathioprine combination therapy (mortality rate: 6% vs. 7% vs. 41% in the placebo group) [179]. However, the combination regimen was associated with fewer side effects (10% vs. 44%) [185]. Histological remission was achieved in 75% of patients after 18 months of active prednisone based treatment but lagged behind clinical and biochemical

remission by several months. This trial further illustrated that azathioprine monotherapy, used as induction therapy, resulted in a high mortality (36%). Murray-Lyon *et al.* also reported a higher mortality rate of azathioprine monotherapy as induction therapy, compared to prednisone (24% vs. 5%) [177].

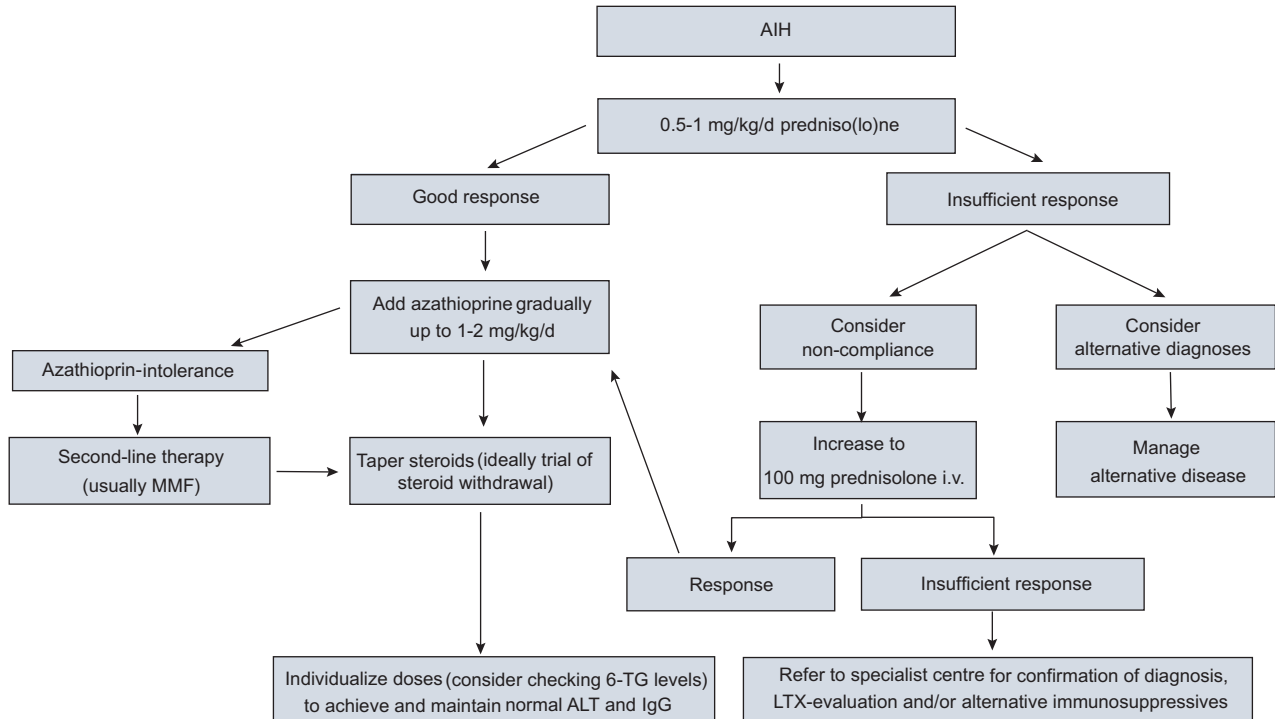
Comparing another strategy with titrated doses of prednisone (starting also at 60 mg/day) to maintain serum transaminase activity at less than twice the upper limit of normal, Summerskill *et al.* showed that this led to less severe side effects compared with the fixed dose regimen (starting with 60 mg/day and reducing to 20 mg over four weeks) with comparable effect on clinical symptoms and biochemical parameters. However, histological remission was achieved in only 25% and 30% after 24 and 36 weeks respectively [186]. In 1982 Tage-Jensen *et al.* demonstrated once more superiority of prednisone monotherapy over azathioprine monotherapy in inducing remission [187].

Despite the limitations of these early studies (no testing for HCV available at that time), they provide compelling evidence that the use of a prednis(ol)one/azathioprine combination regimen has the best profile in combining high efficacy with minimal side effects. Although prednisolone monotherapy and prednisolone/azathioprine combination therapy is considered equally effective [34], frontline combination therapy with use of azathioprine may be preferable, particularly in patients with a high anticipation of side effects such as in post-menopausal women, individuals with emotional instability, pre-existent osteoporosis, brittle diabetes, labile hypertension or obesity. Similarly, young female patients are often concerned about weight gain and cosmetic side effects due to steroid treatment which might adversely affect adherence and outcome. A pragmatic approach to this issue is needed to ensure the best long-term outcomes. A proposed dosing regimen is shown in Table 7. Caution for the use of azathioprine is advisable in patients with malignancy, cytopenia and established thiopurine methyltransferase (TPMT) deficiency (see below) as well as pregnancy, and in these situations, a risk-benefit analysis should be undertaken at an individual patient level (see below).

Additional to the classical prednisolone/azathioprine regimen that are also recommended in the AASLD [34] and BSG guidelines, [40] several slight modifications have been proposed and are being used in clinical practice in many expert centres. A higher dose of prednis(ol)one (up to 1 mg/kg/day) in combination with azathioprine was shown to result in a more rapid normalisation of serum transaminases in patients without cirrhosis [188]. Although the absence of an early fall of transaminases [185,189] and failure to normalise [190–192] are negative predictors of treatment success, this strategy seems promising. It needs to be confirmed that this translates into better long-term outcome and is really suitable for all patients.

Another reasonable strategy is to delay institution of azathioprine and start with prednisone monotherapy. Delaying introduction of azathioprine (usually by about two weeks) can be pragmatically helpful in managing patients with AIH, as it may on the one hand help to resolve diagnostic uncertainties while on the other hand avoids the diagnostic dilemma of discrimination between azathioprine-induced hepatotoxicity from primary non-response. Although hepatotoxicity of azathioprine is uncommon, its frequency is increased in patients with advanced liver disease [3]. In general, treatment of AIH should be response guided and treatment regimens should be individualised

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**Fig. 4. Therapeutic strategy in autoimmune hepatitis.** Treatment requires induction of remission and prolonged maintenance therapy. Induction is delivered by steroids and thiopurines are added as steroid sparing strategy. Laboratory endpoints are normalisation of IgG and ALT. MMF, mycophenolate mofetil.

**Table 7. Treatment proposal for adult patients with AIH (e.g. 60 kg).**

Week	Prednisolone (mg/day)	Azathioprine (mg/day)
1	60 (= 1 mg/kg body weight)	-
2	50	-
3	40	50
4	30	50
5	25	100*
6	20	100*
7 + 8	15	100*
8 + 9	12.5	100*
From week 10	10	100*

Reduction of prednisolone to 7.5 mg/day if aminotransferases reach normal levels and after three-months to 5 mg/day, tapering out at three-four months intervals depending on patient's risk factors and response. \*Azathioprine dose of 1–2 mg/kg according to body weight.

according to the response of the patient and tolerance of treatment. A suggested induction strategy is shown in Fig. 4.

Therapy is aimed to obtain complete biochemical and histological remission. In patients showing a prompt response with complete normalisation of transaminases and IgG within the normal limits of a follow-up, liver biopsy to demonstrate also histological remission is normally not required, as chances of significant inflammatory activity requiring increased immunosuppression are very low. Follow-up biopsy is, like any invasive procedure, recommended, if a change of management is somewhat likely to result from the procedure; this is particularly the case in patients with sub-optimal response to immunosuppression, and in patients with treatment side effects. In these cases,

individual risk assessment of disease progression needs to be weighed against (possible) treatment side effects, and assessment of disease grading can help in this. Ongoing studies suggest that Fibroscan can also be used in follow-up. Increase in liver stiffness can be due to either disease reactivation with increased inflammatory infiltrates and oedema, or due to progressive fibrosis (or both).

In a recent prospective, double blind, randomised, phase IIb trial of patients without cirrhosis [193], budesonide (9 mg/day) and azathioprine (1–2 mg/kg/day) given for six months was compared to conventional prednisone and azathioprine-based immunosuppression. Budesonide/azathioprine was shown to normalise transaminases more commonly and had fewer side effects compared to prednisone (40 mg/day tapered to 10 mg/day) azathioprine (1–2 mg/kg/day) combination, and was superior in a combined endpoint. A complete biochemical remission without steroid specific side effects was achieved in 47% of patients given budesonide vs. 18.4% given prednisolone. However, follow-up data on histology and long-term data are not available. Remission rates in the control arm in this trial were very low, and clearly lower than in earlier published case series, presumably due to fixed dose reduction schedule in the prednisone group and a fairly low used prednisone dose. While budesonide in this trial was given at a high dose until response was observed and treatment was response guided, the control arm was not, introducing a bias in the trial. Nonetheless, this trial has demonstrated efficacy of budesonide in AIH. The successful use of budesonide in AIH has also been reported in other small case series [194–196], but failure was also described in other series [197].

The decision to use budesonide in a particular patient should balance the anticipated beneficial side effect profile against

uncertainties in strength and long-term efficacy. Budesonide has a 90% first pass hepatic clearance and should not be used in cirrhotic patients, or those with peri-hepatic shunting, because of the high risk of side effects in patients not protected by effective first pass metabolism [198,199]. In addition, the decision should be influenced by the presence of concurrent extra-hepatic immune-mediated diseases as exacerbations of these might be possible [197,200]. Budesonide (9 mg/day) plus azathioprine may therefore be considered in treatment-naïve non-cirrhotic patients with early stage disease and in whom untoward major steroid specific side effects are highly anticipated. However, we have little information about the best approach to dose reduction in budesonide treatment. Due to the short half-life of budesonide, it is not clear if reduction to twice daily (6 mg) and to once daily (3 mg) dosing is reasonable, or if the thrice daily dosing should be continued, reducing individual dose from 3 mg to 2 mg and 1 mg.

24. Predniso(lo)ne as initial therapy followed by the addition of azathioprine after two weeks is the first line treatment of AIH (I)  
Initial dose of predniso(lo)ne should be between 0.5 and 1 mg/kg/day. Higher initial doses can induce remission more quickly albeit at the expense of steroid related side effects (II-2)
25. Azathioprine can be initiated whenever bilirubin levels are below 6 mg/dl (100 µmol/L) and ideally two weeks after the initiation of steroid treatment. The initial dosage should be 50 mg/day, and increased depending on toxicity and response up until a maintenance dose of 1-2 mg/kg (II-2)
26. Treatment of AIH should be response guided and treatment regimens should be individualised (III)

A complete clinical, biochemical and histological remission with a sustained off-treatment response after treatment withdrawal is the most desirable treatment endpoint. However, this cannot be reached in the majority of patients. In 80 to 90% of patients, transaminases promptly improve after institution of immunosuppressive treatment. In approximately 20% of patients, a sustained remission following withdrawal of immunosuppressive treatment can be achieved by finite treatment therapy (with a median follow-up of more than six years) [201], which might be improved by the application of stringent endpoint criteria before treatment withdrawal (see below). Primary non-response to immunosuppressive treatment is experienced in only a small proportion of patients with AIH. Non-response (or very slow response) should therefore always lead to a careful reconsideration of the diagnosis and/or re-evaluation of adherence to treatment. In particular, young, non-Caucasian patients with an acute or fulminant presentation and the finding of confluent necrosis in liver tissue have a higher risk of treatment failure [20,202–205]. Patients with liver failure and lack of improvement of serum bilirubin and MELD score during treatment should be referred early to a transplant centre and LT should be considered since this disease phenotype has a high mortality without LT [42,202–206]. In patients without liver failure and not responding to initial treatment an increased dose regimen or alternative treatment strategies can be applied (as discussed in detail in section ‘Special patient populations’) [207].

27. A failure of adequate response should lead to a reconsideration of diagnosis or re-evaluation of adherence to treatment (II-2)
28. In patients with sub-optimal response despite reconfirmation of diagnosis and adherence, dosage of prednisolone and azathioprine should be increased or alternative medications should be used (please see section on “difficult to treat patients”) (II-2)
29. Patients with acute severe AIH should be treated with high doses of intravenous corticosteroids (≥1 mg/kg) as early as possible. Lack of improvement within seven days should lead to listing for emergency liver transplantation (III)

*Treatment withdrawal (Fig. 5)*

The majority of AIH patients respond well to steroid based immunosuppressive treatment and serum transaminases improve to levels within the normal range [190,208–210]. Complete normalisation of transaminases as well as normalisation of IgG levels should be the aim of treatment in patients with autoimmune hepatitis as persisting elevations of transaminases are predictive of; (i) a relapse after treatment withdrawal; (ii) activity on liver biopsy; (iii) progression to cirrhosis; and (iv) poor outcome [185,190–192,208,211,212].

Histological resolution of disease typically lags behind after reaching the biochemical endpoint [176]. There is no clear evidence of optimal treatment duration. However, treatment should be continued long enough to reach histological remission as residual interface hepatitis is still found in patients with normalised ALT levels and is predictive of disease relapse [212]. Together with normalised serum transaminases normalisation of serum IgG appears to also be predictive of histological resolution [108].

Treatment should be continued for at least three years and for at least 24 months after complete normalisation of serum transaminases and IgG levels (biochemical remission). Longer treatments may decrease the frequency of relapse and may therefore be considered. For patients with severe initial presentation and low tolerance of induction treatment, performance of a liver biopsy prior to treatment withdrawal is advisable as histological findings are predictive of fibrosis progression and relapse [108]. In patients with continued histological disease activity (HAI >3), immunosuppressive treatment should not be discontinued, as relapse is almost certain to occur. A recent paper showed that ALT levels below half the upper limit of normal together with IgG levels below 12 g/L were highly predictive for successful treatment withdrawal [213]. A trial of treatment withdrawal should be undertaken by stepwise reduction of immunosuppressive agents, and patients monitored closely. Flares of AIH activity during maintenance therapy or following treatment reduction require increased doses of immunosuppression and preclude complete drug withdrawal (Fig. 5).

A relapse of the disease is frequent (50–90%) after drug withdrawal and typically occurs in the first 12 months after stopping treatment [201,214–216]. However, later relapse can also occur and underscores the need for regular lifelong monitoring of patients even without immunosuppressive therapy [217]. A

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relapse is defined as reappearance of ALT elevation >3 times the ULN according to the IAIHG criteria, but may also present with milder ALT elevations and/or increase in IgG levels. A liver biopsy is usually not necessary to confirm the relapse as ALT elevations are highly predictive. A higher frequency of relapse has been reported to be associated with; (i) slow response to immunosuppressive treatment; (ii) persistent elevation of serum transaminases and/or serum globulins and IgG; (iii) residual inflammation on liver biopsy; and (iv) shorter treatment duration [191,209,211,218,219]. In patients with an identifiable (and avoidable) trigger of initial presentation, a relapse seems to be more uncommon [74].

Treatment of the relapse corresponds to initial treatment with prednis(ol)one and azathioprine and is equally effective in inducing a remission as in primary induction therapy. However, close monitoring after treatment withdrawal with early detection of relapse allows lower doses of immunosuppressants to re-induce full remission. Importantly, patients with multiple relapses were shown to experience more side effects and have adverse outcomes [201,208,216,220]. Therefore, long-term, probably permanent, maintenance treatment is advisable in patients after a relapse.

30. Biochemical remission is defined as normalisation of IgG and transaminases. Histological remission is defined as normal histology or minimal hepatitis (HAI <4 or equivalent) (II-2)
31. Immunosuppressive treatment should be continued for at least three years and for at least two years following complete normalisation of transaminases and IgG (II-2)
32. In patients without biochemical remission, treatment should not be discontinued. In patients who have been in biochemical remission for more than two years, a liver biopsy should be considered prior to treatment withdrawal. In patients with continued histological disease activity (HAI >3), treatment should also not be discontinued (II-2)
33. Only a small minority of patients stay in remission without maintenance therapy. A trial of treatment withdrawal requires close cooperation between patient and physician. A relapse occurs most commonly within 12 months after treatment withdrawal. However, relapse may even occur many years later. Patients should therefore be closely monitored after treatment withdrawal, and surveillance continued lifelong. An increase in IgG can precede the rise of transaminases in a relapse (II-2)
34. Treatment of the relapse or flare may require steroid doses similar to the induction regimen. Earlier detection of relapse allows lower doses of immunosuppressants to re-induce full remission (II-2)
35. Patients who have received adequate immunosuppression and have relapsed during drug withdrawal, or who experienced a flare during adequate maintenance therapy should be kept on immunosuppression permanently (II-2)

### Maintenance treatment

After reinstatement of therapy and achievement of clinical and laboratory resolution, the dose of azathioprine should be increased to 2 mg/kg/day as the dose of prednis(ol)one is gradually withdrawn. Azathioprine should subsequently be continued indefinitely as a continuous maintenance therapy. The data regarding maintenance therapy with azathioprine monotherapy at a dosage of 2 mg/kg/day are encouraging in terms of prevention of steroid specific side effects and relapse, with no relapse during azathioprine maintenance therapy after one year and 83% remission rate over a median follow-up of 67 months [179,221,222]. During azathioprine maintenance therapy, patients should be monitored for cytopenias. An increased risk of malignancies is possible, although this is, as discussed, controversial [223]. In a small case series of azathioprine withdrawal after a median of five years, 50% of patients relapsed after a median of seven years [35]. The major advantage of the azathioprine regimen is the avoidance of corticosteroids and their possible detrimental long-term side effects.

An alternative strategy is to administer prednisolone at the lowest dose possible to maintain the serum transaminase levels within normal limits. The major advantages of the low dose prednisolone schedule are avoidance of long-term azathioprine therapy in fertile young adults and elimination of the theoretical risks of onco- and teratogenicity. The benefit and potential risks of a maybe lifelong azathioprine or prednisolone maintenance therapy should be discussed with the patients and the choice of which strategy to apply in patients who have achieved remission should be individualised. Factors taken into consideration include the stage of liver disease and severity of initial presentation, tolerance of induction treatment, bone density measurements, associated diseases and risk factors as well as the age of the patient.

36. In patients with mild disease and intolerant to azathioprine, prednisolone monotherapy can be considered (II-2)
37. In all other patients, steroid-free monotherapy with azathioprine (or MMF) should be the goal of maintenance therapy. Maintenance treatment should be adapted in dose to sustain stable remission with normalised transaminases and IgG levels. The rate of relapse after prednisolone withdrawal can be reduced by application of azathioprine at a dose of up to 2 mg/kg/day (II-2)

### Monitoring during treatment

Patients initiated on prednisolone/azathioprine combination therapy should have baseline clinical and laboratory parameters monitored during the first four weeks. As the steroid dose is tapered, monitoring intervals can be extended to one- to three-months. Patients with AIH require lifelong monitoring, as disease flares and relapses are frequent even after complete remission. A relapse after treatment withdrawal occurs commonly within 12 months. Patients should therefore be closely monitored after treatment withdrawal. During maintenance treatment, patients should be seen in three- to six-month intervals.



TPMT deficiency

TPMT is an enzyme involved in azathioprine metabolism. Azathioprine is converted to 6-mercaptopurine (6-MP), and this intermediate metabolite is subsequently converted in the liver to either 6-thioguanine, 6-thiouric acid or 6-methyl mercaptopurine. [224] Genotyping of or measuring activity of the TPMT enzyme, which catalyses conversion of 6-mercaptopurine into inactive products, may to some extent predict azathioprine toxicity [225–227].

The 6-thioguanine nucleotides (6-TGN) which are responsible for immunosuppressive and anti-inflammatory properties of azathioprine can also cause myelosuppressive toxicity [228]. Impaired conversion of 6-MP to 6-thiouric acid can increase the conversion of 6-MP to the 6-TGN and can therefore increase toxicity of fixed dose azathioprine [229]. Low TPMT activity is associated with various alleles with the most common being the \*3A allele. Homozygosity with full TPMT deficiency is rare (0.3%) and is associated with a very low enzyme activity, serious toxicity may be encountered due to an accumulation of active 6-MP metabolites, although TPMT genotyping has shown rather variable results in predicting toxicity [230,231]. This is likely due to alternative pathways of metabolism, variable penetrance and possible substrate induction of TPMT activity [232]. Therefore, patients who develop azathioprine related side effects cannot be reliably identified by measuring TPMT activity or genotyping and patients with azathioprine intolerance were shown to have normal or near normal TPMT activity [230,233].

In addition, it has been shown in patients with inflammatory bowel disease that this toxicity may be avoided by use of low doses with careful monitoring of metabolites in the blood [234–236]. Heterozygosity for the low-activity allele with intermediate enzyme activity is found in about 10% of the patients. In patients with autoimmune hepatitis neither heterozygosity nor 6-MP metabolite levels were shown to be reliable predictors of azathioprine efficacy or toxicity [231,233,237] and cytopenia is frequently encountered due to cirrhosis.

However, given the potentially serious consequence of azathioprine treatment in patients with TPMT deficiency, the benefit in terms of safety and reassurance may outweigh the arguments against universal testing so that, if available, TPMT testing may be performed prior to initiation of azathioprine therapy in patients with AIH. In patients with TPMT deficiency, prednisolone monotherapy regime or a lower dose of prednisolone combined with mycophenolate mofetil (MMF) may be used. However, as azathioprine toxicity is more frequently encountered in the absence of TPMT deficiency, close monitoring of all patients started on azathioprine is mandatory, even following TPMT activity testing.

38. TGN-measurements may help to guide azathioprine dosage and to detect possible non-adherence. Undetectable TGN-levels may be due to altered metabolism or non-adherence. High TGN-levels may suggest toxicity (II-2)

Special patient populations

Pregnancy

For patients with stable AIH, the issue of conception and pregnancy frequently arise. An evolving literature on which to base recommendations now exists.

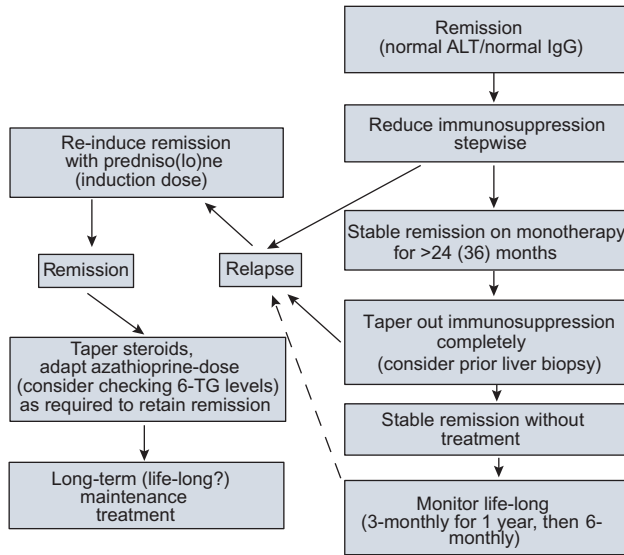
In a large series of patients that attended King's College Hospital between 1983 and 1998, 18 patients had 35 pregnancies; 31 live births were reported with birth abnormalities seen in only two cases [82]. Flares in disease activity occurred during four pregnancies and in additional four within three-months of delivery. In an expanded series from the same institution, 81 pregnancies were reported in 53 women with 41% of pregnancies occurred in the context of cirrhosis [81]. At conception, 61 pregnancies (75%) were on therapy for AIH and 75% of patients were receiving pharmacotherapy. Of these, 27 patients were on prednisolone monotherapy (mean dose 10 mg/day, range 2.5 mg–40 mg), seven were on azathioprine monotherapy (range 1 mg/kg/day–2 mg/kg/day) and 25 patients were on combination therapy of azathioprine (range 1–2 mg/kg/day) and prednisolone (mean dose 5 mg/day, range 2.5–20 mg). In addition, one patient received tacrolimus (2 mg/day) in conjunction with prednisolone [81]. Among those patients on medication, 46 (74%) were stable on their medication regimen for over one year prior to conception.

The live birth rate (LBR) was 73% (59/81). Prematurity occurred in 12/59 (20%) and six infants (11%) required admission to special care baby unit (SCBU). In mothers who were cirrhotic at the time of conception the LBR was lower and need for admission to SCBU was higher. The overall maternal complication rate was 31/81 (38%) conceptions. A flare in disease activity occurred in 26/81 (33%) pregnancies. A serious maternal adverse event (death or need for liver transplant) during or within 12-months of delivery, or hepatic decompensation during or within three-months of delivery, occurred with nine pregnancies (11%) and was significantly more common in women with cirrhosis. Maternal therapy had no significant impact on the LBR, termination rate, miscarriage rate or gestational period. Flares of the underlying AIH were more likely in patients who were without therapy or who had a disease flare in the year prior to conception. Patients who had a flare in association with pregnancy were more likely to decompensate from a liver standpoint. Importantly, no further birth abnormalities were reported beyond those reported in the original report [81].

In a German series, 42 pregnancies in women with AIH, 11 adverse outcomes were reported with serious maternal complications in four [238]. The unexplained adverse outcomes were associated with the presence of anti-SLA/LP and anti-Ro/SSA antibodies. Flares during pregnancy occurred in 21% of patients, whereas 52% of patients had post-partum flares. In a survey of 63 pregnancies in patients with AIH, higher caesarean section rate but no increase in stillbirth or fetal malformation rate was observed [239].

In all these large series, no apparent relationship existed between azathioprine use during pregnancy and an adverse outcome. In large studies of patients with inflammatory bowel disease (IBD), the relative safety of azathioprine or 6-MP during pregnancy has also been well established [240]. Indeed, results

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**Fig. 5. Follow-up of autoimmune hepatitis patients who have achieved remission.** Note that drug-free remission of autoimmune hepatitis is infrequent and cannot be achieved in the majority of patients.

of a meta-analysis evaluating the outcome of women with IBD exposed to thiopurines, the pooled odds ratio for low birth weight, preterm birth, and congenital abnormalities were 1.01 (95% CI (confidence interval) 0.96, 1.06), 1.67 (95% CI 1.26, 2.20), and 1.45 (95% CI 0.99, 2.13), respectively. In men, the pooled OR for congenital abnormality was 1.87 (95% CI 0.67, 5.25) [241].

Therefore continuation of this drug during pregnancy appears to be justified. Moreover, in a small case series of 14 patients in whom immunosuppression was reduced during pregnancy, following delivery (or stillbirth in one patient), 12/14 patients had a rapid flare of AIH [79].

AIH may also present for the first time during pregnancy or (more frequently) in the immediate post-partum period [80,242]. Index presentations should be treated in the same fashion as the non-pregnant patients. Overall, the available large series support a strategy of minimal adjustment to standard immunosuppression (prednisolone/azathioprine) during the course of pregnancy so that the risk of flare can be minimized both during pregnancy and post-partum. Similar, due consideration should be given to calcineurin inhibitor (CNI) therapy, although exact data pertaining to the use of ongoing CNI use in pregnancy can only be derived from transplant series [79,80,243].

The final decision to modify immunosuppression either pre-conception or during pregnancy should be based on the perceived risk to the patient and the pregnancy. Unquestionably, patients with established cirrhosis are at greatest risk of adverse outcomes both during pregnancy and in the first year following delivery and therefore this group should have closest attention during this time. Notwithstanding the fact that azathioprine is considered a category D drug by the US Food and Drug Administration [244], azathioprine and 6-MP have both demonstrated relative safety in pregnancy. In contrast, MMF which is in the same category, has significantly greater risk of

teratogenicity and should be withdrawn prior to considering pregnancy and avoided entirely [245].

With regard to breastfeeding in the context of autoimmune hepatitis and immunosuppression, little data exist. The data available is derived from use for other conditions such as IBD or rheumatological disorders. In general, azathioprine or 6-MP is considered safe for breastfeeding although small amounts of metabolite can be detected in breastmilk. However, this does not appear to result in complications for the feeding infant [246,247].

39. Controlled AIH is neither a contraindication to pregnancy nor to breastfeeding (II-2)  
Maintenance treatment of azathioprine plus/minus predniso(lo)ne should be continued (II-2)  
Mild flares can occur in the first trimester and in particular after delivery and may require transient increase in immunosuppression (II-2)  
MMF is contraindicated in pregnancy (II-2)

### Children

As discussed in section 'Epidemiology of AIH', AIH is seen in all ages and races, and a considerable cohort of patients is increasingly derived from transition or adolescent clinics. The general principles of management of AIH presenting in childhood are similar to those presented in adult patients with some caveats. Indications for therapy are similar [248]. Multiple large series have demonstrated that the disease entity appears to be more aggressive at presentation than that seen in adults with AIH. Whether this relates to the presence of other autoimmune diseases, delays in diagnosis or genetic susceptibility is unclear [249]. Similarly, the potential overlap with an alternative disease entity, specifically AISC complicates the diagnostic pathway [52,248,250,251].

Since at diagnosis, more than 50% of children will have evidence of cirrhosis, and the milder forms of disease are not usually seen, this justifies initiation of early treatment following diagnosis [52,248,250,251]. The aggressive course of disease and reports that delays in diagnosis may affect prognosis, legitimizes early drug therapy. As with adult AIH, treatment may be withheld in only rare circumstances, most specifically in the context of burnt out cirrhosis without inflammatory activity, and only in consultation with a specialised hepatologist.

#### Treatment regimens in childhood AIH

In comparison to adult AIH, treatment regimens in children have been derived primarily from large single-centre practices and reflect the experience and experience bias of these institutions [52,248,250–257]. Until recently, no randomised trial in the management of AIH in childhood had been undertaken [258]. However, despite the lack of controlled trials in children with AIH, multiple reports have documented the efficacy of induction treatment regimens at a level similar to adult patients with normal liver enzymes in up to 90% of patients after six-nine months of therapy [52,248,250–252].

Until now, prednis(ol)one has been the mainstay of therapy in virtually all reported regimens for children, and it is typically administered initially in a dose of 1–2 mg/kg daily (up to 60 mg daily) [52,248,250,251]. Variability exists regarding the tapering of steroid dose. Opinion varies regarding this aspect of care with some institutions advocating rapid switch to alternate day steroid therapy in order to minimize the effects on growth retardation. In contrast, other centres favour a low dose daily schedule of prednis(ol)one.

Since a concern exists for physicians, parents and children of high dose therapy on linear growth, bone growth, and cosmesis, early introduction of azathioprine (1–2 mg/kg daily) or 6-MP (1.5 mg/kg daily) for all children is usually recommended unless contraindications exist [52,248,250,251].

A recent important study evaluated an alternative induction regimen in children and adolescents with AIH [258]. It currently represents the only double blind, controlled trial of therapeutics in AIH in childhood. Using budesonide as an alternative to prednisone, 46 patients were enrolled in a six-month, prospective, double blind, randomised, active-controlled, multicentre phase IIb study that compared budesonide in 19 patients (dosed at 3 mg twice or three times daily) with 27 patients that received prednisone (40 mg/day tapered to 10 mg/day). Both groups received azathioprine (1–2 mg/kg/day), followed by a further six months of open-label budesonide therapy.

The primary efficacy endpoint was defined as complete biochemical remission (normal serum ALT and AST) without predefined steroid specific side effects. The results identified no statistically significant difference in the percentage of patients who met the primary endpoint between the budesonide (3/19; 16%) and prednisone groups (4/27; 15%) after six months of treatment, nor in the percentage of patients who experienced biochemical remission (budesonide, 6/19 [32%]; prednisone, 9/27 [33%]), lack of steroid specific side effects (budesonide, 10/19 [53%]; prednisone, 10 of 27 [37%]). Overall, there was significantly less weight gain in the budesonide group ( $1.2 \pm 3.5$  kg vs.  $5.1 \pm 4.9$  kg in the prednisone group ( $p = 0.006$ )). In the subsequent six-month open-label limb of the study, a total of 42 patients received open-label budesonide after which, 46% of these patients achieved complete remission. Based on these data, oral budesonide with azathioprine can both induce and maintain remission in paediatric patients with AIH and may be considered an alternative therapy to prednisone in non-cirrhotic patients. Long-term effects of this regimen on bone growth and linear growth remain to be assessed.

The use of azathioprine in isolation as a maintenance regimen in children is limited. In five eligible patients, who were withdrawn from steroids 4/5 remained in remission [252]. Cyclosporine A has also been used as alternative induction regimen, although, no advantage to conventional therapy can be identified over standard initiation regimens [255]. MMF has been utilised in children as a rescue regimen in unresponsive disease [253]. Of 26 patients with autoimmune liver disease, 18 responded with 14 having complete normalisation of transaminases in follow-up [253]. Interestingly, of the non-responders, six had AISC.

Like all adult patients, all children should be assessed for evidence of immunity against hepatitis A and hepatitis B virus (HBV) infection and vaccinated accordingly [259]. Similarly, assessment of bone density should be undertaken at diagnosis and during follow-up as described in adults.

40. Children with AIH require higher doses of steroid at initiation of therapy. The principles of management of AIH in children are otherwise similar as in adults (II-2)

#### *Co-morbidity and old age*

Individualisation of therapy may be appropriate for certain groups of patients. In making the decision to devise strategies in management, one needs to consider the presence of co-morbidity in conjunction with the severity of disease and the goals of treatment. In that regard, it is possible to identify certain categories of patients, i.e. patients with evidence of osteoporosis at disease onset, patients with established diabetes mellitus and metabolic syndrome, patients with co-existing viral hepatitis such as HBV or HCV infection. In a similar way, consideration needs to be given to strategies of treating patients who present in older age, who may have a more responsive disease process and who will also have less symptoms at onset of disease [35,44,260].

#### *Old age*

Older patients are often less symptomatic at presentation [35,44] and will also be more biochemically responsive to therapy [35,260,261]. Moreover, genetic influences in particular a higher prevalence of the HLA DR4 alleles in this group seems to at least contribute in part in Western populations to this clinical phenotype of more responsive disease [260]. In a large US single-centre experience, the prevalence of cirrhosis at accession was identified to be 33% in patients >60 years compared to a prevalence of 10% in a comparison group of patients who were aged <30 years at presentation [260]. Similar findings regarding the prevalence of cirrhosis or more advanced fibrosis (F3) at accession have been reported from Japan [261]. These patients also had a higher prevalence of concurrent autoimmune disease [260,262]. In these studies, patients >60 years were all treated with standard regimes of corticosteroids and azathioprine.

In contrast to the elderly patient with established cirrhosis or marked inflammation, an unresolved question particularly among elderly patients, is the presence of mild interface activity with low necroinflammatory scores on liver biopsy [263]. In that context, an unanswered question is whether these patients should be treated, especially if other co-morbidity exists. In a series of patients from the 1970s, ten-year survival was 90% [180], although a more recent study from the Mayo Clinic described a range of outcomes including progressive liver failure, ascites, and HCC during a follow-up interval of ten years (range, 2.7–19.9 years) [181]. These untreated patients with mild disease also were less likely to improve (12% vs. 63%) and had a ten-year survival of 67% compared to a treated control group whose survival was 98% [181]. It is noteworthy, however, that these outcomes reflect only a small number of patients. In a Canadian study, the absence of symptoms at presentation did not translate to poorer outcomes when compared to treated patients, although in follow-up, 25% of patients developed symptoms [44]. Pragmatically, clinical judgement is required if embarking on a watchful waiting strategy. Close follow-up of these patients is essential, as activation and relapse can occur any time, occasionally decades after the initial presentation. If liver function tests

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remain abnormal or worsen, then repeat liver biopsy is appropriate and treatment initiation should be undertaken.

In elderly patients or in those with co-morbidity, the choice of steroid therapy should be considered carefully. For patients without cirrhosis, when severe steroid-related side effects are likely to exacerbate poorly controlled diabetes, osteoporosis, and psychosis, budesonide 9 mg/day plus azathioprine 1–2 mg/kg/day may be an appropriate choice [193]. Although, these endpoints have not been evaluated at a long-term, current management would favour this approach. Clearly attempts at early steroid withdrawal should be undertaken.

### *Presence of osteopenia/osteoporosis*

In the classic early standard immunosuppression trials in AIH, side effects were particularly problematic in the steroid-only regimens. The presence of Cushingoid facies and buffalo hump were reported in up to 50% of patients, diabetes mellitus in between 15–20% of patients [176–178,186]. Reports of hypertension, psychosis, cataract development, osteoporosis and vertebral collapse related to osteoporosis were of the order of between 5 and 10% and although less commonly seen on combined regimens, the prevalence of these side effects is nonetheless approximately 5% [176–178,186].

Worldwide, it is estimated that over 200 million individuals suffer with osteoporosis with the major complication relating to increased bone fragility and subsequent reduced quality of life, morbidity and mortality [264]. Although steroid induced osteoporosis represents only a fraction of the osteoporotic population, its impact is important in terms of complications. For example, patients with AIH who may receive several courses of high dose steroids (daily dose  $\geq$  15 mg and cumulative exposure  $>$ 1 g) have a substantially increased risk of fracture [265]. There is a considerable scope to intervene in susceptible patients using preventive measures. Moreover despite numerous data being available in relation to intervention to bone health, it is estimated that only between 5 and 62% of patients on glucocorticoid therapy in the United States and Europe receive appropriate preventive therapies [266].

In 2003, the combined guidelines of the American College of Gastroenterology (ACG) and the American Gastroenterological Association (AGA) were published, recommending lifestyle modifications and medical therapy, including supplemental calcium, vitamin D and bisphosphonates, to prevent or treat bone loss in patients who receive long-term steroid therapy [267]. Indeed implementation of these guidelines concurrently in a population of patients with IBD led to the detection of osteopenia and osteoporosis with initiation of specific therapies in a majority of gastroenterology clinic patients who met the guidelines' criteria for dual energy X-ray absorptiometry (DEXA) scanning [268]. Interestingly, evaluation of a similar type of strategy at a US based Gastroenterology and Hepatology tertiary centre suggested that tertiary care physicians were most likely to recommend bone health medications, lifestyle changes or DEXA scan to patients if they had AIH, IBD, or were current smokers, had liver disease or had a history of osteoporosis or osteopenia. Remarkably, previous fracture, advanced age, steroid use and reduced body mass index were not associated with tertiary physician bone health recommendations in the study [269].

Pragmatically, and consistent with previous recommendations relating to cholestatic liver disease and in particular PBC, for patients with AIH bone mineral density assessment (DEXA)

is a useful guide for treatment and should be undertaken when possible in probably all patients at presentation, along with follow-up assessment between one and five years depending on outcome and general osteoporosis risk, although, no specific data can be used to support this assertion. The use of calcium and vitamin D supplements is supported by epidemiological data with proven reduction or reversal in the natural rate of bone loss, but no trial data supports or refutes this approach in AIH, while as a general principle hormone replacement therapy is effective in post-menopausal female patients. There are trial data to support the use of bisphosphonates (particularly alendronate) when osteoporosis is present [270,271].

41. Measurement of bone density is recommended at the initiation of steroid therapy. Supplementation of Vitamin D and adequate calcium intake should be recommended to all patients receiving steroid therapy (II-2)

### **Difficult to treat patients**

Most, but not all patients respond well to conventional treatment, and those who do respond may develop side effects related to the treatment. Depending on the remission criteria used (full response with normal aminotransferase activity, normal immunoglobulin concentration and normal histology or only biochemical normalisation), at least 10–15% of patients seem to be refractory to standard treatment, as a result of non-compliance, partial compliance or true non-response. Furthermore, some patients might have variant syndromes with features of PSC or PBC precluding full normalisation of liver enzymes. Finally, co-morbidities may limit therapeutic options and thus alter the management.

Biochemical response to standard immunosuppression is the rule and is often viewed as an additional diagnostic criterion. As a result, non-response should question the diagnosis and adherence to treatment. Non-response is not well-defined in AIH. A lack of a reduction of transaminase by more than 25% after two weeks should be regarded as non-responsive. Numerous diseases can resemble AIH including Wilson's disease, NASH, DILI and atypical forms of PSC or PBC (variant syndromes). These conditions may be unrecognised at presentation and should be reconsidered if apparent non-response is observed. Moreover, AIH may undergo transitions during its course, with a cholestatic syndrome emerging that might be refractory to the original treatment (secondary non-response). Lastly, another condition may be superimposed upon the original process during the course of AIH such as viral infection, drug toxicity or fatty liver.

### *Non-response*

Different grades of non-response have to be considered; null response (treatment failure) with or without immediate severity and incomplete (partial) response requiring individualised therapeutic management. In patients with sub-optimal response despite reconfirmation of diagnosis and adherence, dosage of prednisolone and azathioprine should be increased or alternative medications should be used.



Treatment failure

A) With immediate severity

A particularly challenging scenario is the setting of severe acute presentation. Indeed, treatment failure is more likely to be seen in patients presenting (sub) fulminant disease. Unfortunately, there is a paucity of published data on patients with acute severe AIH at presentation; consisting mostly of anecdotal case reports or small case series with varying inclusion criteria [42,206,272,273]. As a result, it remains unclear whether such patients should be given a trial of corticosteroids, be priority listed for LT, or both; and if corticosteroids are indeed initiated, how and at what time point failure of medical treatment should be defined [274]. Nevertheless, prognosis is poor with overall mortality ranging from 19% to 45% and rate of LT required range from 9% up to 81%. The largest study came from the UK and included 32 patients with acute severe AIH as an acute presentation with an INR of  $\geq 1.5$  at any time without histological evidence of cirrhosis [272]. Twenty-three patients were treated with corticosteroids ( $\leq 40$  mg/day) of whom ten (48%) required LT, while all nine untreated patients required LT ( $p = 0.01$ ). Untreated patients demonstrated higher MELD scores at presentation and a non-significant decrease in episodes of sepsis but no difference in sepsis or mortality was observed between untreated or treated patients. Among treated patients, no difference in MELD scores was observed between responders or failures and two patients already demonstrating hepatic encephalopathy were rescued from LT by corticosteroids. Six deaths (19%) occurred, all post-transplant. Taken together, the available data suggests (with a very low level of evidence) that all patients should be considered for a trial of corticosteroids at the earliest opportunity and in sufficiently high doses ( $\geq 1$  mg/kg) and probably best intravenously [275], but the risk of infections in liver failure has to be kept in mind and may justify the use of prophylactic antibiotics and antifungal agents [206]. LT needs to be considered as an alternative, but the optimal timing is unknown. While no general futility threshold can be identified, it has been shown that failure to improve serum bilirubin, MELD-Na or UKELD within seven days in icteric presentations of AIH has a strong negative prognostic value and should lead to the early consideration of alternative therapeutic strategies including LT [204].

B) Without immediate severity

Other patients may experience treatment failure defined by a lack of, or only minimal, improvement in clinical and laboratory features after several weeks of standard treatment but without liver failure. It is a rare event (probably less than 5%) once the original diagnosis has been corroborated and the compliance with therapy confirmed. When lack of compliance or altered metabolism of azathioprine is suspected, measurement of active TGN metabolites may be helpful although the target range has not been fully determined in AIH. Usually 235–450 pmol per  $8 \times 10^8$  red blood cells by analogy with Crohn's disease is recommended [276,277]. Recently, TGN concentrations  $>220$  pmol per  $8 \times 10^8$  red blood cells were shown to be associated with remission in AIH patients [278]. In these non-responding or very slow responding patients,

the usual recommendation, based on limited data [207], is to increase predniso(lo)ne to about 60 mg/day (for at least one month) and azathioprine to 2 mg/kg/day if tolerated, as endorsed by the AASLD and BSG guidelines [34,40]. Clinical and laboratory features may improve but most patients remain at risk for drug-related side effects and/or disease progression [207]. In true non-responders, alternative immunosuppression might be required (see below), and expert advice should be sought early for these patients.

*Incomplete response*

Incomplete response is defined by the occurrence of some improvement in clinical, biochemical and histological parameters but without reaching complete resolution. It includes abnormal liver enzymes or presence of interface hepatitis on a liver biopsy performed in patients with normal liver tests. Once the possibility of non-compliance has again been considered, the optimum strategy remains unclear. In some patients treated with budesonide-based regimen, budesonide (9 mg/day) is insufficient to induce and/or maintain remission and replacement of budesonide with predniso(lo)ne ( $>20$  mg/day initially) should be considered [279]. In other patients treated with predniso(lo)ne-based regimen, increasing the dose of predniso(lo)ne to  $>10$  mg/day is not generally recommended in the long-term because of side effects [40]. Increasing the dose of azathioprine to 2 mg/kg/day, the dose to prevent relapse without corticosteroids [222], together with 5–10 mg/day predniso(lo)ne is a more attractive option. Alternatively, other immunosuppressive drugs may be considered (see below). Whatever regimen is used, a repeat liver biopsy is recommended after a further 18–24 months [40]. The ideal endpoint with complete biochemical and histological resolution may not be attainable in some patients and the goal should be the lowest achievable biochemical activity with a minimum of side effects. While no transaminase threshold has been clearly identified, it is generally assumed that treatments should be adjusted to maintain serum transaminase level below threefold greater than ULN to reduce the likelihood of aggressive interface hepatitis and progression of the disease [212,280]. Histological measures of attenuated disease activity (e.g. HAI  $<5/18$ ) may be a more reliable guide for these difficult to manage cases.

*Alternative drug therapies for unsatisfactory responses*

The current choices of second line immunosuppressive therapy include MMF and CNI (cyclosporin or tacrolimus). Many agents have been used with variable success but none have been tested in a randomised controlled trial. Their use in AIH has largely been extrapolated from experience in LT. Their major benefits are potent immunosuppressive activity with a rapid onset of action but these agents exhibit their own side effects: hypertension, renal dysfunction, diabetes mellitus, hyperlipidemia and neurological disturbances for CNIs; diarrhoea, leukopenia and teratogenicity for MMF as well as long-term increased risk of malignancy for both [281]. Unfortunately, available evidence for their use in AIH is mainly based on small, predominantly retrospective case series whose interpretation is hampered by heterogeneity of outcome measures, dosing and indication for therapy (non-response or intolerance).

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### MMF

MMF is an inosine monophosphate inhibitor with both anti-T and -B cell proliferation effects [45]. A prospective but uncontrolled study has examined the role of MMF (1.5–2 g/day) in combination with prednisolone as first line therapy in 59 treatment-naïve AIH patients and found that 88% were responders (normalisation of transaminases and  $\gamma$ -globulins), 37% achieved remission off prednisolone and only two had to discontinue MMF because of severe side effects [45]. Even if these results look promising, further data, including histological outcome, are needed before MMF can be recommended as an alternative first line treatment. A number of case series have reported experience with MMF in patients intolerant to azathioprine or with insufficient response to this drug. Most studies have used 2 g/day in divided doses and, although generally well tolerated, up to one third of patients discontinued MMF due to side effects in some series [282]. In patients intolerant to azathioprine, MMF seems to be an effective alternative with response rates ranging from 43% (12/28) to 88% (8/9) [283,284]. In adult patients with refractory disease, efficacy appears much lower since only 0% (0/12) to 25% (2/8) of patients enter biochemical remission but biochemical improvement occurs in a majority and steroid requirement decreases as well [283,284]. Experience in children is more favourable with a 67% (14/20) response rate [253]. It should be kept in mind that MMF is contraindicated in pregnancy, potentially making other drugs preferable in patients of potential child-bearing age.

### CNI

CNI have been shown to be effective in a variety of case series in refractory patients. However, it appears that once CNI are started, it is almost always impossible to taper out these drugs again.

#### a) Cyclosporin

Experience of cyclosporin in AIH in the paediatric population is mainly as a primary therapy in severe disease or to prevent steroid side effects. Series consistently reported good efficacy with a biochemical response rate ranging from 84 to 100% [255,256,285]. Evidence for cyclosporin in adults with non-responsive AIH is much smaller but again a high biochemical response rate ( $\geq 80\%$ ) was reported at a dose of 2–3 mg/kg/day in small series (with a maximum of six patients) [286,287]. However the number of patients is limited and no long-term reports are available.

#### b) Tacrolimus

The picture is similar with tacrolimus that has been used predominantly as salvage therapy in small series with a maximum of 13 patients or case reports at a dose of 1 to 6 mg/day [288,289]. In the largest single-centre experience with refractory AIH or intolerance to other immunosuppressive drugs, 12/13 patients achieved normalisation of liver tests under tacrolimus (mean trough level of 6 ng/ml) [290]. Furthermore tacrolimus was successful in 7/9 well documented non-responsive severe AIH as reported recently by another centre [204]. Taken together, these data suggest that tacrolimus shows promise in non-responsive AIH and is probably safe although the limitation of all series relates to the short degree of follow-up.

### Other immunomodulatory therapy

Other agents have been used with anecdotal evidence of efficacy, including cyclophosphamide (1–1.5 mg/kg/day) [291], methotrexate (7.5 mg/week) [292], rituximab (1000 mg two weeks apart) [293] and infliximab (5 mg/kg at day 0, weeks two and six, and thereafter every four to eight weeks depending on laboratory and clinical course) [294]. Anti-tumour necrosis factor (TNF) antibodies may also induce an immune-mediated liver disease resembling AIH. [295,296]. The use and efficacy of sirolimus has been reported initially in the context of post-transplant AIH [297] and recently for refractory AIH in a non-transplant setting (median trough level of 12.5 ng/ml): a sustained  $>50\%$  fall in ALT was achieved in 4/5 patients including normalisation in two [298]. Main side effects of sirolimus include hyperlipidemia, proteinuria and oedema, but its relatively good safety profile makes it an interesting option. No strong recommendations can be drawn from such small sample sizes and it should be kept in mind that stronger immunosuppression is associated with severe infectious complications, especially in cirrhotic patients [294].

The decision is based on local expertise, AIH severity and patient circumstance. The available evidence does not allow a recommendation as to which of the possible second line drugs should be preferred in an individual patient. Therefore, expert advice should always be sought for applying these experimental second line therapies. In general, at initiation of treatment with non-standard therapy, the doses of current immunosuppression drugs are left unchanged (conversion of azathioprine to MMF excepted) but are gradually decreased thereafter in case of response.

42. In patients requiring high dose, long-term ( $>20$  mg/day) steroid therapy, conventional treatment should be optimized (high doses of predniso(lo)ne combined with 2 mg/kg/day azathioprine). Alternatively, a trial of CNIs (cyclosporine or tacrolimus), infliximab, methotrexate, or cyclophosphamide can be initiated. The relative effectiveness of second line treatments has not been examined in clinical trials. Therefore, these drugs should be used after consultation with a specialist centre only (**II-3**)
43. In patients with incomplete response under budesonide-based regimen, replacement of budesonide with predniso(lo)ne ( $>20$  mg/day initially) should be considered (**III**)
44. In patients with incomplete response under azathioprine-predniso(lo)ne-based regimen, increasing the dose of azathioprine to 2 mg/kg/day, together with 5–10 mg/day predniso(lo)ne may be tried, with repeat liver biopsy after a further 12–18 months (**II-3**)
45. Complete response may not be attainable in some patients and the goal should be the lowest achievable biochemical activity with a minimum of side effects. Histological control of treatment effect and/or disease progression may be necessary (**II-3**)

Non-compliance

As in any chronic disease, compliance can be a problem during long-term follow-up, especially in paediatric patients entering puberty [299]. Adolescents frequently display poor compliance with medical advice together with poor adherence to therapy and clinic appointments. This may be exacerbated by the cosmetic side effects of steroids. Disease can be even denied in an attempt to be “normal” in a context of need to become self-reliant. As a consequence, non-adherence in this population plays a major role in relapse [300]. Regular monitoring of immunosuppressant drugs is indicated. The management of non-adherence is difficult and relies on a non-judgemental approach. Efforts to improve education, social functioning and behavioural strategies to encourage self-motivation; is better achieved by an active multidisciplinary team including psychologists, youth workers and dedicated nurses who can provide education and support during this difficult period and the transition to adult care. During this time, both paediatric and adult hepatologists should be included. [301,302].

46. Maintaining treatment-adherence is of particular importance in adolescents and young adults (II-2) Management of the transition to adult care is better achieved in specialised transition services with a multidisciplinary approach (II-3)

Drug intolerance and side effects

Drug toxicity compels dose reduction or premature discontinuation of the offending drug. Prednisone or prednisolone in AIH has numerous adverse effects (up to 80% after two years) including cosmetic changes (weight gain, facial rounding, and hirsutism), diabetes, emotional instability or psychosis, hypertension and osteoporosis. Severe adverse effects occur mainly at doses >20 mg/day for more than 18 months and lead to treatment discontinuation in about 15% of patients. The combination regimen with azathioprine is associated with much lower occurrence of corticosteroid related adverse events [179]. In the large randomised study by Manns *et al.* (207 non-cirrhotic patients), comparing prednisone and budesonide (9 mg/day), most of the difference between the two groups at six months was a reduction of steroid side effect in the budesonide group (51.5% vs. 26.0%, respectively) [193]. At the end of the six-month trial, the prednisone group was crossed over to budesonide (6 mg/day) and a 40% reduction of the incidence of steroid side effects was observed in a six-month period. As a result, in predniso(lo)ne responders presenting steroid side effects, a switch to budesonide (6 mg/day) may be considered; alternatively, higher doses of azathioprine (2 mg/kg) should be applied; furthermore conversion of azathioprine to MMF (2 g/day) with subsequent tapering of predniso(lo)ne may be tried, if azathioprine dose is limited by drug toxicity or side effects [283,284].

Up to 25% of patients with AIH develop side effects on azathioprine requiring withdrawal of the drug in about 10% of cases. Side effects are more common in cirrhotic patients. About 5% of patients develop a severe and early reaction with arthralgias, fever, skin rash or pancreatitis within a few days or weeks which

warrants its immediate discontinuation. Resolution of symptoms usually occurs in a couple of days. As already discussed above, in patients intolerant to azathioprine, MMF (2 g/day) seems to be a good alternative. 6-MP may be tried even in apparent azathioprine intolerance, as some patients may nonetheless tolerate this active metabolite [303]. Other alternatives are steroid monotherapy in patients with mild disease and little steroid risk factors including good bone density, or those drugs that are also used in case of non-response. The efficacy and tolerance of long-term budesonide monotherapy have not been assessed.

- 47. In patients without cirrhosis, budesonide plus azathioprine may be used as induction therapy and can be considered for patients with co-morbidities that might be exacerbated by predniso(lo)ne treatment (II-2) Long-term data on budesonide safety and efficacy in AIH are lacking (I)
- 48. If adequately dosed therapy with azathioprine is insufficient to maintain remission in predniso(lo)ne responders with severe steroid side effects, a switch from predniso(lo)ne to budesonide may be considered (II-3)
- 49. In patients intolerant to azathioprine, mycophenolate is the second line drug of choice (II-2) The relative efficacy and tolerability of MMF in other patients compared to azathioprine has not been established (II-2) A trial of 6-MP or 6-TG in patients intolerant to azathioprine is an alternative option (III)

Variant syndromes

The low prevalence of the variant syndromes as well as the lack of universal agreement on definition has made it impractical to perform randomised controlled trials in this setting.

Patients with features of both PBC and AIH

Patients with features of both PBC and AIH seem to have a more severe disease compared to conventional PBC as illustrated by a higher frequency of extensive fibrosis at presentation (despite a younger age in some reports) and most series (but not all) support a worse outcome in terms of biochemical response to UDCA, progression of fibrosis and liver-related mortality [58,170,304,305]. Despite the lack of controlled trials, EASL guidelines, based on the results of small series, have recommended adding steroids (predniso(lo)ne or budesonide) either at the time of diagnosis of “variant syndrome” or in case of inadequate biochemical response after three-months of UDCA [58,60,304,306]. The results of a large multi-centre study (88 patients) have been recently reported: as first line therapy, 30 patients received UDCA alone and 58, a combination of UDCA and immunosuppression (prednisone ± azathioprine); in patients with moderate interface hepatitis, UDCA alone and combination therapy had similar efficacy (80%) in terms of biochemical response whereas in patients with severe hepatitis, efficacy of UDCA alone was much lower (14 vs. 71%, respectively). The presence of extensive fibrosis was associated with a lack of response

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to the combination therapy but not to UDCA alone; second line immunosuppressive agents (cyclosporine, tacrolimus and MMF) led to biochemical remission in half of the patients who were non-responders to initial immunosuppression [307]. These findings strongly support the use of a combination of UDCA and immunosuppression as first line therapy in PBC patients with severe interface hepatitis. Interestingly, it has been suggested that, in responders, the dose of immunosuppressors in the long-term could be lower and rate of successful withdrawal higher than in classical AIH [304,307]. In UDCA-treated PBC developing AIH (“sequential variant syndrome”) use of immunosuppressive treatment is mandatory [308].

### *Patients with features of both PSC and AIH*

Various results of therapy (usually prednisolone and azathioprine with or without UDCA) have been reported in patients with features of both PSC and AIH [51]. It is difficult to draw any firm conclusions because of the small number of patients, the usually retrospective nature of the studies and the heterogeneity of the regimens. In the paediatric AISC form treated with immunosuppressors, liver biopsies may show improvement in inflammation but cholangiographic appearances may progress and transplant-free survival at ten years (65%) is lower than in AIH (100%) [52]. The combination of UDCA and immunosuppressive therapy may improve liver biochemistry and this approach has been advocated by EASL guidelines [60]. In the series with the most homogeneous regimen (UDCA, prednisolone and azathioprine) including seven patients with a mean follow-up of eight years, a significant fall in transaminases was observed but not in alkaline phosphatase levels, and more interestingly, the Mayo Risk score did not change and transplant-free survival was much better (100%) than that of 34 classical PSC (43%) with the same follow-up and treated with UDCA [309]. However, in the long-term (>10 years), progression towards cirrhosis seems to occur in the majority of patients [64]. Another study reported a similar proportion of patients with AIH-PSC “variant syndrome” (mainly young adults) and AIH achieving AIH biochemical response within one-year of therapy (although the exact combination of azathioprine, prednisone and UDCA varied between individual patients), but the long-term prognosis of patients with an PSC-AIH “variant syndrome” was worse than in AIH without PSC features [310]. Taken together, all these data support the use of UDCA in combination with an immunosuppressive regimen in most patients with features of both PSC and AIH despite the lack of adequate studies [65].

50. In AIH patients with features of PBC (“AIH-PBC variant syndrome”), combined therapy with UDCA and immunosuppressants is recommended (III). In AIH patients with PSC features (“AIH-PSC variant syndrome”) addition of UDCA to immunosuppressant can be considered (III)  
In patients with dominant AIH features, an alternative approach is to start with immunosuppressants only and then add UDCA if response is insufficient (III)

### *AIH following LT*

Recurrent and “*de novo*” AIH may occur years after grafting and must be distinguished from acute rejection, chronic rejection, viral infection, and drug toxicity. Diagnosis is often challenging because of the lack of a specific marker. Recurrent AIH is reported in about 20–25% of cases [311,312] and is usually managed by increasing the dose of corticosteroids or re-instituting its use with or without azathioprine or MMF [311,313]. In non-responders, conversion of azathioprine/MMF to sirolimus may be successful [297]. Prophylactic use of azathioprine in patients transplanted for AIH has not been evaluated systematically, but appears prudent.

“*De novo*” AIH has been described in 2–7% of patients undergoing LT for a range of diseases unrelated to autoimmunity, particularly in the paediatric setting [91,312]. The management strategy is similar to that proposed for recurrent AIH [297,314].

Finally, re-transplantation should be considered in patients with recurrent or “*de novo*” AIH that is progressing to graft loss, a rare event provided that a prompt therapeutic management has been provided [91].

51. Treatment of AIH following liver transplantation (recurrent or *de novo*) should follow the standard management principles of AIH (II-3)

### *Treating AIH in the context of liver co-morbidity*

#### *Non-alcoholic fatty liver disease (NAFLD)*

NAFLD is the hepatic manifestation of the highly prevalent metabolic syndrome which includes obesity and insulin resistance that are known to increase the risk of progression of other liver diseases, especially chronic HCV infection [315,316]. As both AIH and NAFLD may cause persistently elevated aminotransferases and presence of autoantibodies, it is important to have a clear picture of what has to be treated. Liver biopsy is very helpful, and often indispensable, for this distinction. In patients with AIH, the prevalence of the metabolic syndrome or the impact on outcome is unknown, but it is reasonable to presume that the presence of steatohepatitis in patients with AIH will increase the risk of progressive disease. Features of the metabolic syndrome, including diabetes, hypertension and obesity, are exacerbated by corticosteroids. Thus, associated NAFLD should be considered and treated according to current recommendations (lifestyle interventions and pharmacological measures if appropriate). In this population, every effort to use the lowest dose of corticosteroids (combination regimen) should be encouraged.

#### *Chronic viral hepatitis*

Although hepatitis B or C should to be excluded before making a diagnosis of AIH, AIH can sometimes develop in patients with HBV or HCV infection either spontaneously or under interferon treatment, and patients with AIH can contract viral infection. Vaccination against hepatitis A virus and HBV should be given



to all AIH patients not showing previous vaccination or virus exposure. In patients with hepatitis B or C virus replication and features of AIH at diagnosis, anti-viral (HBV or HCV) interferon-free regimen should be used first and the need for immunosuppressive therapy reassessed after viral eradication or suppression. Reactivation of hepatitis B has been reported during treatment of AIH and baseline HBV serology is recommended for all patients receiving immunosuppressive drugs. According to EASL recommendations [317], HBsAg-positive candidates should be tested for HBV DNA levels and should receive pre-emptive nucleoside/nucleotide analogues administration during immunosuppressive therapy (regardless of HBV DNA levels) and for 12 months after cessation of therapy. In patients with expected lengthy immunosuppression and in all AIH patients, use of either entecavir or tenofovir is recommended.

52. Hepatitis A and B vaccination as well as yearly influenza vaccination should be given to all AIH patients (III)

*HIV infection*

*De novo* AIH, as an immune reconstitution, has been described in HIV patients receiving highly active antiretroviral therapy [318]. Liver biopsy findings are critical in establishing AIH diagnosis and discriminating other numerous causes of abnormal liver tests in this setting [319]. Standard immunosuppressive therapy for AIH can be effective but is sometimes associated with life-threatening infections, and treatment for AIH in HIV-infected patients should be individualised after careful consideration of the potential risks and likely benefits [320].

**Management issues, quality of life, and delivery of care**

*Delivery of care*

AIH is a rare disease and patients require access to care from medical professionals with expertise in AIH, according to the evolving evidence on best practice. Currently AIH care is not organized and this has resulted in uneven distribution of health care delivery [321]. In order to overcome this, the German rare disease plan in accordance with EU guidance calls for a tiered care model that involves assignment of three types of clinical care centres with increasing expertise [322]. According to this model, patients should have access to referral and to specialist centres. Referral is encouraged for aspects such as diagnostic uncertainties, prognostic assessment, and exploration of optimal disease management strategies and management of (liver) related complications. Depending on the complexity of the clinical issue, the patient may move up and down the ladder of care. The delivery of such care will depend on the local, regional or national healthcare services, but will improve the efficiency of healthcare provision. Coordinated care is likely to reduce the unnecessary duplication of tests, facilitate targeting of novel diagnostic and therapeutic interventions tailored to clinical need and expected benefit and has the potential for improved patient outcomes. Access to specialist care should also result in better quality standards for laboratory testing, in particular for

immunoserology. There is evidence of integration benefits and impressive cost savings in the care of patients with rare diseases [323].

*Practical integrated patient support*

The first diagnosis contact between the patient and physician is of major importance. Anxiety and distress levels can be alleviated if the physician recognizes the patient's psychosocial needs and conveys reassurance and support during the first consultation [324]. However, there are no studies about the ways to communicate AIH to the newly diagnosed and how patients respond to the diagnosis. There is evidence to suggest that the expertise on AIH is unevenly distributed among health care professionals which may lead to misconceptions. Patient education programs and tools for patients with liver diseases are available, but there is little research about their implementation, effectiveness, and relevance for AIH. AIH patients need simple, disease specific information initially with practical implications such as potential impact on work, insurance, lifestyle and family planning. This allows them to engage fully in shared decision-making. Patients should be provided with contacts and access to local or national support groups. Consultations with AIH should be individualised, reassuring and tailored to the patient's literacy level and culture/language and retain a positive attitude.

*Patient reported outcomes*

Instruments such as Patient reported Outcome Measures (PROM) have been developed mainly as endpoints for clinical trials. PROM provides insight into the patient perspective on the impact of disease and treatment, and have the potential to identify those treatment strategies that benefit the HRQoL of most patients. The clinical trials executed in AIH have used biochemical markers of response and the evidence suggests that biochemical improvement does not immediately translate in to higher HRQoL levels. The development of PROM may assist here to track and trace the needs of AIH patients. However there is no disease specific questionnaire available nor has a validation of PROM for AIH been developed.

*Quality control*

Expert centres for the care of patients with autoimmune hepatitis should evaluate the quality of the clinical services by a variety of quality control measures. These should include survival statistics, critical incident reporting systems as well as peer and patient involvement in quality control measurements. Key results should be published, and clinical research projects should be undertaken and supported. Both physician training and further education as well as patient education measures should be in place, in addition to consultation services for referring physicians.

*Quality of life*

AIH is a chronic liver disease with flares and remissions that may impart significant medical and economic burdens on patients' life and health care delivery systems. The physical and psychological burden to AIH patients are significant, yet incompletely characterized [325]. In a survey among members of the Dutch Liver patients' organization, HRQoL was investigated using three instruments including the extended version of the disease specific liver disease symptom index 1.0 (LDSI 2.0), the Dutch Short Form 36, and MFI-20. Patients with AIH

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**Table 8. Research agenda.**

<p><b>Epidemiology and pathogenesis:</b></p> <ul style="list-style-type: none"> <li>• How common is AIH among different populations?</li> <li>• Is the incidence rising in different populations?</li> <li>• What are risk factors and associated diseases?</li> <li>• Triggers of disease manifestation</li> <li>• Triggers of disease flares</li> <li>• Factors associated with spontaneous disease improvement/remission</li> <li>• What is the triggering autoantigen?</li> <li>• What are the underlying immunoregulatory disturbances?</li> </ul>
<p><b>Diagnosis:</b></p> <ul style="list-style-type: none"> <li>• Improvement and standardisation of autoantibody testing</li> <li>• Definition of sensitivity and specificity of autoantibody profiles in different age groups, ethnic groups and both sexes</li> <li>• Possible development of an all-in-one immunoassay</li> <li>• Evaluation of the various individual histological criteria (rosetting, interface hepatitis etc.)</li> <li>• Criteria (clinical, laboratory and histological) for acute and fulminant AIH</li> <li>• Value of non-invasive testing for fibrosis and cirrhosis</li> <li>• Criteria for the variant syndromes (PBC and AIH as well as PSC and AIH)</li> </ul>
<p><b>Treatment and monitoring:</b></p> <ul style="list-style-type: none"> <li>• Definition of best induction protocol in different patient groups (according to age, co-morbidity, severity of inflammation, fibrosis staging, symptoms and side effects)</li> <li>• Are short-term steroids feasible in induction therapy (&lt;4 weeks)?</li> <li>• Can remission be induced without steroids?</li> <li>• Prognosis of mild disease without treatment - do all patients need therapy?</li> <li>• Best protocol for acute and fulminant disease - steroid dose? i.v.? Is there a role for other immunosuppressants (e.g. infliximab) in fulminant disease? Should antibiotics be given prophylactically? Best timing for emergency transplantation?</li> <li>• Comparison of alternative maintenance drug - is azathioprine still the best drug?</li> <li>• What is the best second line drug in azathioprine intolerance?</li> <li>• What is the best second line drug in patients with insufficient response?</li> <li>• Role of 6-TGN blood levels in maintenance treatment</li> </ul>

<ul style="list-style-type: none"> <li>• % "non-responders", % slow responders, speed of response, what is non-response?</li> <li>• Tapering schedule in budesonide-treated patients</li> <li>• Management approach to patients with variant syndromes (PBC and AIH, PSC and AIH) - criteria for immunosuppression; drug dosage; response criteria</li> <li>• Clinical and serological criteria for good and poor treatment response</li> <li>• Non-invasive treatment monitoring</li> <li>• Predictors of relapse and predictors of spontaneous remission after drug withdrawal</li> <li>• Best protocol for (stepwise) drug withdrawal</li> <li>• Need for follow-up biopsies</li> <li>• Post-LTX management protocols</li> <li>• Diagnosis and management of treatment side effects</li> <li>• Improving psychosocial outcome</li> <li>• Conception in AIH</li> <li>• Management of pregnancy and post-delivery care</li> <li>• HCC screening: Whom? How often? How?</li> </ul>
<p><b>Delivery of care:</b></p> <ul style="list-style-type: none"> <li>• Patient compliance: prevention and treatment of non-compliance</li> <li>• Quality control measures</li> <li>• Cost-effectiveness of care delivery approaches</li> <li>• Role of specialist care - is quality of life and life expectancy improved in specialist centres?</li> <li>• Patient education</li> <li>• Doctors education</li> <li>• Management of transition (childhood - adolescence - adulthood)</li> <li>• AIH in the elderly</li> <li>• Care in serious co-morbidity</li> </ul>
<p><b>Patient perspective:</b></p> <ul style="list-style-type: none"> <li>• What are the patients' aims in the management of AIH?</li> <li>• Role of dietary advice</li> <li>• Is alcohol allowed? Which amount?</li> <li>• Is there a role for sports?</li> <li>• Is there a role for stress?</li> <li>• Is there a role for alternative medicine? Are herbal drugs harmful?</li> <li>• How to communicate to family and friends about the disease?</li> <li>• Role of and treatment of fatigue</li> </ul>

(n = 142) scored lower in all SF-36 scales, but particularly in scales that measured role limitations due to physical problems or general health. AIH patients report more fatigue as assessed with the MIF-20 questionnaire [326]. Another cross-sectional study in 24 children with AIH or with PSC/AIH overlap using the PedsQL 4.0 instrument demonstrated significant impairment of HRQoL which was associated with the presence of frequent liver disease related symptoms. Particularly, abdominal pain, fatigue, and mood symptoms negatively affected HRQoL results [327]. The most definitive study to date, considered HRQoL using the 12-item Short Form Health Survey (SF-12) in 103 AIH patients [36]. Some 77% patients were in biochemical remission. While physical component scores did not deviate from the general population, the mental component scores were significantly reduced. The authors observed a high rate of severe depression and anxiety symptom levels in AIH that were related to (often unwarranted) concerns about the inheritance, status and trajectory of AIH. Despite the fact that AIH was clinically

stable in the majority, there was a high rate of major depressive symptoms. The authors detected a correlation between use of prednisolone and depression, suggesting that one of our treatment goals in AIH should be to develop steroid-free treatment.

53. The heterogeneity and complexity of AIH, requires specialised diagnostic and therapeutic services. Patients should be provided with access to specialised care in order to improve outcome, survival and quality of life; either in specialised centres or through managed clinical networks (II-3)
54. There is increased recognition of decreased quality of life in AIH patients. Management of AIH should therefore also address psychosocial needs (II-2)

Research agenda

Diagnosis and treatment of AIH have seen enormous progress over the past 50 years, and the majority of affected patients can be treated very successfully with a normal or near normal life expectancy and good quality of life. Nonetheless, many patients still experience considerable morbidity and mortality, primarily due to:

- delayed or missed diagnosis
- drug intolerance
- drug side effects
- insufficient treatment response
- poor management and poor delivery of care
- poor compliance

Discussion of this CPG has shown the many numbers of open or poorly answered question and thus is the basis of the clinical research agenda. Table 8 gives a list of points and questions that should be addressed in future research. A key problem in clinical research in AIH is the rarity of the disease. Therefore, establishing major treatment centres with specialised expertise and coordinated cooperation of such centres will be a key factor in improving clinical research in AIH. At the same time, methods of delivery of care, different approaches, questions of cost-effectiveness such as factors of psychosocial impairment and support clearly need our attention in the future. Patient involvement in setting the research agenda may also be needed to be sure to address those questions relevant to those affected.

In addition to clinical research, basic research focussing on the aetiology of AIH and aiming to understand the underlying pathophysiology will be the key to improved treatment of the disease. At present, the majority of patients need drug treatment every day of their life, leading to both physical as well as psychosocial impairment in the quality of life in many of them. Patients want cure, not suppression of disease activity, and for most patients, if not all, we are at present unable to provide a cure for their disease. In order to reach curative treatment, we have to closely collaborate with basic scientists and follow development in immunology and related disciplines.

Conflict of interest

Ansgar W. Lohse, Frank Lammert, Harald Hofer, Marco Lenzi, Joost Drenth, and George Dalekos declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript. Michael Heneghan has completed sponsored lectures for Falk, and Olivier Chazouillères received travel grants for the 2013 AASLD meeting by Astellas.

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