Diagnosis and Management of Paediatric Autoimmune Hepatitis (AIH)

The purpose of this guide is to outline the diagnostic and management issues related to AIH and to provide guidance for complicated clinical scenarios.

AIH is the prototype autoimmune liver disease in adults and children and is a progressive inflammatory hepatopathy which, if not treated, progresses to end stage liver disease requiring liver transplantation.

Diagnostic Criteria

There is no single diagnostic test for AIH, so diagnosis is based on a combination of clinical, biochemical, immunological, and histological features and the exclusion of other known causes of liver disease that may share serological and histological features with AIH (e.g., hepatitis B, C, and E, Wilson disease, non-alcoholic steatohepatitis, and drug-induced liver disease). Liver biopsy is needed to confirm the diagnosis and to evaluate the severity of liver damage.

NOTE TO CLINICIANS

The International Autoimmune Hepatitis Group (IAIHG) has devised a diagnostic system which gives a value indicative of probable or definite AIH, but this is not suitable for the juvenile form of the disease.

Pathologic Features

The typical histological feature of AIH is interface hepatitis, which is not exclusive to this condition. Other common features include: female preponderance, hypergammaglobulinemia/increased immunoglobulin G (IgG), seropositivity for circulating autoantibodies, and a positive family history for autoimmune conditions.

When AIH presents acutely, and during episodes of relapse, a common histological finding is panlobular hepatitis with bridging fibrosis. Other nonspecific features that may point to the diagnosis of AIH are emperipolesis and hepatocyte rosetting, which have been suggested to be stronger indicators of AIH than interface hepatitis or plasma-cell rich infiltrate, but these findings are not present in all patients.

Hyaline droplets in Kupffer cells maybe a useful diagnostic marker to distinguish AIH from other forms of chronic hepatitis. The hyaline droplets occur specifically in AIH regardless of the type and are positive for IgG by immunohistochemical analysis, correlating with a >2-fold increase in serum level of IgG.

FACTS & STATS

Two types of AIH defined by serological profile

(AIH-1) is positive for antinuclear antibody (ANA) and/or anti-smooth muscle antibody (SMA)

(AIH-2) is defined by positivity for anti-liver kidney microsomal type 1 antibody (anti-LKM-1) and/or for anti-liver cytosol type 1 antibody (anti-LC-1).

Autoantibodies

Key to the diagnosis of AIH is positivity for circulating autoantibodies, although autoantibodies can be present in other liver disorders and are not diagnostic in isolation. Their detection by indirect immunofluorescence on a rodent substrate not only assists in the diagnosis but also allows differentiation into the 2 forms of AIH: ANA and SMA characterize AIH-1; anti-LKM1 and anti-LC-1 define AIH-2.

As interpretation of the immunofluorescence patterns can be difficult, guidelines have been provided by the IAIHG regarding methodology and interpretation of liver autoimmune serology.

Autoimmune hepatitis is more aggressive in childhood than adulthood

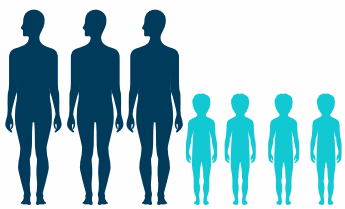
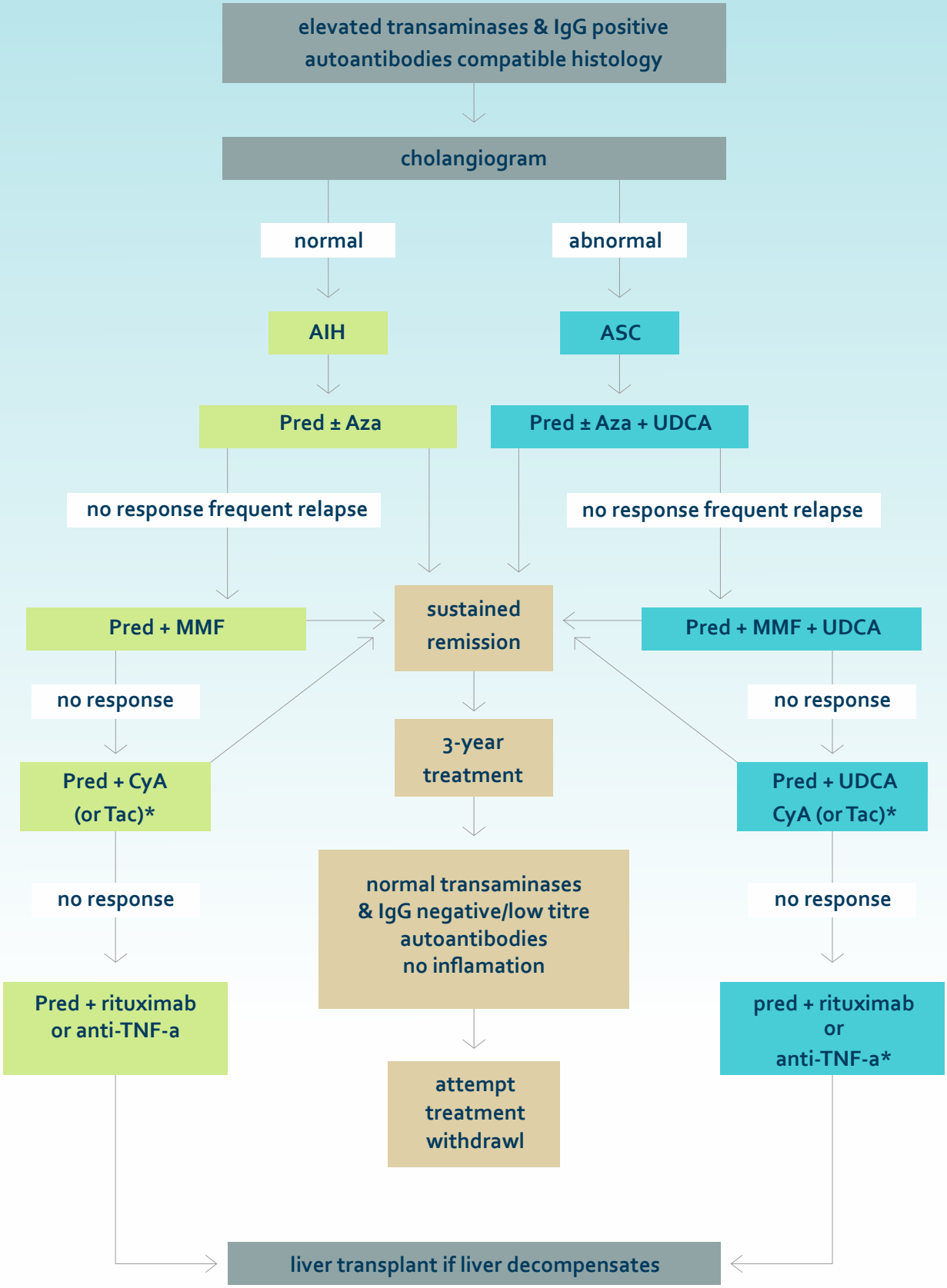


Figure 1.
Flow chart for treatment decision making in children with autoimmune liver disease



*Second and third-line treatments to be decided and monitored only in specialised pediatric hepatology centers.
(modified from (62).

Clinical Features of AIH

Clinical presentations include:

1. Acute onset resembling that of viral hepatitis, with nonspecific symptoms of malaise, nausea/vomiting, anorexia, joint and abdominal pain, followed by jaundice, dark urine, and pale stools (40%–50% of patients with AIH-1 or AIH-2)
2. Acute liver failure (ALF) with grade II to IV hepatic encephalopathy developing 2 weeks to 2 months after the onset of symptoms (~3% of patients with AIH-1 and ~25% of patients with AIH-2)
3. Insidious onset, characterized by nonspecific symptoms (progressive fatigue, relapsing jaundice, amenorrhea, headache, anorexia, joint and abdominal pain, diarrhoea, weight loss) lasting from 6 months to a few years before diagnosis (~40% of patients with AIH-1 and ~25% of patients with AIH-2)
4. Complications of cirrhosis and portal hypertension (haematemesis from oesophageal/gastric varices, bleeding diathesis, splenomegaly), without previous history of jaundice or liver disease (~10 of both AIH types).
5. Incidental finding of raised hepatic aminotransferases, without any symptoms or signs (rare in large series, but real prevalence unknown)

NOTE TO CLINICIANS

AIH disease should be suspected and excluded in all children presenting with symptoms and signs of prolonged or severe liver disease. AIH should always be suspected when known causes of acute hepatitis are excluded.

Disease Severity and Associated Conditions

Severity of disease is similar in the 2 AIH types. AIH-2, however, has a higher tendency to present as ALF and is more refractory to eventual treatment withdrawal.

In both types, a family history of autoimmune disease is frequent (40%) and approximately 20% of patients have associated autoimmune disorders either present at diagnosis or developing during follow-up, including thyroiditis, inflammatory bowel disease (IBD), haemolytic anemia, vitiligo, coeliac disease, insulin-dependent diabetes, Behcet disease, Sjögren syndrome, glomerulonephritis, idiopathic thrombocytopenia, urticaria pigmentosa, hypoparathyroidism, and Addison disease (mainly in AIH-2).

AIH-2 responsive to immunosuppressive treatment can be part of the autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome, an autosomal recessive genetic disorder (APECED) characterized by the triad of chronic mucocutaneous candidiasis, hypoparathyroidism, and Addison disease, in which AIH-2 is present in approximately 20% to 30% of cases.

Patients with AIH and coeliac disease have been reported to achieve treatment-free sustained remission in a significantly higher proportion of cases, when compared with patients with AIH without coeliac disease, suggesting a possible long-term adjuvant effect of the gluten-free diet.

FACTS & STATS

75% of patients with either type of AIH are female

AIH has been recently reported in a range of diverse populations

Although most adult patients with AIH-1 have a chronic disease course with nonspecific symptoms such as fatigue, nausea, abdominal pain, and arthralgia, in children and adolescents, AIH could have a more aggressive phenotype.

IgG are usually raised at onset in both types, although 15% of children with AIH-1 and 25% of those with AIH-2 have levels within the normal range, particularly when the disease presents acutely.

AIH-2 affects mainly children and young adults and is rare in adults

In paediatrics, AIH-1 accounts for at least two-thirds of the cases and presents usually during adolescence, whereas AIH-2 could present at a younger age, including during infancy.

Partial IgA deficiency is common in AIH-2, affecting approximately 40% of patients

Treatment

When and how to treat

Unless it is a sudden and severe presentation with encephalopathy, AIH responds satisfactorily to immunosuppressive treatment whatever the degree of liver damage, with remission rates reported up to 90%. AIH responds to immunosuppressive treatment in the majority of cases and treatment should be instituted promptly upon diagnosis.

Standard treatment of AIH

Conventional treatment consists of prednisolone (or prednisone) at a dosage of 2 mg/kg/day (maximum 60 mg/day), which is gradually decreased during a period of 4 to 8 weeks, adjusted according to the decline of transaminase levels, to a maintenance dose of 2.5 to 5 mg/day.

Monitoring

During the first 6 to 8 weeks of treatment, liver function tests should be checked weekly to allow frequent dose adjustments, avoiding severe steroid side effects.

Use of azathioprine

85% of patients eventually require the addition of azathioprine as a steroid-sparing agent but the timing varies according to the protocols used in different centres:

- In some, azathioprine is added only in the presence of serious steroid side effects, or if the transaminase levels stop decreasing on steroid treatment alone, at a starting dose of 0.5mg/kg/day. In the absence of signs of toxicity, the dose is increased up to a maximum of 2.0– 2.5mg/kg/day until biochemical control is achieved.
- In other centres, azathioprine is added at a dose of 0.5 to 2mg/kg/day after a few weeks (usually 2 weeks) of steroid treatment.
- Some centres use a combination of steroids and azathioprine from the beginning, but caution is recommended because azathioprine can be hepatotoxic, particularly in cirrhotic and severely jaundiced patients – and could result in increased side effects and higher relapse rate compared with those AIH children treated with steroid induction followed by azathioprine addition only when indicated (relapse rate 33%–36%; side effects 18%–38%).

Definition of remission

In paediatric age, remission is defined as complete clinical recovery with transaminase levels within the normal range and is achieved in 60% to 90% of patients. Recently, 3 further criteria have been added to the definition of remission: normalization of IgG levels, negative or very low-titre autoantibodies, and histological resolution of inflammation. As liver biopsy cannot be repeated frequently, for clinical purposes, the remission is considered complete when transaminase and IgG levels are normal, ANA and SMA are negative or low-titre (<1:20), and anti-LKM1 and anti-LC-1 are <1:10 or negative.

Definition and risks of relapse

Relapse is characterised by an increase of serum aminotransferase levels after remission has been achieved. An important element in relapse is played by nonadherence which is common, particularly in adolescents. In more aggressive cases, the risk of relapse is higher if steroids are administered on an alternate day schedule, which is often instituted on the assumption that it may have a less negative effect on the child's growth. Small daily doses, however, are more effective in maintaining disease control and minimise the need for high-dose steroid pulses during relapses with the consequent more severe side effects and do not affect final height.

Full references for the advice within this guide can be found within the following paper, which this guide is based upon: Mieli-Vergani, Giorgina, et al. "Diagnosis and Management of Pediatric Autoimmune Liver Disease: ESPGHAN Hepatology Committee Position Statement." Journal of Pediatric Gastroenterology and Nutrition 66.2 (2018): 345-360.

ALTERNATIVE TREATMENTS

Alternative AIH treatments have been proposed; to induce remission at disease onset in an attempt to decrease steroid side effects and to treat refractory patients (those intolerant of or unresponsive to standard immunosuppression – often referred to as "difficult-to-treat").

For induction of remission

A suitable drug for the induction and maintenance of remission in AIH is budesonide, a drug with hepatic first-pass clearance of >90% of the oral dose and fewer side-effects than predniso(lo)ne, representing an ideal "topical" liver treatment. However, it cannot be used in the presence of cirrhosis.

For refractory cases

Options for juvenile AIH patients in whom standard immunosuppression is unable to induce stable remission, or who are intolerant to azathioprine include:

- Mycophenolate mofetil (MMF) at a dose of 20 mg/kg twice daily, together with prednisolone, has been used successfully.
- Infliximab has also been reported to be effective in the treatment of refractory AIH in a paediatric setting, but its use should be carefully evaluated in view of the potential serious infection-susceptibility side-effects.

How and when to stop treatment

Treatment for paediatric AIH should last for at least 2 to 3 years and withdrawal of treatment should only be made if transaminase and IgG levels have been normal and autoantibodies-negative for at least one year.

A liver biopsy should be undertaken before deciding to stop treatment as residual inflammatory changes, even with normal blood tests, predict relapse. The conventional treatment has seen long-term complete withdrawal from treatment in 20% of cases of AIH-1 but not in AIH-2 where 45% suffered relapse.

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