# Autoimmune hepatitis

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**Autoimmune hepatitis is a disease of the hepatic parenchyma that can present in acute or chronic forms. In common with many autoimmune diseases, autoimmune hepatitis is associated with non-organ-specific antibodies in the context of hepatic autoimmunity. This dichotomy has made definition of a unifying hypothesis in the pathophysiology of the disease difficult, although data from the past 8 years have drawn attention to the role of regulatory T cells. Several triggers have been identified, and the disease arises in genetically susceptible individuals. Clinical and biochemical remission is achievable in up to 85% of cases. For the remaining patients, alternative immunosuppression strategies are an option. Liver transplantation provides an excellent outcome for patients with acute liver failure or complications of end-stage liver disease, including hepatocellular carcinoma. Variant or overlapping syndromes are worthy of consideration when unexpected disease features arise.**

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## Introduction

In September, 1950, Jan Waldenström described the usual clinical phenotype of a patient with autoimmune hepatitis: a young woman with hepatic dysfunction and associated hypergammaglobulinaemia.[1] Since then, diagnostic criteria have been developed.[2,3] Despite successful classification, autoimmune hepatitis is a challenge—clinically and immunologically—because its aetiology remains uncertain. In this Seminar, we will review progress in the epidemiology, pathogenesis, and management of the disorder, and will discuss some of the challenges in the development of strategies to deal with the disease.

## Epidemiology

Autoimmune hepatitis can be diagnosed in patients of all ages and in both sexes, and is increasingly recognised as a global disease. The mean annual incidence of the disorder in white northern Europeans ranges from 1·07 per 100 000 individuals to 1·9 per 100 000, with a point prevalence of 16·9 per 100 000 people.[4,5] In other homogenous populations, such as Alaskan Natives, a point prevalence as high as 42·9 per 100 000 individuals has been reported.[6]

Early reports suggested that autoimmune hepatitis has a bimodal age distribution, with the first peak between the ages of 10 and 30 years, and a second between 40 and 50 years; however, this finding might have been biased by reporting from tertiary referral centres.[7] Furthermore, the disorder has been increasingly recognised in all age groups—from infants to octogenarians.[8–10] Autoimmune hepatitis might have been underdiagnosed outside of the age ranges initially described, although type 2 autoimmune hepatitis has a peak in young individuals.[11] The female-to-male ratio in type 1 autoimmune hepatitis is about 4:1, but the ratio is 10:1 in type 2 disease.[12] However, male patients might have an increased chance of survival, despite having a younger disease onset and more disease flares than do women.[13]

The clinical manifestations, severity, and outcome of autoimmune hepatitis can vary substantially according to region and ethnic origin. Cirrhosis is identified more frequently at index presentation in African-American patients (56–85%) than in those of northern European origin (38%).[14,15] A European study[16] that included patients of African, Arabian, and Asian ethnic origin showed that these individuals presented at a younger age, were more likely to have cholestatic biochemical and histological features, and were less likely to respond to standard immunosuppression than were white patients. In another study,[17] patients from Brazil tended to have more severe disease than did those from the USA. Additionally, Japanese patients tend to have late-onset disease that responds to less potent immunosuppressant medication than is necessary for patients from the USA.[18,19]

Whether aetiological factors or modifiers indigenous to specific areas naturally select patients with genetic predispositions that favour disease propagation is a matter of debate. However, this hypothesis is attractive because it could explain differences in both disease presentation and apparent severity from region to region, including the relative rarity of type 2 autoimmune hepatitis in the USA and its severe phenotype in adults and children.[20–22]

## Pathogenesis

### Overview

Autoimmune hepatitis is a complex disease: it is a multifactorial polygenic disorder that is probably caused by the interaction of a trigger and environmental factors in a genetically susceptible individual. Specific genetic variants or polymorphisms increase or decrease the risk of disease, and possession of a potential disease-causing

#### Search strategy and selection criteria

We identified reports largely from our own personal databases of literature about autoimmune hepatitis. Additionally, we searched PubMed with the terms "autoimmune hepatitis", "epidemiology", "pathogenesis", and "treatment" to identify any important studies that might have been missing from our own databases. We used no date or language restrictions. Referenced reports are predominantly original research articles from peer-reviewed journals. Reference lists in identified reports were also reviewed to further identify studies of relevance to this Seminar.

mutation in itself does not cause disease. Many polymorphisms probably interact to affect clinical phenotype in a patient with autoimmune hepatitis, although the evidence for such interaction has been reported in type 1 disease only.[23–25] Additionally, autoreactivity against liver autoantigens—ie, cytochrome P450IID6 (CYP2D6) in type 2 disease and soluble liver antigen in type 1 disease—is pivotal in the pathogenesis of this disorder.

Although the exact mechanisms leading to breakdown of immune tolerance in autoimmune hepatitis have not been fully clarified, impairment of immune regulation probably has a central role. Thus, in a healthy individual, the balance between liver-antigen-specific regulatory T cells (ie, $CD4^{pos}CD25^{high}FOXP3^{pos}$) and effector cells sharing specificity for the same autoantigenic regions results in tolerance (figure 1). If regulatory T cells are impaired or effector cells are poorly responsive to their control, tolerance to liver autoantigens is lost, leading to initiation and perpetuation of autoimmune liver damage (figure 1). Whether breakdown of immune tolerance to liver autoantigens is uniquely due to a numerical and functional defect in regulatory T cells only[26,27] or whether it is accompanied by an impaired responsiveness of effector lymphocytes to regulatory T cell control has yet to be clarified.

Liver-autoantigen-specific regulatory T cells have been described in patients with type 2 autoimmune hepatitis and probably act as guardians of effector immune responses by controlling proliferation, secretion of pro-inflammatory cytokines (eg, interferon-γ and interleukin 17), and cytotoxicity of effector CD8 T cells.[28] They probably also control B cells, because a strong inverse correlation between numbers of regulatory T cells and autoantibody titres (anti-liver-kidney microsomal antibody type 1 [anti-LKM-1] in type 2 disease, and anti-soluble-liver-antigen antibody in type 1 disease) has been reported.[26]

If liver-autoantigen-specific regulatory T cells are unable to exert control, liver-specific effector cells become unchecked (figure 2). Monocytes and macrophages are recruited to areas of damage because they can migrate and produce increased amounts of the pro-inflammatory cytokine tumour necrosis factor α.[29] NK cells are also recruited to the site of damage, where they can mediate cytotoxicity in conjunction with autoantibodies; antigen-specific and non-antigen-specific CD4 T cells intervene to provide help to CD8 lymphocytes. Once activated, CD8 lymphocytes amplify liver damage by secreting interferon gamma and exerting cytotoxicity. Th17 cells—an effector subset implicated in the pathogenesis of autoimmune disorders in mice and man[30]—secrete interleukin 17, which amplifies liver damage. Patients with autoimmune hepatitis have an increased number of γδ T cells, especially during active disease phases, and their expression of granzyme B—an effector-cell molecule—directly correlates with biochemical indices of liver damage, such as alanine aminotransferase (ALT) and bilirubin.[31] The induced expression of HLA class II molecules on hepatocytes renders these cells able to act as antigen-presenting cells and therefore contribute to perpetuation of liver damage.[32]

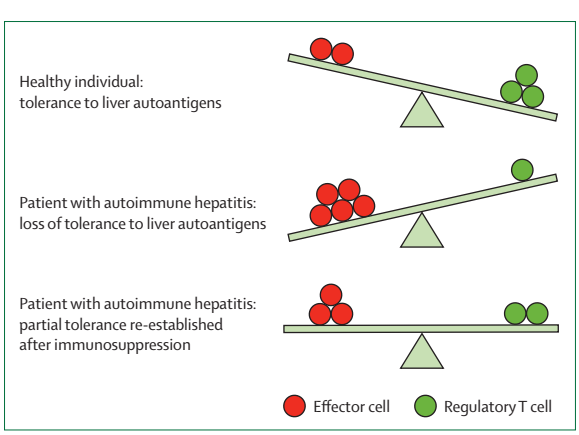


*Figure 1:* **Interaction between regulatory T cells and effector cells**

## Animal studies

Most mouse studies are limited by the absence of predisposing genetic alterations that lead to autoimmune hepatitis and development of an acute rather than chronic (relapsing) hepatitis.[33–36] Furthermore, the use of infective triggers coupled with little autoantibody formation in association with the hepatic process restricts their applicability.

In the Concanavalin A (Con A) model, mice present with acute liver failure and a dose-dependent increase in aspartate aminotransferase (AST) within 8 h of the injection with Con A, although histopathological lesions of autoimmune hepatitis are not common.[34] Gorham and colleagues[37] developed a mouse model by backcrossing mice deficient in transforming growth factor β with the BALB/c background; these animals developed lethal hepatitis with an ALT increase.

Kido and colleagues[38] produced a mouse model of spontaneous autoimmune hepatitis by inducing concurrent loss of two controlling mechanisms: $FOXP3^{pos}$ regulatory T cells and PD1-mediated signalling. After neonatal thymectomy to substantially reduce the number of $FOXP3^{pos}$ regulatory T cells, $PD1^{(-/-)}$ mice develop fatal autoimmune hepatitis characterised by severe T lymphocyte infiltration and increased titres of antinuclear antibodies. Importantly, adoptive transfer of regulatory T cells can suppress the progression of fatal hepatitis after initiation of autoimmune hepatitis, confirming both the role of autoreactive T lymphocytes in liver damage and that of regulatory T cells in tolerance.[38]

By contrast with these studies that emphasise the importance of breakdown of immune tolerance in induction and progression of autoimmune hepatitis, work to develop a mouse model of type 2 disease is in progress, in which the autoantigen CYP2D6 has been identified and characterised in detail. Lapierre and colleagues' findings[39]

were generated through DNA immunisation of C57BL/6 mice with the human autoantigens CYP2D6 and formiminotransferase cyclodeaminase (another autoantigenic target recognised in type 2 disease). Another study of type 2 disease[40] showed that transgenic mice express human CYP2D6 in the liver after they are infected with an adenovirus-CYP2D6 vector to break selftolerance.

## Autoantibodies

Despite the well established associations between the presence of detectable non-organ-specific autoantibodies (eg, antinuclear antibodies) and anti-smooth-muscle antibody in the serum of patients with autoimmune hepatitis, the exact function of these antibodies in the disorder is unknown. From a practical standpoint, autoimmune hepatitis has been broadly categorised into two distinct disease subtypes on the basis of antibody profiles: type 1, which is associated with either antinuclear antibodies or anti-smooth-muscle antibodies in serum; and type 2, which is much less common than type 1 and is associated with the presence of either anti-LKM-1 or anti-liver-cytosol antibody type 1 (table 1).[3]

About 65% of patients with autoimmune hepatitis will have detectable antinuclear or anti-smooth-muscle antibodies (which are usually directed against actin). Additionally, 58% of patients with type 1 autoimmune hepatitis will have detectable antibodies to soluble liver antigen or liver pancreas antigen, with or without antinuclear or anti-smooth-muscle antibodies. These antibodies, which target the same antigen, seem to have greater specificity for autoimmune hepatitis than do antinuclear or anti-smooth-muscle, and might be a useful adjunct in the diagnosis of type 1 disease when conventional autoantibodies are negative.[42] The existence of a third subtype of autoimmune hepatitis defined by the presence of antibodies against soluble liver antigen has caused further controversy.[43] However, present data suggest that individuals with this autoantibody have all the clinical and pathological hallmarks of type 1 disease and should be treated as such.[42,44,45] Although atypical perinuclear anti-neutrophil cytoplasmic antibodies are also frequently recorded in type 1 autoimmune hepatitis, their applicability is limited by their poor sensitivity and specificity.[41]

As an autoantigen capable of initiating autoimmune hepatitis, the asialoglycoprotein receptor is a 50 kDa protein with specificity for the hepatocyte membrane that is highly expressed in periportal hepatocytes.[41,46] Investigators have identified antibodies to the asialoglycoprotein receptor in patients with autoimmune hepatitis.[47] Additionally, soluble liver antigen shares aminoacid sequences with the asialoglycoprotein receptor, suggesting a possible role for antibodies to soluble liver antigen in pathogenesis.[48] In type 2 autoimmune hepatitis, anti-LKM-1 antibodies are known to target several epitopes of hepatic cytochromes, specifically CYP2D6.[49–52] Moreover, crossreactivity has been shown between several viruses known to infect humans, including hepatitis C virus.[53–55] The implications of these findings are that viruses might mimic self and, by crossreactivity with CYP2D6 epitopes, trigger hepatic autoimmunity.[55]

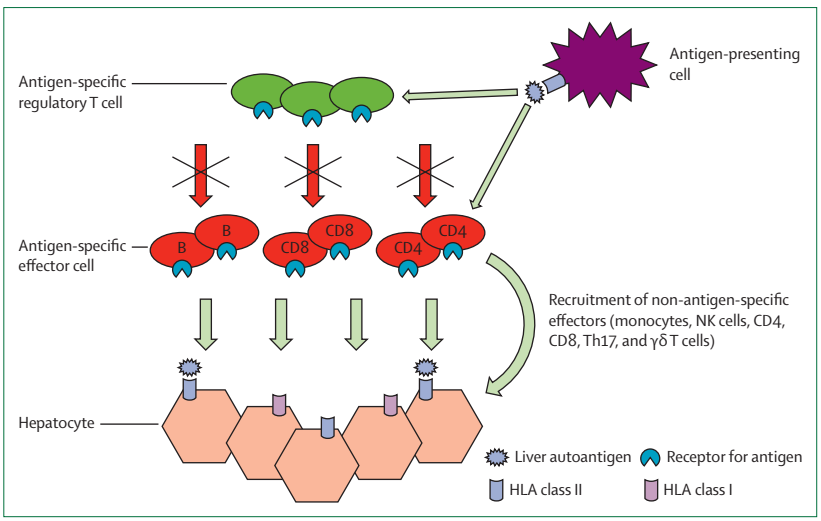


***Figure 2:*** **Pathogenesis of autoimmune liver damage**
Liver-autoantigen-specific regulatory T cells control effectors of liver damage (CD4, CD8, and B cells) sharing the same antigen specificity. When they are numerically or functionally impaired, or when the effectors are less susceptible to their control, liver damage occurs as direct result of antigen recognition and recruitment. Induced expression of HLA class II molecules (ie, HLA-DR3 and HLA-DR7) on hepatocytes renders them able to act as antigen-presenting cells for CD4 and CD8 effectors, causing amplification and perpetuation of liver damage.

| | Type 1 | Type 2 |
|---|---|---|
| Characteristic autoantibodies | Antinuclear antibody (20% of patients are negative for all conventional autoantibodies)<br>Anti-smooth-muscle antibody<br>Anti-actin antibody<br>Anti-soluble-liver-antigen or anti-liver-pancreas-antigen antibodies | Anti-liver-kidney microsomal antibody type 1 (rarely detected in North America)*<br>Anti-liver-cytosol antibody type 1 antibody<br>Anti-liver-kidney microsomal antibody type 3 |
| Geographical variation | Worldwide | Worldwide |
| Age at presentation | All ages | Usually childhood and young adulthood |
| Female-to-male ratio | 4:1 | 10:1 |
| Clinical phenotype | Variable | Generally severe |
| Histopathological features at presentation | Broad range: mild disease to cirrhosis | Generally advanced: inflammation and cirrhosis common |
| Treatment failure | Rare | Common |
| Relapse after drug withdrawal | Variable | Common |
| Need for long-term maintenance | Variable | About 100% |

*Although immunofluorescence is the most appropriate method to measure conventional autoantibodies in autoimmune hepatitis, many laboratories (especially those in the USA) are increasingly using ELISA-based methods to detect these antibody profiles. The profiles of anti-liver-kidney microsomal antibody type 1 can be erroneously reported as detectable antimitochondrial antibodies.[41]

***Table 1:*** **Classification of autoimmune hepatitis on the basis of autoantibody profiles**

## Role of MHC and other genes

Most genetic data for autoimmune hepatitis is derived from studies of MHC genes, specifically those that code for HLA. HLA molecules are crucial elements in the

generation of an immune response, specifically in the initiation of T cell-mediated immune responses.[56]

Type 1 autoimmune hepatitis is a typical autoimmune disease which has a strong association with the HLA 8.1 haplotype. In northern Europe and North America, three haplotypes are associated with the disease: two (characterised by the presence of HLA *DRB1*0301* allotype and the extended *DRB1*0401-DQA1*03-DQB1*0301* haplotype) are at increased frequency, and the third (HLA *DRB1*1501-DQA1*0102-DQB1*0602*) is at lower frequency in patients than in disease-free individuals.[56] In Brazilian populations, an increased frequency of HLA *DRB1*1301* has been reported compared to individuals from the USA.[17] Patients from Japan seem to have an association with the *DRB1*0405-DQB1*0401* haplotype.[57]

Although susceptibility and resistance to autoimmune hepatitis is mediated by HLA alleles, HLA alleles can also act as modifiers to the clinical phenotype.[58] Presence of the HLA DR4 subtype (*DRB1*0401*) is associated with less severe disease, a lower frequency of relapse, and presentation at an older age than in patients with *DRB3*0101*.[58] Other susceptibility alleles that increase susceptibility for the disorder are vitamin-D-receptor-gene polymorphisms[59] and *CTLA4*.[25] However, the association with *CTLA4* was not confirmed in a Brazilian population.[60]

Although genetic predisposition to type 1 autoimmune hepatitis has been linked mainly to HLA class II genes, a case-control association study of 400 polymorphic microsatellite markers in Japan[61] identified markers on chromosomes 11 and 18, in addition to 17 regions that might contain resistance genes. A whole-genome screen is therefore necessary in populations of northern European origin with autoimmune hepatitis—populations in which most studies of the genetics of autoimmune hepatitis have been done—to fully clarify the genetic associations.

By comparison, the role of HLA in type 2 disease is not well studied because of its low prevalence. However, available data suggest associations with HLA *DRB1*07* and HLA *DQB*0201*.[52,62,63]

### Triggers

Several environmental agents, such as viruses, have been suggested as putative triggers for autoimmune hepatitis. The suggestion of molecular mimicry and crossreactivity between epitopes of viruses, drugs, and hepatic antigens is attractive, and viral antigens or triggers might need to hit several times to activate a final common pathway. In that situation, priming of the immune system could occur years before the development of overt disease, and the identification of a triggering virus or drug is rarely possible.

So far, several viruses have been associated with the development of autoimmune hepatitis, such as hepatitis A,[64–66] hepatitis C,[67,68] hepatitis E,[69] measles,[70] Epstein-Barr,[71] and herpes simplex viruses.[53,72] In addition to viruses, research has identified several agents that precipitate autoimmune hepatitis, such as minocycline,[73,74] tienilic acid,[75] nitrofurantoin,[74] pemoline,[76] melatonin,[77] ornidazole,[78] diclofenac,[79] propylthiouracil,[80] and statins.[81,82] Herbal remedies, such as dai-taiko-so (da chai hu tang; commonly used in Japan), have also been associated with the disorder.[83]

| | Definite autoimmune hepatitis | Probable autoimmune hepatitis |
|---|---|---|
| Liver histology | Interface hepatitis of moderate or severe activity with or without lobular hepatitis or bridging necrosis<br>No biliary lesions, granulomas, or other prominent changes suggestive of a different aetiology | Same as for definite autoimmune hepatitis |
| Laboratory features | Any serum aminotransferase abnormality, especially if alkaline phosphatase activity is normal<br>Normal concentrations of α1-antitrypsin, copper, and caeruloplasmin | Same as for definite autoimmune hepatitis, but patients with abnormal concentrations of copper and caeruloplasmin can be included on the basis of exclusion of Wilson's disease by other appropriate investigation |
| Serum immunoglobulins | Globulin, γ-globulin, or IgG concentrations >1·5 higher than upper normal limit | Any increased in globulin, γ-globulin, or IgG concentrations above the upper normal limit |
| Serum autoantibodies | Antinuclear antibody, anti-smooth-muscle antigen, or anti-liver-kidney microsomal antibody type 1 at titres ≥1:80<br>Lower titres acceptable for children, especially for anti-liver-kidney microsomal antibody type 1<br>No antimitochondrial antibody | As for definite autoimmune hepatitis, but at titres ≥1:40, or with presence of other specified autoantibodies |
| Viral markers | No markers of present infection with hepatitis A, B, and C viruses | Same as for definite autoimmune hepatitis |
| Other exposures | Average alcohol consumption <25 g/day<br>No recent use of known hepatotoxic drugs | Average alcohol consumption <50 g/day<br>No recent use of known hepatotoxic drugs<br>Patients who have consumed larger amounts of alcohol or have had exposure to known hepatotoxic drugs might be considered if continuing damage after abstinence or withdrawal |

Adapted from Alvarez et al.[3]

***Table 2:*** **Descriptive criteria for diagnosis of autoimmune hepatitis**

## Clinical presentation and diagnostic criteria

Established criteria for the diagnosis of autoimmune hepatitis were created by an international panel of experts in 1992,[2] and further updated in 1999 (table 2).[3] They were developed as a research instrument originally to compare study populations in clinical trials, but they have been adapted widely for clinical practice. However, weighting of clinical, biochemical, and histological variables in conjunction with responsiveness to treatment designates patients as definitely, probably, or not having autoimmune hepatitis on the basis of composite scores (table 3).[3] In the past 5 years, simplified criteria that use detectable autoantibodies, IgG, histology, and exclusion of viral hepatitis have been promulgated and independently validated.[84–86] These criteria have a sensitivity of more than 80% and specificity of more than 95% at the cutoff level of seven points or higher.[84]

Although these criteria are available, the diagnosis of autoimmune hepatitis needs to be made clinically. Presentations vary from subclinical disease to acute liver failure[87] and end-stage liver disease.[88] Typical symptoms—eg, anorexia, fatigue, abdominal and joint pain, itching, and maculopapular rashes—are non-specific and so delays in diagnosis often occur.[10,13,88] Physical examination often does not identify anything, except in the context of liver failure. Jaundice can be present irrespective of the degree of histological fibrosis.

Therefore, autoimmune hepatitis is diagnosed on the basis of a combination of factors, including compatible biochemistry and serological markers, such as increased activity of serum aminotransferases (especially ALT and AST), high immunoglobulins, and the presence of high titres of circulating autoantibodies (titres of >1:80, except in children for whom lower titres can be diagnostic). Moreover, other disorders associated with immune activation or substantial necro-inflammation on liver biopsy (eg, Wilson's disease, chronic hepatitis C virus infection, and drug-induced injury) must be excluded. Autoimmune hepatitis can also develop during or after pregnancy (usually within the first 3 months post partum),[89,90] and many series have shown that immuno-suppression therapy is fairly safe when the disease has to be treated during pregnancy.[91–94]

Liver biopsy is important in both initial diagnosis and long-term follow-up of patients with autoimmune hepatitis. First, histological examination allows for disease staging and assessment of inflammation and fibrosis. Second, histology is crucial for diagnosis because up to 20% of patients do not have detectable autoantibodies. Third, biopsy examination allows for differentiation between autoimmune hepatitis and other autoimmune liver diseases (such as primary biliary cirrhosis, primary sclerosing cholangitis, and autoimmune cholangitis) and can identify variant syndromes of the disorder.[95] Finally, during treatment, biopsy is useful for management of the disorder; often, histological findings and biochemical variables might not match.[96] For overall assessment of disease activity, combined analysis and interpretation of overall data is necessary. Moreover, hepatic fibrosis can progress despite apparent adequate control.[97]

Although no pathognomonic features can be identified with liver biopsy, a mixed inflammatory infiltrate with a predominance of lymphocytes and plasma cells extending from the portal tract into the surrounding parenchyma is a frequent finding (figure 3).[3,98] The term interface hepatitis has been applied to the sharp difference between the inflammatory zone and the normal hepatic parenchyma, and this finding coupled with that of a plasma cell infiltrate supports the diagnosis. Variable degrees of inflammation can be present, ranging from little to submassive necrosis and collapse in the context of severe disease, which can present as the clinical syndrome of acute or subacute liver failure.

## Therapeutic management

Typically, an increase in aminotransferases of more than double, together with interface hepatitis on liver biopsy is an indication for treatment.[3] Patients should always be treated when they have an acute presentation with serum AST or ALT exceeding ten times the upper limit of normal, histological evidence of bridging or multilobular

| | Score |
|---|---|
| Female sex | +2 |
| Ratio of alkaline phosphatase to aspartate aminotransferase (or alanine aminotransferase) | |
| <1·5 | +2 |
| 1·5–3·0 | 0 |
| >3·0 | –2 |
| Serum concentrations of globulins or IgG above normal | |
| >2·0 | +3 |
| 1·5–2·0 | +2 |
| 1·0–1·5 | +1 |
| <1·0 | 0 |
| Titres of antinuclear antibodies, anti-smooth-muscle antigen, or anti-liver-kidney microsomal antibody type 1 | |
| >1:80 | +3 |
| 1:80 | +2 |
| 1:40 | +1 |
| <1:40 | 0 |
| Positive for antimitochondrial antibody | –4 |
| Hepatitis viral markers | |
| Positive | –3 |
| Negative | +3 |
| Drug history | |
| Positive | –4 |
| Negative | +1 |
| Average alcohol intake | |
| <25 g/day | +2 |
| >60 g/day | –2 |
| Liver histology | |
| Interface hepatitis | +3 |
| Predominantly lymphoplasmacytic infiltrate | +2 |
| Rosetting of liver cells | +1 |
| Biliary changes | –3 |
| Atypical features | –3 |
| None of the above | –5 |
| Other autoimmune disease in either patient or first-degree relative | +2 |
| Optional additional variables | |
| Seropositivity for other defined antibodies | +2 |
| HLA DR3 or DR4 | +1 |
| Response to treatment | |
| Remission alone | +2 |
| Remission with relapse | +3 |

Adapted from Alvarez et al.[3] Definite autoimmune hepatitis when score >15 before treatment or >17 after treatment. Probable autoimmune hepatitis when score 10–15 before treatment or 12–17 after treatment.

***Table 3:*** **Modified diagnostic scoring for the diagnosis of autoimmune hepatitis**

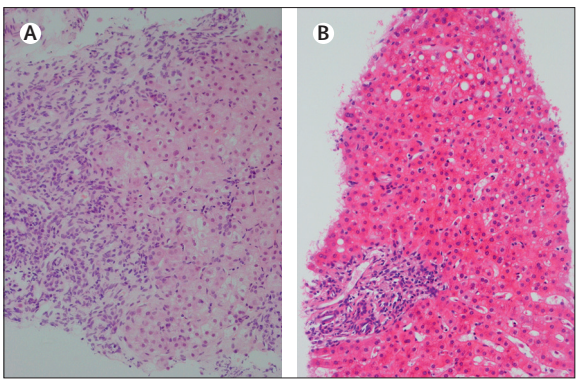


***Figure 3:*** **Liver biopsy specimen at presentation (A) and after 2 years of treatment with corticosteroids and azathioprine (B)**
At presentation, the patient had jaundice, dark urine, and pale stools, but no evidence of synthetic liver failure. The biopsy (A) showed a portally-based moderate mixed inflammatory infiltrate, consisting of lymphocytes and plasma cells affecting the interface. 2 years after treatment with corticosteroids and azathioprine, the patient had had a satisfactory biochemical and symptomatic response. The biopsy (B) showed little inflammatory activity, which is consistent with treated autoimmune hepatitis. The mild steatosis noted could be related to corticosteroid treatment.

necrosis, or severe hepatic and extrahepatic symptoms. Left untreated, 10-year survival is only 27%.[99,100] Patients who progress rapidly to fulminant (or subacute) liver failure should be put forward for liver transplantation. The question of how to manage patients with autoimmune hepatitis who have normal concentrations of serum aminotransferases is a difficult issue, because serum AST and ALT concentrations do not reliably indicate underlying necroinflammation.[7]

Early trials from the 1970s and 80s showed a clear survival benefit with corticosteroids compared with placebo,[100,101] and with corticosteroids compared with azathioprine.[102] Subsequently, controlled studies[103,104] focused on the use of azathioprine monotherapy to minimise corticosteroid side-effects while maintaining disease remission. Despite the limitations of early studies, use of corticosteroid therapy with or without azathioprine in clinical practice is associated with remission in about 85% of patients and thus has become the standard of care in the treatment of autoimmune hepatitis (table 4).

In a prospective, double-blind, randomised, phase 2b trial of patients without cirrhosis,[105] patients given budesonide (9 mg/day) and azathioprine (1–2 mg/kg/day) seemed to achieve complete biochemical remission with fewer steroid-related side-effects than did those given conventional prednisone and azathioprine-based immunosuppression. Although steroids have a fairly short biological half-life, azathioprine takes 3 months or more to become fully effective.[106] Therefore, introduction of azathioprine at an early enough timepoint to allow early weaning of corticosteroids is desirable. However, because azathioprine can induce an idiosyncratic hepatitis, treatment should begin only once AST is less than two times the upper limit to differentiate this result from treatment non-response.

When azathioprine is begun, testing for a polymorphism in *TPMT* should be considered, or alternatively the concentration of TPMT enzyme should be measured before treatment. For *TPMT* homozygotes with negligible concentrations of or no enzyme, azathioprine should be avoided, because death from cytopenic and septic complications is possible. For *TPMT* heterozygotes, treatment with azathioprine should begin at a reduced dose with monitoring of white cell count during treatment.[107] However, neither *TPMT* genotype nor enzyme activity predicts toxic effects in all patients.[107,108] Thus, the role of phenotyping and genotyping needs to be fully assessed.

In responsive patients, the AST concentration usually becomes normal within 6–12 weeks of treatment, although histological remission lags 6–12 months behind.[109] Even in the context of fibrosis and cirrhosis, substantial regression of scarring with steroid treatment has been reported.[97,110,111] What constitutes complete response to treatment is difficult to categorise,[112] but the need for a composite endpoint of normal aminotransferase activity, normal immunoglobulin concentrations, and normal histology is increasingly recognised.[113–115]

Several controlled trials have investigated withdrawal of treatment after long periods in remission on maintenance treatment (low doses of prednisolone or azathioprine). In one study of 30 patients who had been in remission for between 1·5 and 9 years,[116] only three remained in remission 1 year after treatment withdrawal, and ultimately all relapsed. However, withdrawal of steroid treatment and replacement with azathioprine at a dose of 2 mg/kg per day can maintain remission without relapse,[104] and greatly improves side-effects associated with steroids.[117]

Whilst laudable as an aim of management, whether all immunosuppressive treatment can be completely withdrawn in patients with autoimmune hepatitis is unclear. Cessation of all immunosuppression should probably only be attempted after biochemical and histological remission has been sustained for at least 2 years, and treatment should be gradually and systematically reduced before being stopped completely. Consistent with previous reports,[103] a 2001 uncontrolled study[118] showed that the probability of sustained remission in patients who had received 2–4 years of continuous treatment was 17%, by contrast with a 67% probability for those who had received more than 4 years of continuous treatment.

Reinforcing the idea that a goal of treatment should be the return to normal concentrations of aminotransferases, investigators have identified associations between increased aminotransferases during remission and relapse after treatment withdrawal.[115] In view of these findings, serum aminotransferase concentrations should be closely monitored after treatment withdrawal and a further flare in disease activity could warrant

lifelong low-dose immunosuppression, although this idea is controversial.

Steroid-related side-effects—eg, diabetes mellitus, osteoporosis, cataracts, and psychiatric disturbance—have been reported. Azathioprine has its own profile of toxic effects, such as nausea, vomiting, rashes, pancreatitis, hepatotoxicity, and bone-marrow suppression.[108,117] These problems are usually reversible.

10–15% of patients with autoimmune hepatitis seem to be refractory to standard treatment, which could be a result of non-compliance, partial compliance, or true non-response. Other patients might have another underlying condition such as primary sclerosing cholangitis, primary biliary cirrhosis, or a variant syndrome. For patients with true non-responsive disease, alternative immunosuppression might be required. In autoimmune hepatitis, many agents have been used with variable success, and none have been tested in a randomised controlled trial.

Calcinurin inhibitors, such as ciclosporin A and tacrolimus, are the most commonly used alternative immunosuppressants in both adults and children with autoimmune hepatitis.[119–123] Similarly, in treatment-naive children with autoimmune hepatitis, ciclosporin A might have a role, although clinical trials have not been done.[124–127] The major issue preventing the widespread acceptance of these agents as primary treatment relates to their toxic effects, which include hypertension, renal insufficiency, hyperlipidaemia, hirsutism, infection, and malignant disease. Budesonide and deflazacort have a 90% first-pass metabolism in the liver, making them an attractive option for the management of hepatic inflammation both in terms of the side-effect profile and efficacy. They have been formally assessed, but with mixed results.[128–132]

Mycophenolate mofetil is a non-competitive inhibitor of inosine monophosphate dehydrogenase that blocks the rate-limiting enzymatic step in de-novo purine synthesis.[133] In clinical settings, responses vary in terms of responsiveness[123,134–137] and toxic effects.[135,138] For other agents, such as ursodeoxycholic acid,[139] cyclophosphamide,[140] methotrexate,[141] sirolimus,[108] and alternative biologic agents such as etanercept or rituximab (used in the context of treatment of other refractory autoimmune disease in patients with co-incident disease),[142,143] experience is limited to single case reports or small case series.

| | Standard treatment | Alternative treatment* |
|---|---|---|
| Induction | Prednis(ol)one 40–60 mg/day (taper to 10 mg/day in 6–12 weeks); add azathioprine† when aspartate aminotransferase decreased to 2–3 times normal range<br>Alternative 1: prednis(ol)one 20 mg/day; azathioprine† 1 mg/kg/day<br>Alternative 2 (for patients without cirrhosis): budesonide 9 mg/day (taper over 6-18 weeks); azathioprine 1 mg/kg/day | Alternative 1: mycophenolate mofetil 1g twice a day; ciclosporin to achieve trough concentrations of the drugs of 150–250 ng/mL |
| Maintenance of remission | Increase azathioprine to 2 mg/kg per day; steroid withdrawal during 3 months<br>Alternative: steroid monotherapy | Tacrolimus to achieve trough concentrations of the drugs of 6–10 ng/m |
| Cholestatic features | Addition of 12–15 mg/kg per day ursodeoxycholic acid in divided doses | Cyclophosphamide, methotrexate, sirolimus |
| Relapse | Prednis(ol)one 40–60 mg/day (slow taper to 15 mg/day); institute azathioprine when not previously used | .. |
| Treatment failure of fulminant disease | Orthotopic liver transplantation | .. |

*When standard treatment fails or when there are contraindications to steroids (severe osteoporosis, psychosis, morbid obesity, and severe diabetes mellitus). †Check *TPMT* genotype: if homozygous, no azathioprine; if heterozygous, begin azathioprine at dose of 0·5 mg/kg/day and monitor white cell count every week.

***Table 4:*** **Treatment options**

## Long-term outcomes

Untreated severe autoimmune hepatitis is associated with poor short-term and long-term prognoses when compared with treated patients.[100,101] For patients with established cirrhosis at presentation, treatment can induce remission and improve long-term outcome, with 10-year life expectancies of greater than 90%,[118,144] although some data suggest that survival might not be so favourable outside tertiary referral centres.[88,145] Moreover, a 2009 Scandinavian study[146] showed that hepatobiliary and lymphomatous cancers are frequent in long-term follow-up of patients with autoimmune hepatitis. In two series,[147,148] hepatocellular carcinoma was identified at a mean of 9 years and 10 years after the development of cirrhosis, which suggests that screening for hepatocellular carcinoma should be mandatory in cirrhotic patients with autoimmune hepatitis.[147]

For patients with the severe acute phenotype, failure to respond to treatment within the first 7–14 days after presentation is associated with a mortality of almost 50%.[149] Moreover, that patients presenting with indeterminate causes of acute liver failure might have autoimmune hepatitis as their underlying aetiology is increasingly recognised.[87] Autoimmune hepatitis is an acceptable reason for liver transplantation, with frequency of survival exceeding 75% at 5 and 10 years after transplant.[150,151]

Recurrent disease after liver transplantation is well described.[151,152] Its pathogenesis—occurring as it does in the context of HLA mismatch and immunosuppression treatment after liver transplantation—is poorly understood. Despite this finding, graft loss and need for retransplantation for recurrent autoimmune hepatitis is rare. As yet, no association between recurrence of disease and post-transplant immunosuppression has been identified.[153]

The idea of an autoimmune type of hepatitis occurring in recipients of liver transplants who underwent transplantation for reasons other than autoimmune hepatitis has evolved in the past decade.[154,155] First described in children,[154] this syndrome of graft dysfunction is associated with the presence of increased serum aminotransferases and immunoglobulins and the histological features of interface hepatitis coupled with a rich plasma cell infiltrate. As an entity, it is increasingly recognised

after the treatment of hepatitis C recurrence after liver transplantation with antiviral therapy.[156,157] The terms de-novo autoimmune hepatitis and indeed alloimmune hepatitis have been coined, although a more accurate term reflecting the liver graft dysfunction and the immune activation is graft-dysfunction-mimicking autoimmune hepatitis.[155] Universally, the syndrome is responsive to corticosteroids and, with early recognition and appropriate management, liver graft loss can be avoided in most cases.[158]

## Variant syndromes

In clinical practice, some patients do not fit discretely into a specific subgroup or diagnostic category on the basis of clinical, serological, and histological criteria. With time, several terms—eg, overlap syndrome, antimitochondrial-antibody-negative primary biliary cirrhosis, and autoimmune cholangitis—have been introduced into the scientific literature to describe these variant forms of autoimmune hepatitis.[95,159–161] The term variant implies a resemblance of the disorder to autoimmune hepatitis, yet recognises that features of other disease states, such as primary biliary cirrhosis and primary sclerosing cholangitis, could coexist in combination. Whether or not these variant syndromes represent distinct disease entities or are the result of overly precise diagnostic criteria is a subject of debate.[162] Moreover, the increased recognition that a predominant hepatic process could evolve with time into a distinct cholestatic disease state (eg, primary sclerosing cholangitis[163]) or that a biliary process (eg, primary biliary cirrhosis[164]) can evolve into autoimmune hepatitis, adds confusion to the specialty.[164,165]

Variant syndromes are typically indolent and similar to autoimmune hepatitis, and are characterised by asymptomatic presentations or non-specific symptoms, including fatigue and flu-like symptoms.[88] Patients can be of either sex and of any age, but are most commonly women aged 40 years or younger.

Histological findings are consistent with the diagnosis of autoimmune hepatitis, but unusual morphological features are often recorded, such as bile-duct injury, steatosis, and portal lymphoid aggregates.[166–168] One difficulty in the interpretation of histology in these patients is the recognition that up to 24% of patients with definite autoimmune hepatitis as defined by the International Autoimmune Hepatitis Group criteria might have biliary changes.[169]

Finally, autoimmune hepatitis can occur in the context of the autoimmune polyendocrine syndrome type 1.[170] Therefore, consideration should be given to this clinical entity when extrahepatic autoimmune features are prominent and appropriate genetic testing obtained.[171]

The low prevalence of variant syndromes has made it impracticable to do randomised controlled trials. Therefore, treatment of these variant syndromes is not validated and is based on the treatment of the predominant parent disorder (autoimmune hepatitis, primary biliary cirrhosis, or primary sclerosing cholangitis). This premise has been reinforced by a consensus document of the International Autoimmune Hepatitis Group.[162] The addition of ursodeoxycholic acid in patients with a cholestatic component to their disease is common in clinical practice.[172] For patients with a hepatic component, corticosteroid treatment is effective.[172,173]

Autoimmune sclerosing cholangitis is a syndrome that has been described in childhood and is associated with steroid responsiveness in the context of cholangiographic evidence of bile-duct damage.[174] More patients with autoimmune sclerosing cholangitis need a liver transplant than do patients with autoimmune hepatitis alone.[174] For adult patients with overlap syndrome, a substantial reduction in survival was identified in patients with the overlapping variant of primary sclerosing cholangitis and autoimmune hepatitis—with a two-times higher risk of death or need for a liver transplant—than patients with autoimmune hepatitis alone or primary biliary cirrhosis and autoimmune hepatitis.[168]

In view of the role of regulatory T cells in the control of adaptive and innate immune responses and because of their numerical and functional impairment in patients with autoimmune hepatitis, efforts have been made to generate and expand them in vitro with the aim to use them as a new form of immunotherapy. Expanded regulatory T cells express higher levels of the transcription factor FOXP3 and suppress more effectively than do unexpanded regulatory T cells. Longhi and colleagues[28] reported generation of antigen-specific regulatory T cells in the context of type 2 autoimmune hepatitis and showed that these cells control effector function of CD4 and CD8 T cells of the same antigen specificity much more efficiently than do non-antigen-specific polyclonal regulatory T cells. They could therefore offer a novel therapeutic, even curative approach to autoimmune hepatitis, because these antigen-specific regulators could control effectors of damage that share the same antigen specificity without inducing pan-immunosuppression (ie, they do not affect effectors with different specificity often not involved in liver damage), while boosting immune tolerance to liver autoantigens.

## Conclusion

Autoimmune hepatitis is a recognised clinical disorder and many patients have asymptomatic presentations, insidious disease onset, or non-specific symptoms, which adds complexity to the diagnostic pathway. Even in the context of validated diagnostic criteria, autoimmune hepatitis is a clinical diagnosis, and, in practice, variants of the disease arise which can be difficult to identify.

Although immunotherapy alters the natural history of disease and improves overall survival and prognosis for up to 20 years, it can be a lifelong burden. However, whether lifelong immunosuppression is necessary is an unanswered question. Moreover, with novel and

potent immunosuppression, the issue of cost-effectiveness arises; standard treatment is effective in 85% of patients. Prospective, randomised, multicentre studies are needed to address these unresolved issues. The findings for the pathogenesis of type 2 autoimmune hepatitis and the possibility that liver-autoantigen-specific regulatory T cells that control effectors of the same antigen specificity can be generated[28] are promising for the development of novel treatment strategies.

#### Contributors

All authors wrote and revised this report.

#### Conflicts of interest

MAH has received travel bursaries from Roche Laboratories and Astellas. The other authors declare that they have no conflicts of interest.

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