# Autoimmune hepatitis and overlap syndrome

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## Abstract

Autoimmune hepatitis (AIH) is an acute or chronic liver disease that causes significant inflammation at a cellular level and leads to cirrhosis if left untreated. The basis of diagnosis is increased liver enzymes and immunoglobulins with positive autoantibodies and necroinflammatory changes on liver biopsy. Clinical presentations can vary. Asymptomatic patients may only have raised liver enzymes detected on routine testing, the other extreme of presentation being represented by fatigue, jaundice and liver failure. Other autoimmune liver diseases such as primary biliary cholangitis and primary sclerosing cholangitis can evolve during the clinical course. AIH typically responds well to immunosuppressant therapy. Patients should be monitored closely for adverse effects of drugs and, more importantly, to detect possible non-response or partial response to therapy to avoid disease progression and initiation of early second-line therapy. Monitoring for adverse effects should also cover bone health, diabetes and skin-related issues.

**Keywords** Autoantibodies; autoimmune hepatitis; cirrhosis; immunosuppression; MRCP; overlap syndrome; transplantation

## Key points

- Autoimmune hepatitis (AIH) should be considered in all patients with elevated liver enzymes, especially if they have positive antibodies and serum hypergammaglobulinaemia
- Prompt treatment should be started to prevent complications such as cirrhosis
- Corticosteroids and azathioprine are effective in most patients with AIH
- Consider other add-on treatments in patients with overlap syndrome
- Monitoring patients for adverse effects of immunosuppression and cancer in cirrhotics with 6-monthly ultrasounds is important

## Introduction and epidemiology

Autoimmune hepatitis (AIH) is a chromic liver condition that can cause significant inflammation and lead to cirrhosis if untreated. AIH is diagnosed from a combination of raised liver enzymes — aspartate aminotransferase (AST) and alanine aminotransferase (ALT) — hyperglobulinaemia, positive antibodies and compatible histological findings.

AIH can present at any age but has a bimodal distribution. The first peak is around puberty and the second peak between the fourth and sixth decades. It predominantly affects women. The female to male ratio is 4:1 in type 1 AIH, whereas in type 2 AIH it is 10:1.[1] The incidence of autoimmune liver diseases worldwide is around 1—2 per 100,000 population per year, while the prevalence varies from 4 to 25 per 100,000. It can affect all ethnic groups, but individuals of African and Afro-Caribbean descent have more aggressive disease than non-black individuals and are also less likely to achieve remission and more likely to have cirrhosis at presentation.

## Pathogenesis

AIH is a classical autoimmune disorder in which environmental factors trigger an immune response in genetically susceptible individuals. The genetic predisposition differs across regions and ethnicity. Genome-wide association studies have identified variants in the major histocompatibility complex region associated with type 1 AIH. The two most common allotypes in Northern Europe are HLA-DRB1*0301 and HLA-DRB1*0401.[2]

Specific environmental triggers are unknown, but some evidence suggests an involvement of viral infections such as hepatitis A virus, herpes simplex virus, measles virus and Epstein—Barr virus. The drugs most commonly associated with AIH are nitrofurantoin and minocycline, anti-tumour necrosis factor (anti-TNF) biological agents, herbal medications and supplements. These may mediate their effect through molecular mimicry and this might be the starting point of the immunogenic cascade in a genetically predisposed patient.[3] Dysregulation of regulatory T cells is the most common mechanism of pathogenesis proposed in AIH and this might ultimately become the basis of future therapy.

## Clinical presentation

AIH is associated with a wide spectrum of presentations, from a lack of symptoms in up to 45% of patients to fulminant liver failure in a minority. Up to one-third of adult patients present with cirrhosis at diagnosis. The disease usually has a chronic fluctuating course. AIH must be a differential diagnosis in any patient presenting with elevated liver enzymes. Common symptoms are jaundice, itch and abdominal pain. Fatigue is reported

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in up to 61% of individuals. Patients who present with acute severe liver injury can require life-saving liver transplantation.

AIH is associated with extrahepatic autoimmune disorders in the patient themselves or in a first-degree relative. The most common diseases are Hashimoto's thyroiditis, coeliac disease, type 1 diabetes mellitus, systemic lupus erythematosus, Sjögren's syndrome, alopecia, inflammatory bowel disease and rheumatoid arthritis.

## Diagnosis

As patients can be asymptomatic with only mild impairment of their liver profile, further serological evidence is needed to support the diagnosis. The hallmarks of classical presentations are elevated serum transaminases (AST or ALT with increased serum total immunoglobulin (Ig) G), and positive antinuclear antibodies (ANAs), smooth muscle antibody (SMA), anti-liver −kidney microsomal (LKM) antibodies or antibody to liver cytosol (LC). Around 20% of patients present with negative autoantibodies. Society guidelines suggest that liver biopsy is mandatory for diagnosis. More importantly, other causes of hepatitis, such as viral infections, Wilson's disease, non-alcoholic fatty liver disease, alcohol and drug-induced hepatitis, must be excluded. Simplified diagnostic criteria for AIH are summarized in Table 1. A score of ≥6 indicates probable AIH, and a score ≥7 indicates definite AIH.

### Biochemistry

Transaminitis (raised AST/ALT) is a usual feature in AIH. Bilirubin can also be raised. Alkaline phosphatase (ALP) concentrations are often normal, and a cholestatic liver enzyme pattern should prompt consideration of possible overlap syndrome. AST and ALT can increase to up to 10−20 times the upper limit of normal, and even much higher in acute severe AIH.

### Immunology

The two categories of AIH are classified according to blood autoantibody profile, although in essence they share the same symptomatology and impaired biochemical profile. Type 1 AIH is characterized by the detection of ANA or anti-SMA. Other antibodies such as atypical perinuclear antineutrophil cytoplasmic antibodies (atypical pANCA) and antibodies to the liver-specific asialoglycoprotein receptor (L-ASGPR), anti-soluble liver antigens/liver−pancreas antigens (SLA/LP) and double-stranded DNA (dsDNA) can be positive. The presence of anti-mitochondrial antibody (AMA) is unusual and should raise the likelihood of an underlying diagnosis of primary biliary cholangitis (PBC). These antibodies do not underlie the pathogenesis of AIH but represent a biomarker of disease.

Type 2 AIH is defined by the presence of antibodies to LKM and/or to LC. LKM antibodies are directly associated with the pathogenesis of AIH.

### Histology

There are no specific histological features that define AIH, but typical features include interface activity, hepatocellular rosettes, emperipolesis and plasma cell infiltration. However, their absence does not exclude the diagnosis. It is important to look for clues that might suggest other diseases such as viral infection or copper or fatty deposits, which present very similarly to AIH.

### Diagnosis of overlap syndrome

A summary of the diagnostic features of PBC and primary sclerosing cholangitis (PSC) is presented in Table 2.

## Treatment

### Indications for treatment

Treatment should be individualized to the particular individual, and the regimen should be guided by the response to treatment. Almost all patients need treatment. This should be initiated when AST is 10 times the upper limit of normal, or AST twice the upper limit of normal with histology indicating necroinflammatory change. Debate exists over the treatment of very mild disease.

### Induction and maintenance of therapy (Table 3)

There are several regimens for corticosteroid induction. The European Association for the Study of the Liver (EASL) describes prednis(ol)one 0.5−1.0 mg/kg per day as the initial therapy, followed after 2 weeks by the addition of azathioprine. Azathioprine should be started at 50 mg and increased depending on toxicity and response. Thiopurine methyltransferase (TPMT)

**Simplified diagnostic score for AIH**

| Variable | Cut-off | Points |
|---|---|---|
| ANA or anti-SMA | >1:40 | 1 |
| ANA or anti-SMA or anti-LKM | >1:80 | 2 |
| SLA | Positive | 2 |
| IgG | >Upper limit of normal | 1 |
| | >1.1 Upper limit of normal | 2 |
| Liver histology | Compatible with AIH | 1 |
| | Typical AIH | 2 |

A score of ≥6 indicates probable AIH and a score ≥7 indicates definite AIH.

Adapted from Hennes E, Zeniya M, Czaja A. Simplified criteria for the diagnosis of autoimmune hepatitis. *Hepatol* 2008; **48:** 169-−76.

**Table 1**

**Diagnostic criteria for PBC/AIH overlap syndrome**

At least two out of three diagnostic criteria for AIH and PBC must be present for the diagnosis of PBC/AIH

Criteria for PBC:

1. ALP >2 × ULN or GGT >5 × ULN
2. AMA >1:40
3. Liver biopsy specimen showing a florid bile duct lesion

Criteria for AIH:

1. ALT >5 × ULN
2. IgG >2 × ULN or positive SMA
3. Liver biopsy showing moderate or severe periportal or periseptal lymphocytic piecemeal necrosis

GGT, γ-glutamyl transferase; ULN, upper limit of normal.

Adapted from Chazoullieres et al. Primary biliary cirrhosis-autoimmune hepatitis overlap syndrome: clinical features and response to therapy. Hepatol 1998; 28: 296−301.

**Table 2**

**Treatment approach for patients with autoimmune disease**

| | |
|---|---|
| Induction | Prednis(ol)one 0.5 mg/kg/day[a] *or* prednis(ol)one 40 mg with reduction 2-weekly to maintenance of 5–7.5 mg/day[b] *or* budesonide (in non-cirrhotic disease only) 6–9 mg and reduce according to response[c] |
| Maintenance | Addition of azathioprine 50 mg/day (after TPMT concentrations have been checked)<br>Increase dose of azathioprine to 1–2 mg/kg aiming for monotherapy |
| Second line | Prednis(ol)one and azathioprine<br>**If intolerant to AZA:** try 6-MP; if still intolerant switch to MMF 1 g daily, which can be increased to 1.5–2 g daily<br>**If insufficient response:** check azathioprine metabolites (TGN) and try to increase AZA dose *or* give low-dose AZA and allopurinol *or* increase corticosteroids and AZA |
| Third line | Tacrolimus: 0.1 mg/kg/day aiming for concentrations of 4–6 ng/ml<br>Ciclosporin: 2–6 mg/kg/day aiming for concentrations of 100–200 ng/ml<br>Sirolimus: 1–2 mg/day aiming for concentrations of 4–6 ng/ml<br>Combination of prednis(ol)one + AZA + (tacrolimus/ciclosporin/sirolimus) |
| Experimental | Rituximab intravenous 1 g, then 1 g intravenous after 2 weeks<br>Anti-TNF (Infliximab)<br>Low dose IL-2<br>Clinical trials |

AZA, azathioprine.
[a] According to EASL.
[b] According to AASLD and BSG.
[c] According to EASL, AASLD and BSG.

**Table 3**

concentrations should be checked before starting azathioprine. The dose of azathioprine maintenance using monotherapy is 1–2 mg/kg per day. The British Society of Gastroenterology (BSG) and the American Association for the Study of Liver Diseases (AASLD) advise prednis(ol)one 40 mg/day and corticosteroid reduction every 2 weeks to a maintenance dose of 5–7.5 mg/day, with escalation of the azathioprine dose. Alternatively, induction with budesonide 6–9 mg/day in patients without cirrhosis can be used to minimize systemic adverse effects, with azathioprine added once bilirubin concentrations are <100 micromol/litre.

### Second-line therapy

This consists of optimal dosing of prednis(ol)one and azathioprine. Patients are then divided into three major groups: responders, insufficient responders and individuals intolerant of therapy. Individuals responding to therapy should continue with the same dosage.

For those with an insufficient response, thiopurine metabolites (6-thioguanine (6-TGN)) should be measured to check compliance and, if needed, either an increase in dose of azathioprine or low-dose azathioprine with allopurinol may be indicated. For patients who are intolerant of azathioprine, 6-mercaptopurine (6-MP) 1.0–1.5 mg/kg per day can be a substitute to avoid adverse effects. If patients remain intolerant, mycophenolate mofetil (MMF), a purine antagonist, can be used at a dose of 1 g daily and can be increased to 1.5–2 g daily.[4]

### Third-line therapy

For refractory patients, calcineurin inhibitors (CNIs) such as tacrolimus and ciclosporin have been used. These medications should only be used in specialized liver centres or with a specialist input. Alternatively, optimizing the doses of prednis(ol)one and azathioprine combination therapy with a CNI, and monitoring disease activity with a repeat liver biopsy in 12–18 months, is appropriate.[4]

### Fourth-line therapy

For patients who do not respond to all the above-mentioned lines of therapy, rituximab, infliximab or low-dose interleukin (IL)-2 and participation in a clinical trial is appropriate. Some non-responders require liver transplantation.

### Monitoring adverse effects

Adverse effects of corticosteroids should be monitored by measuring glycated haemoglobin and bone mineral density, as well by prescribing appropriate calcium and vitamin D replacement. Routine skin checks should be performed as appropriate while patients are on immunosuppressants, emphasizing sun-protective measures. Careful monitoring of full blood count is needed while patients are on azathioprine, 6-MP or MMF. MMF should not be used in women who wish to conceive as it is highly teratogenic.

### Liver transplantation

The indications for transplantation in AIH are similar to those for other liver diseases and include acute liver failure and decompensated liver disease. Between 5% and 10% of patients with AIH require a transplant. Recurrent AIH after transplantation occurs in up to 25% of these individuals.

### Treatment endpoints

Disease remission is defined by a lack of signs of inflammation on liver biopsy, correction of IgG values and normal ALT and AST, with resolution of symptoms.

### Treatment withdrawal

The permanent withdrawal of medication is achievable in patients who have a normal biochemical profile and histology. In several cohorts of patients in whom medication was withdrawn, only 15% remained medication free after 1 year. An absence of cirrhosis and the correction of liver function tests are important determinant factors for achieving drug withdrawal. Patients need life-long monitoring to detect relapse.

### Therapeutic intolerance

This occurs in approximately 14% of patients. Up to 30% of individuals on corticosteroids show treatment-ending adverse effects and can develop brittle diabetes, osteoporosis-related fractures, emotional instability and severe cosmetic

transformation. With azathioprine, 5–10% of patients develop treatment-curtailing adverse effects such as pancreatitis, liver toxicity, nausea and rash. Azathioprine-induced cytopenia is reported in <6% of patients.

### Treatment failure

Despite absolute compliance with treatment, patients can show a deterioration in their clinical, laboratory and histological features. They can develop signs of decompensation such as jaundice, ascites and hepatic encephalopathy. For patients deemed to have treatment failure, it is important to revisit the diagnosis as overlap syndrome, viral diseases and Wilson's disease need to be considered.

It is essential to ensure that patients are compliant with therapy before labelling them as having failed treatment, and it can be helpful to check metabolites or trough concentrations of medication. Before escalating treatment to second-line therapy, a repeat liver biopsy must be considered, as should increasing corticosteroid dosages and optimizing immunosuppression.

### Treatment of overlap syndrome (Figure 1)

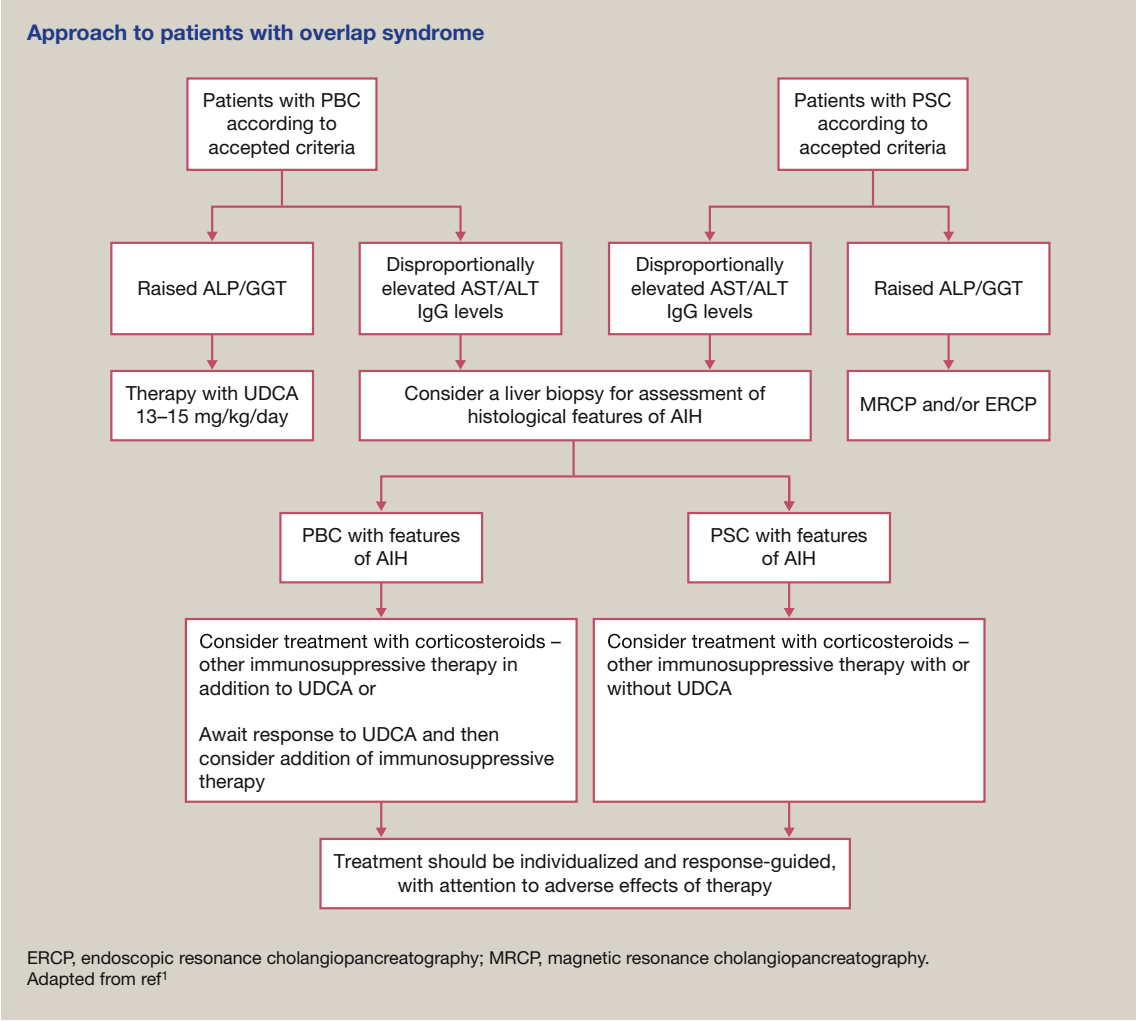
**Autoimmune hepatitis/primary biliary cirrhosis:** in this situation, therapy is as for classical AIH with the addition of ursodeoxycholic acid (UDCA). Another approach is to start UDCA at the outset if there are features of biliary disease on biopsy, and subsequently consider the addition of other immunosuppressants.[5]

**Autoimmune hepatitis/primary sclerosing cholangitis:** unlike AIH/PBC overlap syndrome, where induction with corticosteroids and maintenance with immunosuppressants such as azathioprine is clear, UDCA in this circumstance is optional as it does not alter the course of PSC. Endoscopic intervention is useful in patients with biliary obstruction and sepsis. UDCA can be useful in the context of raised ALP and γ-glutamyl transferase (GGT).[5]

### Pregnancy

Reduced fertility has been associated with AIH, but better control of disease produces a significant improvement in conception and pregnancy rates. It has been demonstrated that poor disease control in the year before pregnancy and the absence of drug therapy are associated with poor outcomes while pregnant.

Azathioprine appears to be generally safe and without adverse outcomes for mother or baby, as seen in several larger studies of inflammatory bowel disease. Higher doses of corticosteroids are




ERCP, endoscopic resonance cholangiopancreatography; MRCP, magnetic resonance cholangiopancreatography.
Adapted from ref[1]

**Figure 1**

an alternative option for those who prefer azathioprine withdrawal during pregnancy. Close monitoring is required during pregnancy and during the postpartum period as patients are prone to flares in disease activity.

## Prognosis

In general, patients with AIH who respond to therapy have a good prognosis. Within 2 years of starting treatment, 70% show an improvement in their clinical and biochemical profile, indicating better survival. Predictors of poor outcome are liver decompensation, cirrhosis, failure to correct ALT concentrations within 12 months of starting therapy, and >4 relapses per decade.

### Hepatocellular carcinoma (HCC)

There is a low incidence of developing HCC in cirrhosis from AIH compared with other causes of liver disease. In a meta-analysis the incidence of HCC complicating AIH-related cirrhosis was 10.07 per 1000 patient−years. The incidence of HCC in AIH without cirrhosis is 3.1 per 1000 patient−years. Patients with AIH cirrhosis should undergo surveillance liver ultrasound every 6 months, with measurement of serum α-fetoprotein to detect early HCC. ◆

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