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British Society of Gastroenterology guidelines for diagnosis and management of autoimmune hepatitis

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ABSTRACT

Autoimmune hepatitis (AIH) is a chronic inflammatory liver disease which, if untreated, often leads to cirrhosis, liver failure and death. The last British Society of Gastroenterology (BSG) guideline for the management of AIH was published in 2011. Since then, our understanding of AIH has advanced in many areas. This update to the previous guideline was commissioned by the BSG and developed by a multidisciplinary group. The aim of this guideline is to review and summarise the current evidence, in order to inform and guide diagnosis and management of patients with AIH and its variant syndromes. The main focus is on AIH in adults, but the guidelines should also be relevant to older children and adolescents.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Understanding of all aspects of autoimmune hepatitis (AIH) has advanced considerably since the last British Society of Gastroenterology guideline in 2011.

WHAT THIS STUDY ADDS

⇒ We provide a comprehensive, evidence-based and up-to-date account of how to diagnose and assess the severity of AIH, and of all aspects of its management.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ We make recommendations for organisation of health services, for assessing care quality and for further research in relation to AIH.

EXECUTIVE SUMMARY OF RECOMMENDATIONS

Presentation and severity assessment

1. We recommend that the presence of encephalopathy in a patient with acute severe (AS) autoimmune hepatitis (AIH) should codify the disease as AIH-related acute liver failure (AIH ALF). This should trigger consideration of urgent liver transplant. *Grade of evidence: moderate. Strength of recommendation: strong.*

2. We recommend that acute-on-chronic liver failure should be differentiated from decompensated cirrhosis, since it identifies a subgroup of patients that might merit expedited liver transplantation. *Grade of evidence: low. Strength of recommendation: strong.*

Diagnostic workup

3. We recommend that patients with suspected AIH should undergo thorough non-invasive liver screening, detailed in box 1 and including (a) liver imaging to exclude biliary obstruction, (b) testing for hepatitis B and C and HIV testing (all cases) and hepatitis A, E, cytomegalovirus (CMV) and Epstein-Barr virus (EBV) (in acute and/or icteric presentations). *Grade of evidence: low. Strength of recommendation: strong.*

4. We recommend that liver biopsy, a major part of the diagnostic workup, should be performed routinely, before starting immunosuppression, unless the risks of biopsy clearly outweigh the benefits of diagnostic certainty. *Grade of evidence: low. Strength of recommendation: strong.*

Differential diagnosis and diagnostic scores

5. We recommend that, following exclusion of viral hepatitis and biliary obstruction, other conditions requiring consideration in patients with suspected AIH should include:

(a) For acute presentations: drug-induced liver injury, Wilson's disease, congestion, ischaemic liver injury and bile duct stones±acute cholangitis.

(b For indolent presentations: metabolic-associated steatotic liver disease (MASLD), primary biliary cholangitis, primary sclerosing cholangitis and congestion. Some of these conditions might co-exist with AIH. *Grade of evidence:low. Strength of recommendation: strong.*

6. We recommend that, if the diagnosis is in doubt, diagnostic scores be used. The simplified 2008 scoring criteria have high specificity, but lower sensitivity than the 1999 criteria, which can be used if the simplified criteria are not met. Consider seeking advice from an expert clinician. *Grade of evidence: low. Strength of recommendation: weak.*

7. We recommend that (since there is no single pathognomonic histological feature of AIH) specialist histopathological evaluation is necessary in conjunction with clinical presentation, biochemistry, immunology, viral serology and imaging. *Grade of evidence: low. Strength of recommendation: strong.*

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Box 1 Diagnostic workup for suspected autoimmune hepatitis

(A) Exclusion of other diseases

1. Ultrasound of liver (all patients)* (+ magnetic resonance cholangiopancreatography (MRCP), if jaundice, rigors or very high serum alkaline phosphatase).

2. Hepatitis viral serology: all cases: HBV$_s$ag and $_c$ab, HCV and HIV antibody.†

Acute icteric presentation: plus hepatitis A virus (HAV), hepatitis E virus (HEV), EBV, CMV.

Immimmunocompromised: also: herpes simplex, Varicella zoster.

3. Tests‡ excluding haemochromatosis, Wilson's disease, α1 antitrypsin deficiency.

4. In children: thyroid functions, coeliac serology, creatine phosphokinase, more extensive viral testing might be required (especially in infants).

(B) Immunology

Serum immunoglobulin G.

Serum autoantibodies (immunofluorescence assay (IFA) of rat triple tissue (RTT) or IFA-HEp-2):

Antinuclear antibody (ANA).

Anti-smooth muscle antibody (ASMA),

anti-mitochondrial antibody (AMA) – present in about 10%.

Anti-liver-kidney microsomal-1 (LKM).

Additional antibodies tests, if ANA and ASMA and LKM negative:

Anti-liver cytosol antibody-1, anti-soluble liver antigen/liver pancreas antibody (anti-SLA/LP), pANCA.

(C) Liver biopsy

Unless (i) there is a relative contraindication and (ii) non-invasive workup strongly suggests AIH.

*Imaging might also show features of advanced chronic liver disease.
†In acute HCV, when anti-HCV antibodies might initially be absent, diagnosis requires HCV RNA detection by PCR. Spurious, low-level reactivity for HEV, EBV or CMV IgM antibodies can be seen in acute AIH; in such cases, viral PCR testing should be performed to exclude EBV or CMV infection. In children, additional virological assessment might be necessary, especially in infants, or if antibody titres and IgG levels are equivocal. An outbreak of hepatitis with adenovirus and adeno-associated virus 2 infection on a specific HLA background has recently been identified in children.[119]
‡Caeruloplasmin, ferritin and α1AT are acute phase reactants. With acute presentations, other tests are needed. Thus, in children and young adults, 24 hour urinary copper, slit lamp examination for Kaiser-Fleisher rings, genetic tests, liver biopsy might be needed to exclude Wilson's disease)[91 92] (see Section G, Differential Diagnosis). Also, serum transferrin saturations ± HFE genotyping to exclude haemochromatosis.

Initial treatment

8. We recommend immunosuppressive treatment (IST) in most patients with AIH, regardless of symptoms. *Grade of evidence: high. Strength of recommendation: strong.*

9. We recommend that in patients with mild AIH (all of: serum lanine aminotransferase (ALT) <50 U/L, Ishak necro inflammatory score <6 and fibrosis stage <2), the decision to offer treatment should be based on balance of benefits and risks. *Grade of evidence: low. Strength of recommendation: strong.*

10. We recommend that patients starting treatment for AIH should:

(a) Ensure immunisation is up-to-date against: COVID-19, pneumococcus, influenza, shingles, hepatitis A, hepatitis B (if HBV markers absent) and (if under 25, or if gay, bisexual or men who have sex with men (GBMSM) and under 45) human papillomavirus.

(b) Receive prophylactic nucleotide therapy if HBV surface antigen positive or if core antibody positive and commencing rituximab.

(c) Be monitored for HBV reactivation if HBV core antibody positive and on other treatments. *Grade of evidence: low. Strength of recommendation: strong.*

11. We recommend that first-line initial therapy should usually comprise a corticosteroid plus azathioprine. *Grade of evidence: high. Strength of recommendation: strong.*

12. Although not routinely recommended over prednisolone, we recommend that budesonide (initially 9 mg/day) be considered in adults without cirrhosis if there is major concern about steroid cosmetic adverse effects. *We do not recommend budesonide in children as first-line therapy. Grade of evidence: high. Strength of recommendation: strong.*

13. We recommend that the initial dose of prednisolone be approximately 0.5 mg/kg/day and not usually exceed 40 mg/day, given as one morning dose, *or up to 2 mg/kg in children to a maximum of 40 mg. Grade of evidence: moderate. Strength of recommendation: weak.*

14. We recommend that if the test is readily available, thiopurine methyltransferase (TPMT) enzyme activity be measured before starting azathioprine, to exclude homozygosity for TPMT deficiency. *Grade of evidence: moderate. Strength of recommendation: strong.*

15. We recommend that the standard starting dose of azathioprine be 1 mg/kg day *(2.0–2.5 mg/kg in children*). In patients with modestly reduced TPMT activity, in the heterozygous range, there is insufficient evidence for routine reduction of the initial azathioprine dose. *Grade of evidence: moderate. Strength of recommendation: weak.*

16. We recommend that in patients homozygous for TPMT-deficiency, mycophenolate mofetil can be substituted for azathioprine (with advice on avoiding pregnancy). Wider use of mycophenolate mofetil as a first-line agent awaits its further evaluation. *Grade of evidence: moderate. Strength of recommendation: strong.*

17. We recommend that steroid monotherapy (prednisolone 0.5 mg/day or maximum 40 mg/day, if tolerated) be considered in patients with decompensated cirrhosis, current/recent malignancy, an uncertain AIH diagnosis or a suspected precipitant, with expectation of a short treatment duration. *Grade of evidence: low. Strength of recommendation: weak.*

18. We recommend monitoring (see table 1) of patients receiving steroids and or thiopurines. This can be done in secondary or primary care if there is a system for accessing and promptly acting on results. Azathioprine should be promptly reduced or stopped if there is significant bone marrow depression and stopped if there are other severe adverse events (eg, pancreatitis). *Grade of evidence: moderate. Strength of recommendation: strong.*

19. We recommend that in most patients, the prednisolone dose be reduced gradually over 1–3 months to 5–10 mg/day (and budesonide to 6 mg/day), guided by the fall in serum transaminases. For dose reduction below 5 mg/day, see Section I. *Grade of evidence: low. Strength of recommendation: strong.*

20. We recommend that as the steroid dose is reduced, the dose of azathioprine can be increased gradually from 1 to 2 mg/kg/day, with appropriate blood count monitoring. *Grade of evidence: low. Strength of recommendation: weak.*

Table 1 Monitoring strategy for patients with autoimmune hepatititis

Test	Interval		
	First 4–6 weeks	Months 2–12	Thereafter
Clinical assessment (actual or remote), with assessment of treatment AEs	1–2 weekly	2-monthly	3–6-monthly
Blood pressure (self-measured if possible)	Once	Monthly	Monthly, while on prednisolone
FBC	Weekly (after starting azathioprine or mycophenolate)	Monthly	3-monthly (while on Aza/MMF)
Blood glucose	1–2 weekly	2-monthly	2-monthly (while on prednisolone)
U&E	Once	6 and 12 months	12-monthly
LFT (including ALT and AST)	1–2-weekly	Monthly	3–6-monthly
IgG		6 and 12 months	12-monthly
HbA1C	Once	2-monthly	3-monthly (while on prednisolone)
Fasting lipids		6 and 12 months	12-monthly
Transient elastography		12 months	1-2 yearly
Ultrasound in cirrhotic patients		6 and 12 months	6-monthly
Eye examination (patients over 60)		After 12 months	Annually while on steroids

AE, adverse effect; AIH, autoimmune hepatitis; ALT, alanine transaminase; AST, aspartate aminotransferase; Aza, Azathioprine; FBC, full blood count; LFT, liver function test; MMF, Mycophenolate; U&E, urea and electrolytes.

21. We recommend that measurement of azathioprine metabolites is not needed routinely, but can be considered if there is leucopenia, or suspected non-adherence. This can also be useful in patients with an inadequate serum ALT response, to inform whether the dose should be increased (see Section G). *Grade of evidence: low. Strength of recommendation: weak.*

22. We recommend routine supplementation with vitamin D and optimisation of dietary calcium intake in patients receiving bisphosphonates and in those with poor calcium intake and/or risk factors for vitamin D deficiency. *Grade of evidence: low. Strength of recommendation: weak.*

23. We recommend consideration of calculating the FRAX (fracture risk) score in adult patients starting steroids. Some older patients will have scores in the 'high risk' fracture category. In these, consider starting bisphosphonates as soon as feasible, pending a DEXA scan report, which then can modify the risk score and need for treatment. *Grade of evidence: moderate. Strength of recommendation: weak.*

24. We recommend that patients with AS AIH (international normalised ratio (INR) >1.5 without encephalopathy) receive prednisolone monotherapy 40 mg/day if INR is <2.5 and sepsis has been excluded. They should be managed in close liaison with a transplant centre because of an approximately 35% chance that (despite treatment) they will require early liver transplantation. *Grade of evidence: moderate. Strength of recommendation: strong.*

25. We recommend that patients with AIH and ALF (including encephalopathy) should be referred promptly to a transplant centre). *Grade of evidence: low. Strength of recommendation: strong.*

26. We recommend that for patients with AIH and decompensated cirrhosis, and those with jaundice but with a model for end-stage liver disease (MELD) score of <27, treatment can be started on prednisolone (after a negative septic screen), but should be discussed with a transplant centre if the MELD score does not fall progressively. *Grade of evidence: low. Strength of recommendation: strong.*

Adequate and inadequate treatment responses

27. Confirmed normalisation of serum ALT/AST and serum IgG should be the aim of treatment. *Grade of evidence: moderate. Strength of recommendation: strong.*

28. We recommend that response to treatment be assessed at the following time points, with inadequate response being defined as:

(a) After 1 month: <50% decrease in ALT/AST

(b) After 6 months: failure of normalisation of ALT/AST and IgG. *Grade of evidence: moderate. Strength of recommendation: strong.*

29. In patients with inadequate response, we suggest review of the diagnosis and assessment of adherence to medication, followed by considering changes to steroid and to azathioprine regimens, to achieve thioguanine nucleotide levels in the therapeutic range. *Grade of evidence: low. Strength of recommendation: strong.*

30. Liver biopsy to confirm histological remission in those with complete biochemical remission is not routinely required, although it might sometimes be useful. *Grade of evidence: low. Strength of recommendation: weak.*

Second-line and third-line treatments

31. We recommend budesonide as an option in non-cirrhotic adult patients with significant prednisolone- associated AEs. Grade of evidence: moderate. Strength of recommendation: weak.

32. We recommend mycophenolate mofetil (MMF) as an option in those who are intolerant of azathioprine, and who are taking active steps not to conceive. *Grade of evidence: moderate. Strength of recommendation: weak.*

33. We recommend that in patients responding inadequately to azathioprine despite treatment optimisation, tacrolimus might be more effective as a rescue therapy, but MMF can also be considered owing to its better side-effect profile. *Grade of evidence: low. Strength of recommendation: weak.*

34. We recommend that second/third-line therapies, other than MMF and tacrolimus, require specific expertise and specialist input should be sought before their use. *Grade of evidence: low. Strength of recommendation: strong.*

Long-term management

35. We recommend long-term follow-up, as AIH is usually a lifelong condition. *Grade of evidence: moderate. Strength of recommendation: strong.*

36. We recommend consideration of non-invasive imaging assessment of fibrosis, at 2–3 year intervals. *Grade of evidence: weak. Strength of recommendation: low.*

37. We recommend that in adults achieving complete biochemical response (CBR) after 6 months and repeated testing 2–4 weeks later, steroids be withdrawn slowly. This can be over 3 months in adults. *In children low-dose steroids should be continued and stopped only after discussion with a specialist centre. Grade of evidence: low. Strength of recommendation: strong.*

38. We recommend consideration of checking endogenous adrenal function with a morning serum cortisol. Low values necessitate a short Synacthen test, and endocrinological advice. Grade of evidence: weak. Strength of recommendation: low.

39. We recommend in patients with sustained CBR over 3–4 years, consideration of withdrawing azathioprine (or other steroid-sparing agent). Withdrawal can be completed in one step, with ongoing monitoring for relapse and for fibrosis progression. We do not recommend routine liver biopsy in adults before treatment withdrawal, but it might be useful in some patients. *Grade of evidence: low. Strength of recommendation: weak.*

40.*Grade of evidence: weak. Strength of recommendation: low.*

41. AIH relapse is usually signalled by a rise in serum ALT/AST with a variable rise in serum IgG. We recommend that other potential causes (including viral) should be excluded, but that liver biopsy is usually not needed for confirmation. *Grade of evidence: weak. Strength of recommendation: weak.*

42. We recommend that relapse usually be treated by restarting prednisolone. If cirrhosis is absent, budesonide is a potential alternative. Azathioprine (or another steroid-sparing agent) should also be restarted, if not already taking. *Grade of evidence: moderate. Strength of recommendation: strong.*

43. We recommend that prednisolone be again withdrawn slowly, when CBR is re-attained after a relapse, and confirmed. However, there is a stronger case for continuing long-term maintenance treatment with a steroid-sparing agent. *Grade of evidence: high. Strength of recommendation: strong.*

44. We recommend that women receiving long-term immunosuppressive therapy be encouraged to undergo regular cervical screening in line with national guidelines and to have HPV vaccination (if under 25, or if under 45 and gay, bisexual or men who have sex with men (GBMSM)). Also, that patients minimise their exposure to sunlight and be vigilant and seek medical advice about newly developing and persisting skin lesions.

45. We recommend that some patients, such as those with decompensated cirrhosis, and those responding suboptimally to treatment, be informed (if potentially eligible) that there is a small chance that they might eventually need liver transplantation. *Grade of evidence: low. Strength of recommendation: weak.*

46. We recommend that all patients be advised to adopt a healthy lifestyle (adequate nutrition, non-smoking, low to moderate alcohol intake, physical activity, maintenance of healthy body mass index (BMI)). *Grade of evidence: moderate. Strength of recommendation: strong.*

47. We recommend that patients with cirrhosis (documented at any time) be monitored for complications, including hepatocellular carcinoma and portal hypertension in accordance with generic cirrhosis guidelines. *Grade of evidence: low. Strength of recommendation: strong.*

48. We recommend individualised end-of life care for patients with advanced liver disease who are unsuitable for transplant. *Grade of evidence: low. Strength of recommendation: strong.*

Long-term outcome

49. We recommend hepatocellular (HCC) surveillance with 6-monthly ultrasound in all patients with AIH and cirrhosis, unless not felt appropriate due to frailty or comorbidity. *Grade of evidence: low. Strength of recommendation: strong.*

Liver transplantation

50. We recommend early referral to a liver transplant centre for patients with AIH with cirrhosis and who have persistent impaired synthetic function: prolonged blood clotting, low serum albumin or symptoms of decompensation (ascites, spontaneous bacterial peritonitis, variceal bleed, encephalopathy, jaundice). *Grade of evidence: moderate. Strength of recommendation: strong.*

51. We recommend early discussion with a liver transplant centre for patients who present with AS AIH (jaundice and coagulopathy) and with AS AIH with ALF (also including hepatic encephalopathy). *Grade of evidence: moderate. Strength of recommendation: strong.*

Patient perspectives

52. We recommend that more attention be focused on health-related quality of life (HRQoL) in patients with AIH, with a holistic approach to adherence issues and consideration of formal monitoring of HRQoL and of medication adverse effects. *Grade of evidence: moderate. Strength of recommendation: strong.*

Pregnancy

53. We recommend that treatment of AIH during pregnancy, with corticosteroids (prednisolone/budesonide) with or without thiopurines, should be continued throughout the pregnancy. For newly diagnosed patients, treatment should be given as for non-pregnant women (apart from not using mycophenolate). Treatment is associated with better maternal and fetal outcomes. *Grade of evidence: moderate. Strength of recommendation: strong.*

54. Although pregnancy in AIH is not usually associated with loss of remission, this might occur post partum. Thus, we recommend that immunosuppressive therapy should be continued, and patients closely followed up for three months post partum and thereafter. *Grade of evidence: low. Strength of recommendation: strong.*

55. We recommend that patients with AIH who become pregnant should be advised that they may have increased rates of gestational diabetes, hypertensive disorders of pregnancy, preterm birth and fetal growth restriction, and so, will need close obstetric surveillance and consideration of aspirin therapy (100 mg/day, started in the first trimester for prevention of pre-eclampsia). There are no restrictions on breast feeding in patients with AIH. *Grade of evidence: high. Strength of recommendation: strong.*

Variant/overlap syndromes

56. We recommend liver biopsy (unless contraindicated) when after non-invasive workup (including MRCP) an overlap syndrome is being considered. *Grade of evidence: moderate. Strength of recommendation: strong.*

57. We recommend that moderate to severe interface hepatitis on liver biopsy be considered a prerequisite for a diagnosis of primary biliary cholangitis (PBC)/AIH overlap syndrome to be considered. *Grade of evidence: low. Strength of recommendation: strong.*

58. We recommend that a variant syndrome be considered and a biopsy performed, if feasible, in patients with clinical features of PBC or primary sclerosing cholangitis (PSC) but who have marked elevation of serum transaminases or IgG and/or serology that could be compatible with AIH. *Grade of evidence: moderate. Strength of recommendation: strong.*

59. We recommend that concurrent PBC be considered in patients with cholestatic pruritus, cholestatic liver blood tests and/or relevant autoantibodies in addition to the typical transaminitis of AIH. *Grade of evidence: moderate. Strength of recommendation: strong.*

60. We recommend that a PSC/AIH variant syndrome be considered and an MRCP performed in all children, and in adults with otherwise typical AIH who have biliary changes on biopsy, cholestatic liver blood tests, pruritus, suboptimal response to immune suppression, inflammatory bowel disease or subsequent development of any of those features. *Grade of evidence: low. Strength of recommendation: strong.*

61. We recommend that the revised and simplified International AIH Group (IAIHG) scoring systems not be used for diagnosis of variant syndromes. The Paris criteria (see Section N can be used, but do not identify all patients. *Grade of evidence: moderate. Strength of recommendation: strong.*

62. We recommend that when the two components of a variant syndrome present simultaneously but one is predominant, this be the first treatment target—for example, ursodeoxycholic acid (UDCA) if cholestatic features predominate. *Grade of evidence: low. Strength of recommendation: strong.*

63. We recommend that combination therapy with UDCA and immune suppression (prednisolone and azathioprine as used in classic AIH) might give the best rates of biochemical response, with less fibrosis progression. *Grade of evidence: low. Strength of recommendation: strong.*

64. We recommend that patients with an overlap syndrome who have severe interface hepatitis and/or bridging necrosis on liver biopsy should be given immunosuppression at diagnosis. *Grade of evidence: moderate. Strength of recommendation: strong.*

65. We recommend that if a trial of immunosuppression is given, there be (a) early review of clinical response, to avoid unnecessary long-term treatment (b) regular re-evaluation, as the disease phenotype might change over time. *Grade of evidence: low. Strength of recommendation: strong.*

Drug-induced autoimmune-like hepatitis

66. We recommend routine consideration of the possibility of drug-induced autoimmune-like hepatitis (DI-ALH) and prompt cessation of any suspected precipitant. *Grade of evidence: low. Strength of recommendation: strong.*

67. We recommend performing a liver biopsy if there is not prompt resolution of liver injury on withdrawal of the suspected precipitant. *Grade of evidence: low. Strength of recommendation: strong.*

68. For DI-AILH, we recommend starting prednisolone (0.5 mg/kg/day or up to 40 mg/day, as for idiopathic AIH), if there is either (a) jaundice (b) advanced fibrosis on liver biopsy or (c) failure of serum transaminases to fall substantially within a week of stopping the suspected precipitant. Patients with liver failure should be discussed with a transplant centre. *Grade of evidence: low. Strength of recommendation: strong.*

69. We recommend that (a) prednisolone be tapered as for standard AIH, until serum transaminases (and IgG, if elevated) have fallen to normal, and then be phased out gradually; (b) patients then be monitored by serial serum transaminases. In the event of hepatitis relapse, subsequent management is that of standard AIH, with prednisolone and a steroid-sparing agent. *Grade of evidence: low. Strength of recommendation: weak.*

70. Features of chronicity (such as advanced fibrosis on biopsy) also make it less likely that the drug is the sole cause. We recommend treating such patients as if they have standard AIH. Always consider seeking an expert clinical opinion. *Grade of evidence: low. Strength of recommendation: weak.*

Covid-19 and autoimmune hepatitis

71. We recommend that patients with AIH with cirrhosis/or those receiving immunosuppressive treatment who develop COVID-19 infection, be considered for appropriate antiviral therapy. *Grade of evidence: high. Strength of recommendation: strong.*

72. We recommend that steroid therapy usually be continued during COVID-19 infection. The decision to withhold steroid-sparing agents should be individualised, based on infection severity. *Grade of evidence: low. Strength of recommendation: weak.*

BACKGROUND

Since the publication of the first British Society of Gastroenterology (BSG) AIH guidelines,[1] there have been few randomised treatment trials, and first-line treatment has not substantially changed. However, our understanding of AIH has advanced in many areas based on large observational studies, systematic reviews and consensus statements.

In this updated guideline we include new topics, such as COVID-19 and adrenal insufficiency; and a summary of a systematic review with meta-analysis, of first-line treatment. We propose diagnostic and management standards potentially usable as care quality metrics, and a research agenda, which the UK is well-equipped to pursue. We focus mainly on AIH in adults, as guidelines exist for AIH in children.[2] However, our guidelines should also apply to adolescents and older children. Aspects of paediatric care which differ from that of adults will be highlighted.

METHODOLOGY

This guideline was commissioned by the BSG and developed in accordance with the BSG National Institute of Health and Care Excellence (NICE)-accredited guideline process. The guidelines confirm to the Appraisal of Guidelines for Research & Evaluation (AGREE) instrument II (www.agreetrust.org) and the BSG's policies on equality and diversity and on climate change and sustainability.

Scope

Diagnosis and management of patients with AIH and its variant syndromes, excluding management following liver transplantation.

Target population

Patients (all ages) meeting 1999 or 2008 IAIHG criteria, or with a clinical diagnosis of AIH.

Target audience

Anyone who manages patients with AIH. Also, patients with AIH and their carers. To inform clinical decisions and standards of care.

Guideline Development Group (GDG)

This group (chosen by DG and MAH) comprised: seven adult hepatologists (representing district general and regional hospitals, including transplant centres) and two paediatric hepatologists, one histopathologist, one specialist nurse, and two patients with AIH. Following disclosure of potential conflicts of interest, the group membership was approved by the BSG. Both patients attended nearly all the 3-monthly virtual group meetings and contributed at all stages.

SYSTEMATIC LITERATURE SEARCHES TO INFORM THE AIH GUIDELINE

Search methods

Systematic literature searches were undertaken in February 2020, with an updated search in July 2022. The strategy was developed by the GDG and by information specialists at the School of Medicine and Population Health, University of Sheffield, UK. We used thesaurus terms and free-text terms relating to patients with AIH (online supplemental table 1). Methodological search filters were used to identify the study types of interest. Searches were limited to human studies only. The searches were conducted on Ovid Medline, EMBASE via Ovid, the Cochrane Database of Systematic Reviews and the Cochrane Central Register of Controlled Trials. Databases were searched from inception. Search results were imported into Endnote reference management software, and duplicates removed.

The searches generated 16 893 unduplicated references. As some search terms were not AIH-specific, many references not relevant to AIH were included. The group members added 1741 further references, necessary to include studies published since July 2022 and studies in areas, such as side effects of medications in other conditions.

Clinical questions

The guideline is structured as evidence summaries, providing answers to specific clinical questions, agreed by the GDG members. These questions were grouped into 16 sections (A–O). Each Section was assigned to two group members, who were responsible for performing evidence searches, and for writing the summaries. The recommendations (at end of each Section) aim to answer the questions.

Inclusion and exclusion criteria

When possible, we incorporated results of systematic reviews, randomised controlled trials and case–control observational studies. Often, information addressing a specific question came from uncontrolled retrospective observational studies of variable quality. We have, when possible avoided citing case reports, small single-centre case series, survey results and studies with overt selection criteria and/or in which relevant parameters were not clearly defined. The guideline does not include a health economic analysis.

Although a systematic approach was encouraged when feasible, most sections are narrative in structure. Attempts at formal evidence synthesis using a PICO (Problem/Population; Intervention; Comparison; Outcome) format (online supplemental table 2) have been made for several questions, regarding first-line treatment (Section F). Full results have recently been published.[3] For the remaining questions, either published meta-analyses are cited, or systematic analysis was not possible, because of insufficient data.

Evidence summary and recommendations

Draft recommendations for each Section were submitted by two members, and refined by group discussion. They were graded: 1 (full agreement) to 9 (complete disagreement) by the 10 clinician members, and rediscussed and modified until the median score was <3.5, and there was resolution of disagreement (≥2 members with scores in both extreme ranges: 1–3 and 7–9).

Recommendations are categorised using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system:

Strength of evidence

A: High quality. Further research unlikely to change confidence in effect estimate.

B: Moderate quality. Further research likely to influence confidence in (and might change) the effect estimate.

C: Low quality. Further research very likely to influence confidence in effect estimate and likely to change it.

D: Very low quality. Any estimate of effect is uncertain.

Strength of recommendations

1. Strong, based on grade of evidence, consensus of opinion and high estimated patient benefit versus risks ratio
2. Weak, based on poor quality evidence and/or, divergence of opinion and low patient benefit versus risk ratio.

The GDG foresees no major barriers to implementation of the clinical recommendations; however, implementation of suggestions on service organisation might require additional resources (particularly, specialist nurses). The guideline has been endorsed by the BSG Liver Section and Clinical Standards and Services Committee. We suggest that this guideline be updated in 5–8 years.

Section A. Epidemiology

Incidence and prevalence

AIH is rare, with annual incidence and prevalence in the UK of 2 and 19–34 per 100 000 population, respectively.[4 5 6] In children, annual incidence and prevalence values are 0.5 and 1.75 per 100 000, respectively.[7] Incidence is higher at higher latitudes,[6] and approximately doubled between 1997 and 2015.[5 8] AIH is more common in females: about 3 to 1 in the UK[5 6]; it affects all ages but is commoner in older people.

Risk factors

AIH is probably immune in origin, given its associations with other autoimmune diseases, specific human leucocyte antigen (HLA) alleles, non-organ-specific serum autoantibodies and hyperglobulinaemia.[9 10] It occurs when a genetically predisposed individual encounters environmental risk factors.

For type 1 AIH (associated with serum antinuclear and anti-smooth antibody positivity), associated HLA alleles include DRB1*03:01 and DRB1*04:01 in populations of European ancestry.[11] In South America and in East Asia, AIH is associated with different HLA alleles. For type 2 AIH (associated with serum liver-kidney microsomal antibody) associated HLA alleles include DRB1*03, DRB1*07, and DQB1*02:0.1.

In genome-wide association studies of type 1 AIH,[12 13] non-HLA risk loci identified at genome-wide significance, harboured the candidate genes, *CTLA4* (at 2q33.3) and *SYNPR* (at 3p14.2).

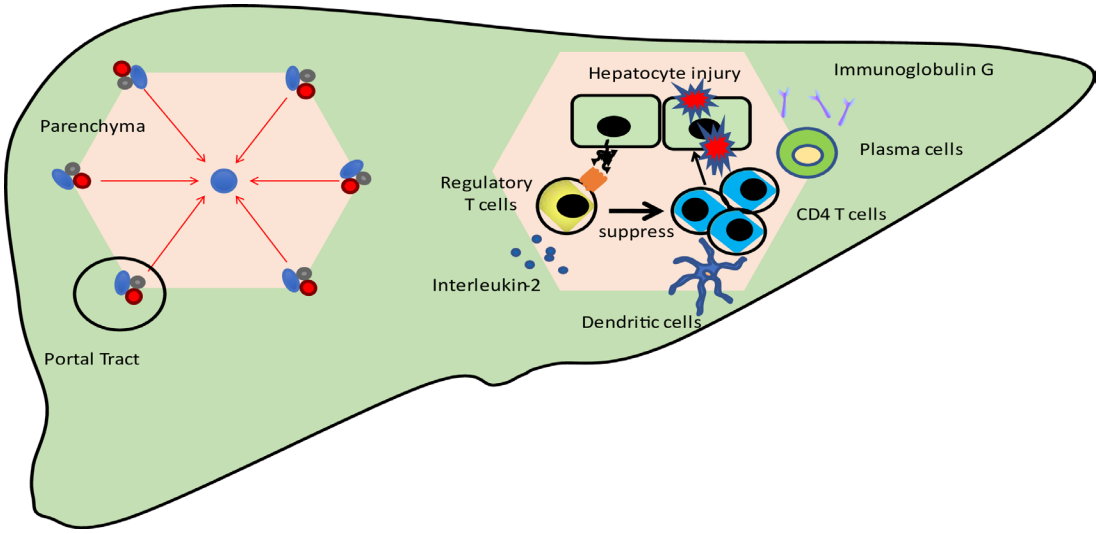


Figure 1 Overview of pathogenesis. Initial hepatocytes injury (acute hepatitis) is initiated by innate immune cells. Subsequently, cytokines and chemokines released from innate cells and injured hepatocytes, recruit adaptive CD4 T cell subsets (effector T helper type 1, Th1 and type 17, Th17 and regulatory T cells) and B cells to the site of lobular and interface hepatitis. T cells require interleukin 2 for their function and survival. Antigen presenting dendritic cells and B cells interact with T cells. Antigen-exposed B cells then become plasma cells and secrete immunoglobulin G.

CTLA4 encodes a T cell receptor involved in costimulatory pathways.[14] Other risk loci identified at suggestive significance levels harbour the genes *STAT1/STAT4* (at 2q32.2), *SH2B3* (at 12q24.12), *IRF8* (at 16q24.1) and *LILRA4/LILRA5* (at 19q13.42). These loci require confirmation.

Autoimmune-like hepatitis[15] is a feature of autoimmune polyendocrinopathy candidiasis ectodermal dystrophy; an autosomal recessive condition caused by mutations in the autoimmune regulator (*AIRE*) gene. This gene encodes a transcription factor essential for immune tolerance. Thus, genes implicated in AIH—HLA alleles, *CTLA4*, and *AIRE*—provide insight into the immunopathogenesis of AIH.

Risk factors for AIH include a personal or family history of autoimmune disease. AIH prevalence is increased fivefold in first-degree relatives and 54-fold in monozygotic twins of patients with AIH.[16] However, given the rarity of AIH, absolute risk in relatives remains low and family screening is not recommended.

Environmental factors could predispose to AIH via epigenetic changes.[11] In one study[17] risk factors for AIH included urinary tract infection, oral contraceptives, current smoking and vaccinations to varicella, rubella, pertussis or pneumococcus. Protective factors included a history of mumps or rheumatic fever, pregnancies and hormone replacement therapy.

There are occasional reports[18] of AIH following, and potentially triggered by, viral infections: including hepatitis A, B, C,E, Epstein-Barr (EBV) virus cytomegalovirus (CMV), varicella-zoster, human herpesvirus-6 and recently, COVID-19.[19 20] AIH has been reported in patients with HIV.[21] However, an aetiological link with these agents remains unproved. AIH associated with viral infection can resolve spontaneously. Immunosuppression is needed for severe or persistent cases, but withdrawal should be attempted once remission is achieved. AIH has also been associated with several drugs (Section O).

SECTION B. IMMUNOPATHOGENESIS

Environmental risk factors in AIH might generate self-antigen, directly (eg, via xenobiotic modification of host proteins) or indirectly (eg, via molecular mimicry), when genetic risk factors are present, such as certain HLA, AIRE and CTLA4 genotypes. The autoantigen in type 1 AIH is unknown, but type 2 AIH is associated with cytochrome P450-2D6 mitochondrial antigen. Hepatocyte antigen epitope shift might contribute to loss of immunological self-tolerance and failure of immune cells to recognise self-antigen.

AIH is characterised by hepatocyte injury from autoreactive lymphocytes, predominantly with a T-cell-rich infiltrate, plasma cells and dendritic cells, especially at sites of interface and lobular hepatitis[22 23] (figure 1). T helper cells, mainly CD4, seem to be important in pathogenesis[24] (figure 1). AIH is characterised by an adaptive effector CD4 T cell immune response to hepatocytes.[24] Acute presentation of AIH is driven by innate immune response orchestrated by natural killer cells.[25]

Thymic derived T regulatory cells (Tregs), help to prevent AIH by controlling tissue-damaging effector T cells.[26 27] Tregs are recruited to the site of AIH to control the inflammation[28]; these cells could be a potential treatment for AIH.

Section C. Clinical and biochemical presentation

Presenting symptoms

At presentation, 12–39% of patients with AIH are asymptomatic,[29–32] and diagnosed after incidental discovery of abnormal liver tests. When present, symptoms are often non-specific: malaise, fatigue, nausea anorexia, weight loss, amenorrhoea and joint pains (rarely swelling).[8 30 32–35] In 25–50% of patients, AIH presents as an 'acute hepatitis' with jaundice, often preceded by nausea, and flu-like symptoms.[34] Some patients report previous episodes of jaundice.[33] Less than 5% of patients present with acute liver failure (ALF), including encephalopathy.[36] Extrahepatic autoimmune diseases coexist in 24–42% of patients with AIH.[37–40]

Biochemistry

Serum alanine transaminase (ALT) and aspartate transaminase (AST) at presentation (while sometimes modestly raised, and occasionally normal) are typically about 10 times higher than

normal (sometimes even higher).[29 32 35] Serum alkaline phosphatase (ALP) can be mildly raised in active disease, but marked elevation suggests primary biliary cholangitis (PBC) or primary sclerosing cholangitis (PSC) variant syndromes (Section N).

AIH presentation might vary between races.[41] African-American patients are (compared with Caucasian patients) younger, with a higher prevalence of cirrhosis and liver failure. Non-Caucasian patients had more cholestatic histological features and a higher rate of non-response to treatment, not fully explained by differences in access to medical care.

Severity assessment

Although no unified severity classification exists for AIH, there are seven distinct patterns. These incorporate current understanding of acute and chronic liver disease and are determined by the severity of the acute (mild, icteric, severe, fulminant) and chronic (mild, fibrosis, and cirrhosis, compensated and decompensated) components of liver injury:

Asymptomatic disease: (a) mild or (b) with fibrosis/cirrhosis

Asymptomatic patients might not have mild disease.[30 31 42] While they tend to have lower serum transaminases than symptomatic patients, severity of necro-inflammation and fibrosis are similar, as is death/transplantation rate.[30 31 42 43] Treating asymptomatic patients is associated with improved survival (Section F).

Chronic hepatitis

This is the most common form of AIH, with insidious onset and non-specific symptoms.

Cirrhosis: (a) compensated and (b) decompensated

About one-third of patients with AIH have cirrhosis at diagnosis.[29 30 35 43] Sometimes patients (usually elderly) present with cirrhosis complications. Cirrhosis and decompensation are poor prognostic features.[44]

Acute hepatitis with or without jaundice

Initial severity of inflammation has prognostic implications. Patients with initial serum AST >10 x ULN are less likely than those with values <10 x ULN) to present with cirrhosis and/or decompensation, and to die due to (or need transplantation for) liver disease.[45]

Acute on chronic liver failure (ACLF)

ACLF is acute injury developing in patients with (often unrecognised) cirrhosis, and sometimes with extrahepatic organ failure. In patients with AIH, a disease 'flare' might precipitate ACLF.[46] Such patients might benefit from corticosteroids and most treated patients recover (Section F). However, in the UK, a label of ACLF is a potential mechanism to expedite liver transplant.

Acute severe autoimmune hepatitis (AS-AIH)

AS-AIH is defined as an 'acute' presentation with jaundice and coagulation disturbance (INR greater than 1.5) but without encephalopathy.[47 48] Definition of 'acute' has varied: 'symptoms for <26 weeks',[48] 'no known history of chronic liver disease'[49] or 'no previous medical history of AIH'.[50] Two-thirds of patients with AS-AIH receiving corticosteroids survive without transplantation (Section F)

AIH-related acute liver failure (AIH-ALF)

When encephalopathy is also present (in addition to jaundice and coagulopathy), the condition becomes that of AIH with ALF (AIH-ALF), sometimes called acute fulminant AIH. In reports, encephalopathy is already present at presentation in 3–6% of patients classified as AS-AIH, and might also develop over 1–3 weeks (especially in patients with higher INR and MELD scores), thus progressing to AIH-ALF.[48–51]

The outcome of AIH with ALF is worse than that of AS-AIH, with recovery in only 9–32% of patients.[49 52] No survival benefit with steroids was seen in AIH with ALF in one multicentre cohort[52] (Section F). Thus, urgent transplantation is usually required.

Section C Recommendations

1. We recommend that the presence of encephalopathy in a patient with AS-AIH should codify the disease as AIH-ALF. This should trigger consideration of urgent liver transplant. *Grade of evidence: moderate. Strength of recommendation: strong.*

2. We recommend that acute-on-chronic liver failure should be differentiated from decompensated cirrhosis, since it identifies a subgroup of patients that might merit expedited liver transplantation. *Grade of evidence: low. Strength of recommendation: strong.*

Section D. Diagnostic workup

In patients with suspected AIH, a comprehensive drug history is needed, including all medications, herbal/dietary supplements and recreational drugs. (Table 1) Always consider stopping or changing medications which either (a) have previously been linked to AIH, (b) were started within 12 months of the liver injury or (c) are not needed or can be substituted. If after drug withdrawal, serum transaminases, do not promptly improve, consider a trial of steroids even if the diagnosis of AIH is uncertain (Section O).

Because there is no single diagnostic marker for AIH, other causes of hepatitis must be excluded. Patients with suspected AIH should undergo a non-invasive liver screen as detailed in box 1.

Immunology

AIH is characterised by polyclonal hyper-gammaglobulinaemia, especially serum IgG. However, in a multicentre study, 130 of 1318 patients (10%) had normal serum IgG at presentation.[53] These patients were similar to those with raised serum IgG, regarding other diagnostic features and treatment response.

Serum IgG is also normal in 25–39% of patients with acute AIH (including acute-severe AIH±ALF),[49 54] thus complicating diagnosis. Serum IgG can also be elevated in cirrhosis due to other causes and in non-hepatic disorders, such as HIV and myeloma.

Serum autoantibodies are also typical of AIH, and its classification is based on the autoantibody present: antinuclear (ANA) and anti-smooth muscle (ASMA) antibodies for type 1 AIH, and anti-liver kidney microsomal type 1 (anti-LKM1) and anti-liver cytosol type 1 antibodies (anti-LC1) for type 2 AIH.

Serum ANAs are found in 50–70% patients with AIH.[29 30 32 35 55] Target antigens are heterogeneous, including double- and single-stranded DNA, ribonucleoproteins, centromeres, histones, chromatin and cyclin A. ANA is detected by indirect immunofluorescence assay (IFA) of rat triple tissue (IFA-RTT) or HEp-2 cells (IFA-HEp-2). The staining pattern is usually homogeneous.[56] ANA is not

Box 2 Role of liver biopsy in autoimmune hepatitis (AIH)

Support diagnosis of AIH, based on characteristic histopathological features. Histological findings are an integral part of AIH diagnostic scoring systems[70 95] (see Section E).
Exclude other conditions (e.g. metabolic-associated steatotic liver disease, Wilson's disease).
Support a diagnosis of autoimmune variant syndromes (with primary sclerosing cholangitis and primary biliary cholangitis; (see Section N) and also, co-existence of steatosis or steatohepatitis.
Assess severity of necro-inflammation (disease grading) and fibrosis (disease staging) and their change in subsequent biopsies. This might inform prognosis and/or a decision to change treatment.

specific for AIH, being found in healthy people, other autoimmune disorders, infections, malignancies and other liver diseases.

Smooth-muscle antibodies (SMA) are found in 52–69% of patients with type 1 AIH.[29 35] Target antigens include filamentous actin (F-actin) and other cytoskeletal components, such as vimentin and desmin. SMA are also detected using IFA-RTT or IFA-HEp-2.[56] Like ANA, SMA also are not specific for AIH, occurring in other liver and extrahepatic conditions. However, co-occurrence of ANA and SMA is more specific for AIH, with diagnostic accuracy about 75%.[57]

Anti-liver-kidney-microsomal-1 (LKM) antibodies are found in only 2–4% of patients with AIH in Northern Europe and North America[29 33] but are commoner in Southern Europe. Anti-LKM-1 antibody is present in about 70% of type 2 AIH cases, the target antigen being cytochrome P450 2D6 (CYP2D6). Anti-LKM-1 antibodies can be detected using IFA-RTT or IFA-HEp-2; antigen-specific assays (eg, ELISA, immunoblot) are also available. Anti-LKM-1 antibodies have high specificity for AIH, although they also occur in hepatitis C.

Other serum autoantibodies in AIH include:

1. Anti-liver cytosol (LC)1 antibodies found in about 30% of patients with type 2 AIH,[58] the target antigen being formiminotransferase cyclodeaminase. Anti-LC1 antibodies can be detected using IFA-RTT or IFA-HEp-2, or antigen-specific assays.[56] They have high specificity for AIH, although they occur rarely in hepatitis C.
2. Antibodies to soluble liver/pancreas antigen (SLA)/LP) are detectable in up to a third of patients with AIH, either type 1 or type 2. The target antigen is O-phosphoseryl-tRNA:selenocysteine-tRNA synthase. Anti-SLA/LP antibodies can only be detected using antigen-based assays, and not by IFA. They are highly specific for AIH. They are associated with a longer time to complete response and higher relapse rate following immunosuppression withdrawal,[59] but not with excess mortality.
3. Atypical (also known as peripheral) anti-neutrophilic cytosolic antibodies (aANCA). These are associated with AIH, although with low specificity.[60 61] They are detected using IF of ethanol-fixed neutrophils. Testing for aANCA is useful when AIH is suspected but ANA, SMA and LKM antibodies are not detected.
4. Antimitochondrial antibody (although strongly associated with primary biliary cholangitis) is also found in 4–9% of patients with AIH (Section N) in many of whom there are no other features of PBC.
5. Finally, in about 15% of patients with AIH, all these autoantibodies are undetectable at presentation, although they might appear during follow-up. Antibody-negative and -positive patients have similar presenting features and response to treatment.[61]

The autoantibody profile of children with AIH is similar to that of adults. Titres tend to be lower. The existence of an antibody-negative phenotype is debated.[2]

For antibody testing methodology, we refer to consensus statements from the International AIH Group (IAIHG) committee for autoimmune serology[62] and other expert bodies.[56] When AIH is suspected, serum should first be screened for ANA, SMA, and anti-LKM-1 antibodies. If these are not detected, antigen-specific assays should be used to look for anti-SLA/LP antibodies and for ANCA.

Histology

A. Usefulness of liver biopsy in clinical practice (box 2, online supplemental table 3).

Because of its diagnostic importance, liver biopsy (unless actively contraindicated), should be performed in the workup of both children and adults with suspected AS-AIH,[23 63] ideally, before

Table 2 Summary of biopsy performance quality requirements and recommended staining techniques.[67]

	Issues	Recommendation / optimal scenario	Reason	References
Patient preparation	Full consideration of rationale, potential contraindications and possible approaches (percutaneous, transjugular, laparoscopic) Fully informed patient consent. Post-biopsy care	Full explanation of recommendation Adequate time for patient's decision and consent Checklist Close monitoring Safety information on discharge	Maximise patient involvement, empowerment and safety	67
Biopsy quality	Biopsy size and number of portal tracts can affect grade and stage reporting of chronic hepatitis, with lower scores in smaller biopsies	16G needle preferable, 18G acceptable. Core integrity, >15 mm long and >8 complete portal tracts	Minimise sampling variation. Core integrity needed to assess architecture	67
Special collagen fibre stains to assess fibrosis	To avoid misinterpretation of recent parenchymal collapse as established fibrosis	Picrosirius red, Masson trichrome, haematoxylin, van Gieson Elastic fibre stains to assess fibrosis maturity (eg, elastic van Gieson, orcein)	To assess fibrosis stage reliably, and avoid misinterpretation of parenchymal collapse as fibrosis	.[78 448]
Stains to assess copper deposition	Chronic cholestasis	Stain routinely for copper or copper-associated protein (eg, orcein, rhodanine, Victoria blue)	Copper-binding protein without severe fibrosis indicates chronic cholestasis; might corroborate subtle early cholangiopathy. Also, to assess Wilson's disease	449
Expert biopsy review	Discrepancies on differential diagnosis, fibrosis staging, recognition of unusual histological patterns as AIH.	Review by an expert liver histopathologist, ideally at a formal clinicopathological meeting	To avoid under- and overdiagnosis	450 451

Table 3 Prevalence of histopathological features in patients with autoimmune hepatitis and with other liver diseases

Author	Number		% Interface hepatitis (n)		% Plasma cell prominence		% Rosettes		% Emperipolesis		% Portal tract/ bile duct lesions		Other features
	AIH	C	AIH	C	AIH	C	AIH	C	AIH	C	AIH	C	AIH
Suzuki[79]	28	19*	100	100	86	32	75	41	75	37	57	53	
de Boer[452]	63	62†	87	63	48	27	49	23	78	50	28	18	Steatosis granuloma
Balitzer[449]	88	20‡ 13§	80	15 77	49	20 8	33	0 38	65	50 77	46	100 62	-. Copper, CK-199 stains
Gurung[453]	43	42†	65	40	60¶	26¶	37	17	51	24	60	25	Endothelitis Kuppfer cell hyalin
Tsutsui[454]	22	10†	10	40	82¶	20¶	44	0	73	50	20	80	
Median (range)			**87 (65–100)**	**53 (15–100)**	**55 (60–86)**	**20 (8–32)**	**43 (33–75)**	**30 (0–41)**	**73 (51–78)**	**50 (24–77)**	**46 (20–60)**	**57 (25–100)**	

C: controls
*DILI *(hepatocllular)
†Chronic viral hepatitis
‡PBC
§Non-autoimune
¶Defined as plasma cell clusters, lobular
DILI, drug-induced liver injury; PBC, primary biliary cholangitis.

starting treatment. However, sometimes, (for example, ASAIH), initiation of steroids pending report (or even performance) of biopsy can be justified.

Some have questioned whether a liver biopsy is needed routinely when non-invasive workup strongly suggests AIH.[64] In a study of 257 patients with AIH, histology was 'atypical' in only 5%, and these patients also responded to immunosuppression, leading to a conclusion that liver biopsy uncommonly overturned a diagnosis of AIH suggested on non-invasive workup. However, this cohort was preselected as diagnosed with AIH, and it was unclear how many additional patients with AIH suspected on non-invasive workup had been excluded owing to atypical liver histology. In two studies of biopsy-proven MASLD,[65 66] 20% and 60% of patients met the 1999 IAIHG criteria for probable AIH, and 3% and 0.5%, the criteria for definite AIH, based on non-invasive tests (before AIH was excluded by histology). Furthermore, even if biopsy is not always needed for initial diagnosis, AIH is a lifelong disease. Response to treatment is sometimes suboptimal, and in these patients, late biopsy might not be diagnostic, due to immunosuppression. Thus, the initial diagnosis of AIH might be questioned, sometimes years later. A firm initial biopsy-based diagnosis helps to avoid such scenarios.

Table 2 summarises how to obtain and process the biopsy. For further discussion, see BSG liver biopsy guidelines,[67] which emphasise the importance of carefully considering the decision, fully informing patients and post-biopsy precautions, and

Table 4 Definition of the consensus recommendation for histological criteria of autoimmune hepatitis (AIH) from the International AIH Group Pathology pathology section[71]

Probable AIH			
When portal-based hepatitis (classic AIH histology)	Portal lymphoplasmacytic inflammation with more than mild interface activity and/or more than mild lobular hepatitis without features suggesting another liver disease		
When lobular hepatitis	More than mild lobular hepatitis with/without centrilobular necro-inflammation with at least one of the following features: ► Lymphoplasmacytic infiltrates ► Interface hepatitis ► Portal-based fibrosis Without features suggesting another liver disease		
Possible AIH			
When portal-based hepatitis	Portal lymphoplasmacytic inflammation when interface activity is not more than mild, and lobular hepatitis is not more than mild, without features suggesting another liver disease	OR	Portal lymphoplasmacytic inflammation with more than mild interface activity and/or more than mild lobular hepatitis, with features of another disease
When lobular hepatitis	Any lobular hepatitis with/ without centrilobular necro-inflammation without: ► Lymphoplasmacytic infiltrates ► Interface hepatitis ► Portal-based fibrosis without features suggesting another liver disease	OR	Any lobular hepatitis with/ without centrilobular necro-inflammation and with any of the following features: ► Lymphoplasmacytic infiltrates ► Interface hepatitis ► Portal-based fibrosis associated with features of another disease
Unlikely AIH			
When portal hepatitis	and interface activity is not more than mild and lobular hepatitis is not more than mild and there are features of another disease		
When lobular hepatitis	Is present without: ► Lymphoplasmacytic infiltrates ► Interface hepatitis ► Portal-based fibrosis AND there are features of another disease		

Ishak's modified histology activity index category grades* considered mild: A≤1, B=0, C≤2; category grades considered more than mild: A ≥2, B ≥1, C ≥3.
Features of another disease: Steatohepatitis, cholangiopathy, vascular disease.
A (periportal/periseptal interface hepatitis)
B (*confluent necrosis)
C (focal/spotty lytic necrosis)

describe in detail the various approaches, limitations, contraindications and complications. Overall mortality directly related to liver biopsy varies from 1/1000 to 1/10 000.[67]

(B) Histopathology of AIH

Representative histological features of AIH, with data on their diagnostic usefulness are depicted in online supplemental table 3).

Diagnosis of AIH requires the presence of hepatitis, including inflammation characterised by predominance of lymphoplasmacytic infiltrates typically rich in plasma cells, sometimes in clusters, along with hepatocellular injury.

The composition, distribution and severity of necroinflammation and fibrosis might vary, depending on when the biopsy is performed. The most common pattern is that of chronic hepatitis, with a predominant distribution around the portal tracts, or at the interface (border between the portal area and the lobule), together with variable fibrosis. However, many patients (especially those with acute presentations of AIH)[68 69] have injury throughout the lobule (pan-lobular hepatitis) with less prominent or even absent portal inflammation or fibrosis.

Recently, there has been a re-evaluation of what constitutes 'typical' histology of AIH. Emperipolesis (presence of an intact leucocyte within the cytoplasm of a hepatocyte) and rosettes (hepatocytes arranged around a small central lumen), are features previously considered important for the diagnosis of AIH and are an explicit part of the simplified diagnostic scoring system (Section E).[70] However, this has been challenged by recent studies (see table 3) that seem to undermine their specificity. Even interface hepatitis, although common in AIH, is seen in other liver diseases.

Revised histological criteria for AIH have been developed in a recent consensus report[71] summarised in table 4. There are two main differences from earlier scores. First, emperipolesis and rosettes are no longer considered as favouring AIH. Second, there is inclusion of both lobular hepatitis and the more typical portal-based chronic hepatitis as potential dominant patterns. This is important to avoid dismissing patients with acute presentation of AIH whose biopsy displays only (or dominance of) lobular hepatitis. Such patients might be underscored using earlier criteria. The report also includes criteria for possible, and for unlikely, diagnoses of AIH. These criteria require validation, ideally incorporating blind assessment of biopsies from patients with AIH and other diseases.

However no single histological abnormality is specific for AIH, and other conditions need to be excluded before establishing the diagnosis (box 1). Some histological features do argue against a diagnosis of AIH. Multiple well-formed granulomas, widespread bile duct injury, copper-associated protein deposition without advanced fibrosis, or steatosis/steatohepatitis, support an alternative or co-existing diagnosis. However given the high population prevalence of steatotic liver disease, it is debatable whether finding features of this condition as 'another liver disease' should diminish the likelihood of AIH.

Additional findings in AIH include lymphocytic apoptotic bodies and intracytoplasmic hyaline droplets in Kupffer cells. Their diagnostic significance and specificity await formal evaluation (online supplemental table 3).

Isolated centrilobular zonal necrosis and syncytial giant cell hepatitis are unusual findings, but do not invalidate the diagnosis, particularly in acute presentations.

Centrilobular zonal necrosis without portal hepatitis or fibrosis[72–74] should be recognised as part of the AIH spectrum, as these patients respond well to immunosuppression[75] and might be underscored as AIH using the diagnostic scoring systems (Section E). A plasma cell rich component, or clusters of plasma cells would further favour a diagnosis of AIH, even without of the more typical portal-based damage.[73 74]

AIH presenting as AS hepatitis (with or without ALF) (Section C) poses particular diagnostic challenges. Liver histology was considered essential for diagnosis in 42% of patients with AS-AIH in a large multicentre cohort.[49] Histological features include central perivenulitis (about 70%), severe hepatic necrosis (about 50%); lymphoid aggregates and plasma cell enrichment.[36 48 49 51 76]

Implications of histology for management and prognosis

The severity (grade) of inflammatory activity and the fibrosis extent (stage) should both be assessed as they are relevant to prognosis. Ishak's modified histological activity index for grading AIH[77] (although not validated for acute hepatitis), has advantages over other systems (Batts and Ludwig, Scheuer, METAVIR), as it provides unique granular information on grading lobular activity, particularly the degree of confluent necrosis. Also, it was used in the recent consensus recommendations for histological diagnosis of AIH,[71] although including only three grading categories from Ishak's score: interface, lobular and confluent (but not intraportal) necroinflammatory activity. This needs consideration if the diagnostic consensus criteria are adapted to evaluate histological remission (with remission defined as a necro-inflammatory score of <4).

The presence of bridging or multilobular necrosis underlines the need for treatment of AIH, and severe necrosis is a prognostic marker in AS-AIH.[49] In contrast, mild or minimal inflammation might influence a decision to defer initiation of treatment (Section F). A definition of mild histology (Ishak's interface activity ≤1, absence of confluent necrosis and four or less lobular necro-inflammatory foci/10X) has been proposed.[71]

AIH might be silent for years and then present as advanced liver disease. Assessment of fibrosis is challenging, and requires special stains for collagen (see table 2), to help to differentiate post-necrotic parenchymal collapse from established fibrosis.[78]

See Section G for the role of follow-up biopsy to confirm histological remission, and Section N for histology of overlap syndromes.

Section D recommendations

1. We recommend that patients with suspected AIH should undergo thorough non-invasive liver screening, including (a) liver imaging to exclude biliary obstruction, (b) testing for hepatitis B and C and HIV testing (all cases) and hepatitis A, E, CMV and EBV (in acute and/or icteric presentations). *Grade of evidence: low. Strength of recommendation: strong.*
2. We recommend that liver biopsy, a major part of the diagnostic workup, should be performed routinely, ideally before starting immunosuppression, unless the risks of

Table 5 Differential diagnosis of autoimmune hepatitis following initial workup

Condition	Prevalence (vs AIH)	Demography	Risk factors	Raised liver tests	Autoantibodies	Raised serum IgG
Autoimmune hepatitis	_	75% F All ages	Other AI diseases Some drugs (Section S)	ALT (median c. 400U/L).	80% ANA or ASMA+, 8% AMA+, 2% LKM+. 30% SLA+	80–90%[53]
Viral hepatitis	Commoner	Variable	Relevant exposure history	Usually variable pattern	10–13% (HBV)[97 98] 22–26% (HCV)[97 98 455]	47–50% (HBV)[97 456 457] 26% (HCV)[458]
Drug-induced liver injury[136]++	Similar	M=F; all ages	Drugs/herbs (Section S)	ALT and/or ALP	ANA+ in 14–20%[97 422]	Variable: up to 36%[420 423]
Ischaemia	Commoner	M=F	Cardiorespiratory disease; episode of ischaemia/ hypotension	ALT usually brief rise and rapid fall	No increase	No
Primary biliary cholangitis[459]++	Similar	90% F over age 30 years	Other AI diseases	ALP usually ALT rarely >150 U/L	ANA+/-, ASMA+ in 20–30%, AMA +in 90%	20–50%[97] IgM in 70%
Primary sclerosing cholangitis[460]++	Similar	M=F; all ages	Inflammatory bowel disease	ALP usually; ALT rarely>150 U/L	ANA+ in 8–77%[376]	20–50%[97]
Metabolic dysfunction associated steatotic liver disease[81]+++	Much commoner	M=F; all ages	Metabolic syndrome	ALT usually; rarely>200 U/L	ANA+ or ASMA+ in 14–19%[65 97]	7–14% [97 461]
Congestion	Commoner	M=F	Heart disease, thrombophilia	ALP and GGT usually also AST (>ALT) and LDH if acute	No increase	No
Wilson's disease[91]*	Much rarer	M=F; most aged <40 years	Family history	Variable	ANA+ ASMA+ described[93]	Up to 50%[93 97]

Coexists in 5–10% (++) and in 25–30% (+++) of patients with AIH.
*If suspected, arrange serum caeruloplasmin 24 hour urinary copper, slit-lamp examination for Kayser-Fleischer rings, MRI brain scan, and genetic testing.
ALP, alkaline phosphatase; ALT, alanine transaminase; AMA, anti-mitochondrial antibody; ANA, antinuclear antibody; ASMA, anti-smooth muscle antibody; LDH, lactate dehydrogenase; LKM, liver-kidney microsomal-1; SLA, soluble liver antigen.

biopsy clearly outweigh the benefits of diagnostic certainty. *Grade of evidence: low. Strength of recommendation: strong.*

Section E. Differential diagnosis

AIH might mimic many liver and biliary diseases. Bile duct obstruction needs exclusion by biliary ultrasound ±MRCP. For other differential diagnoses, see table 5. Importantly, some of these can co-exist with AIH.

Even after full *viral screening* (box 1) confusion might arise. Patients with confirmed chronic HBV and HCV infection might have some 'autoimmune' features (table 5). Liver biopsy usually suggests viral hepatitis (rather than AIH). However, LKM-positive AIH has been associated with HCV infection. If in doubt, options include (a) assessing response of serum transaminases to antiviral therapy and viral clearance, before deciding to start immunosuppressive treatment, and (b) treating both viral hepatitis and AIH simultaneously.

AIH and drug-induced liver injury (DILI) might also overlap in immunological and histological features (table 5). Several drugs can cause liver injury indistinguishable from AIH and recently labelled as drug-induced autoimmune-like hepatitis (DIAILH: see Section O). In a blinded study of biopsies from patients with DILI and with AIH,[79] portal plasma cell-rich inflammation, and absence of cholestasis, were associated with AIH. Eosinophils were not diagnostically useful. The presence of advanced fibrosis might also favour AIH.[80]

Metabolic dysfunction-associated steatotic liver disease (MASLD)

Usually, presentation of MASLD is more indolent, and serum transaminass are lower (uncommonly over 150 U/L) than in AIH.[81] However, immunological features of AIH might be present (table 5). Liver biopsy helps to distinguish AIH from MASLD.[82] Steatosis, ballooning of hepatocytes, Mallory-Denk hyaline, neutrophilic inflammation and pericentral or perisinusoidal fibrosis all suggest MASLD. In contrast, plasma cell infiltrates and interface hepatitis suggest AIH.[83] However, some patients with MASLD and cirrhosis can develop chronic portal tract inflammation. *In children, portal inflammation, periportal steatosis and fibrosis are common and usually mild and without interface activity*.[82]

MASLD and AIH can co-exist. Steatosis (usually mild) is present in 13–35%% of patients with AIH on diagnostic biopsy.[84–87] This probably reflects the high population prevalence of MASLD. Its prognostic implications are unclear. Twelve patients with AIH plus steatohepatitis on diagnostic biopsy had higher adverse outcome rates, than did 61 patients with AIH and simple steatosis.[88] However, based on larger cohorts, the influence of steatosis on disease progression and mortality remains unresolved.[85 87]

For differentiation of AIH from *primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC),* see Section N.

In *liver congestion* (from cardiac disease or hepatic vein obstruction) presentation is usually indolent, with serum alkaline phosphatase and bilirubin increasing more than transaminases.[89] In acute congestion serum transaminases might be markedly raised[90]; often serum ALT more than AST and often also with raised serum lactate dehydrogenase. If the cause is cardiac, the inferior vena cava and hepatic veins are enlarged. If the hepatic vein is obstructed, its flow is reduced or absent.

Ischaemic liver injury is suggested first, by the presence of cardiac or respiratory disease, and second, by an acute precipitant (hypotension, sepsis). If acute, serum transaminases can be over 1000, but then usually fall rapidly.

Wilson's disease[91 92] needs consideration in suspected AIH, especially in young people. As with AIH, clinical presentation

ranges from asymptomatic abnormalities to liver failure. Serum caeruloplasmin, 24-hour urinary copper excretion and, if abnormal, slit-lamp eye examination and genetic screening, should be performed but do not always exclude Wilson's disease.

Liver histology in Wilson's disease includes many abnormalities, none of them specific. Occasionally, the appearances even suggest AIH.[93] If there is any suspicion, we suggest measuring copper level in liver biopsy tissue, sometimes urgently. This is the most reliable test for Wilson's disease. Histochemical staining for copper or copper-associated proteins is insufficiently specific and can be seen in cholestatic disorders. A Wilson's disease scoring system[94] can also be used in cases of doubt.

AIH diagnostic scores

To standardise diagnosis of AIH, and to facilitate comparison between clinical studies, the International Autoimmune Hepatitis Group (IAIHG) developed diagnostic criteria. The first iteration was developed in 1993 and revised in 1999.[95] This represented expert consensus on criteria for definite or probable AIH. However, it was detailed, incompletely validated, and used laboratory information not routinely available.

Consequently, the IAIHG developed simplified diagnostic criteria.[96] These (see table 6) employ four categories to define a patient as definite, probable, or not AIH.

In the initial study[96] the simplified criteria had a sensitivity and specificity 88% and 97% for probable AIH diagnosis. In further validation studies[97 98] they remained highly specific for AIH, but less sensitive than the 1999 criteria. In Dutch[35] and UK[32] multicentre studies, sensitivity of the simplified criteria was only 69–75%.

Thus, a patient meeting the simplified criteria is very likely to have AIH. However, failure to do so does not exclude AIH. When AIH remains suspected, consider (a) testing for additional antibodies (Section D), asking an expert histopathologist to review the liver biopsy.

Histology and the IAIHG diagnostic scores

The 1999 IAIHG criteria[95] allocate up to five diagnostic points for histological features which favour AIH (interface hepatitis, plasma cell infiltrate, rosettes), but subtract up to 11 points if features of other diseases are present (granulomata, bile duct injury or more than mild steatosis) .

In the 2008[96] criteria, two diagnostic points are given if histology is 'typical', one point if 'suggestive' and none, if 'not suggestive'. 'Typical' histology requires all the following: interface hepatitis, a 'lymphocyte-plasmacytic' infiltrate, mainly in the portal area (proportion of plasma cells was unspecified), hepatocyte rosettes and emperipolesis.

It is unclear whether the recent consensus criteria (table 4)[71] will replace these histological diagnostic criteria, embedded in the diagnostic scores. If the consensus criteria are validated, the diagnostic scores will require modification. Pending such validation, we suggest that the histological features of the 1999 and 2008 diagnostic scores be retained.

In suspected AIH in children the IAIHG scores are not suitable for diagnosis.

RECOMMENDATIONS SECTION E

1. We recommend that, following exclusion of viral hepatitis and biliary obstruction, other conditions requiring consideration in patients with suspected AIH should be:

(a) For acute presentations: drug-induced liver injury, Wilson's disease, congestion, ischaemic liver injury and bile duct stones ±acute cholangitis.

(b For indolent presentations: metabolic-associated steatotic liver disease (MASLD), primary biliary cholangitis, primary sclerosing cholangitis and congestion. Some of these conditions might co-exist with AIH. *Grade of evidence: low. Strength of recommendation: strong.*

2. We recommend that, if the diagnosis is in doubt, diagnostic scores be used. The simplified 2008 scoring criteria have high specificity, but lower sensitivity than the 1999 criteria, which can be used if the simplified criteria are not met. Consider seeking advice from an expert clinician. *Grade of evidence: low. Strength of recommendation: weak.*

3. We recommend that (since there is no single pathognomonic histological feature of AIH) specialist histopathological evaluation is necessary in conjunction with clinical presentation, biochemistry, immunology, viral serology and imaging. *Grade of evidence: low. Strength of recommendation: strong.*

Section F. Initial immunosuppressive therapy (IST)

The goals of initial treatment are first, to achieve symptom resolution, complete biochemical response (normal serum transaminases and IgG—see Section G —and ideally, histological remission, with a minimum of medication-related adverse effects. Second, to restore the patient's quality of life to that before AIH developed. An overview of the initial strategy is shown in figure 2.

Which patients do not need treatment?

In three of four early randomised trials,[99] prednisolone (with or without azathioprine) reduced mortality compared with placebo or to azathioprine alone. Most patients had severe AIH, with cirrhosis in 50–60% and one-third developing liver failure.

Most adult cohort studies include patients with a broader range of severity, and 5–15% did not receive steroids. Reasons included mild changes on biopsy, near-normal serum transaminases, variant syndromes, urgent need for liver transplant, patient refusal, and 'burnt-out' cirrhosis, *Non-treatment is unusual in children*.[100]

Outcomes in untreated patients are rarely reported separately, but in two cohort studies,[43 101] 8% and 55% of patients respectively did not receive steroids and these patients had (compared with treated patients) a higher death/transplantation rate. In a meta-analysis of the four randomised trials plus these cohort studies[3 102] prednisolone±azathioprine (vs no treatment or azathioprine alone) was associated with a more than twofold reduction in all-cause death/transplantation. This underlines the need for IST in most patients with AIH.

Table 6 The simplified diagnostic criteria for autoimmune hepatitis (adapted from Hennes)[70]

ANA or ASMA +	Titre>1:40	+1
ANA or ASMA + LKM + SLA	Titre>1:80 or Titre>1:40 or Positive	+2
Serum IgG	>Upper normal limit >1.1× upper normal limit	+1 +2
Liver histology	Compatible with AIH Typical of AIH	+1 +2
Absence of viral hepatitis	No Yes	0 +2

≥6 diagnostic points: probable AIH; 7 diagnostic points: definite AIH.
ANA, antinuclear antibody; ASMA, anti-smooth muscle antibody; LKM, liver-kidney microsome; SLA, soluble liver antigen.

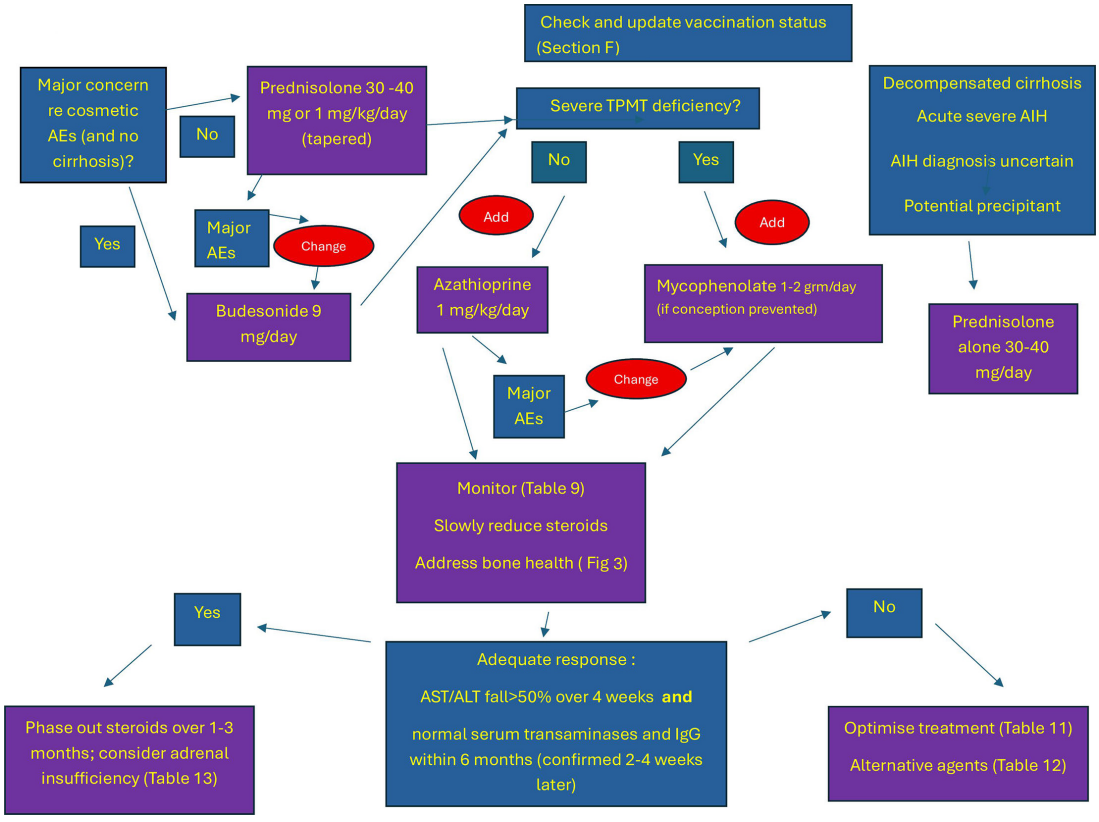


Figure 2 Overview of initial treatment of autoimmune hepatitis. AEs, adverse events; ALT, aanine transaminae; AST, aspartate transaminase; TPMT, thiopurine methyltransferase.

In some subgroups, such as those without symptoms or without cirrhosis, the need for treatment might be questioned. However, in asymptomatic patients[30 31 42 43] and in patients without cirrhosis,[43 101] and with decompensated cirrhosis, meta-analysis[3 102]showed associations between steroid-based treatment and two- to threefold reduction in death/liver transplantation rate.

Treatment has not been statistically associated with lower medium-term mortality in patients with 'mild' AIH,[43] defined as serum transaminases <50 U/L and with no or mild inflammation (necro-inflammatory score <6) and fibrosis (grade <2). In a patient meeting all of these criteria, it might be reasonable to weigh the risks and benefits of treatment against simply monitoring; especially in those with frailty, major comorbidity and who are at increased risk of adverse effects.

Untreated patients should also be carefully monitored (table 1) and the decision not to treat reconsidered if symptoms develop or liver injury worsens.

No evidence supports not treating children with AIH, apart from those presenting with AIH and ALF, who will probably require early liver transplantation.

Testing for, and monitoring of, viruses (HAV, HBV, HCV, EBV, HPV, Varicella)

Viral hepatitis should be excluded by testing as per box 1. HBV core antibody (cAb) should also be measured. While most HBV cAb positive patients and sAg negative patients have resolved infection, HBV DNA might still be present and should be measured before starting IST. Patients with AIH who are HBV sAg and cAb negative should receive early immunisation against HAV and HBV,[103] although this should not delay starting treatment. Patients with AIH who are also, probably coincidentally, sAg positive have been reported[104] but are rare in the UK. However, HBV cAb prevalence is 7% (0.8–19%) in European and North American general populations and is 14.5 (7–26%) in patients with rheumatic conditions.[105]

In patients with AIH and current (sAg positive) and prior (HBV sAg negative, cAb positive) HBV infection, reactivation might occur while receiving IST, with reappearance of serum HBV DNA and recurrent hepatitis.[106] HBV reactivation risk during IST is higher in (a) HBV sAg positive (vs HBV cAb positive),[105] (b) patients receiving treatment for malignancy rather than for patients inflammatory diseases[105] and (c) patients receiving biological therapies, especially B-cell depleting agents such as rituximab, than in those receiving azathioprine. Data on HBV reactivation induced by corticosteroids are limited, as they are usually given with other immunosippressive drugs. The risk might increase with systemic steroids taken for >1 month and in doses of >20 mg/day.[107] Data in AIH are lacking although, the risk seems low.

Antiviral prophylaxis with tenofovir or entecavir is effective in preventing IST-related HBV relapse in patients at risk. Thus, in the few HBV sAg positive patients who have AIH, routine prophylaxis during IST is recommended. In the larger number with prior but resolved HBV (sAg and DNA negative, cAb positive), most[108–110] favour HBV DNA monitoring at 1–3 monthly intervals while patients remain on >10 mg prednisolone per day, with antiviral therapy if HBV DNA levels rise. Routine antiviral prophylaxis might be needed in patients receiving high-dose steroids (>40 mg/day), receiving B cell-depleting therapies and those for whom regular HBV DNA monitoring is unfeasible. A similar strategy seems reasonable for budesonide therapy.

Severe varicella infection might occur in previously unexposed patients receiving steroids[111] The prevalence of varicella

antibodies (indicating prior infection) is over 80% even in those not reporting prior varicella infection.[111 112] However, patients starting treatment for AIH should be advised to avoid people with chicken pox or with shingles on exposed regions. Those reporting recent exposure should (even if also reporting prior exposure) be tested for varicella antibodies, and if absent (or if results are unavailable within 7 days), should have oral antiviral prophylaxis from days 7 to 14 post exposure. For further details, see references.[113 114]

Patients starting steroids should also (if not immunised) be offered the COVID-19, influenza[115] virus and pneumococcal[116] vaccines. Also, if under 25 or if gay, bisexual or men who have sex with men (GBMSM) and under 45, human papiloma[117] vaccines and if over 50, the shingles (herpes zoster) recombinant vaccines.[118]

Children with acute liver disease should have viral aetiologies excluded[119] *and children with AIH should receive their normal vaccinations, including HBV and HAV.*

Once receiving steroid and/or thiopurine therapy, live vaccines are not recommended and so, whenever possible, (in both adults and children) routine immunisations should be up to date before starting IST.

Corticosteroids: primary therapy of AIH

Corticosteroids remain first-line therapy for AIH. Of potential alternative drugs, ursodeoxycholic Acid (UDCA) monotherapy achieved remission (normal serum ALT) in 71% of a Japanese cohort with mild AIH.[120] However, UDCA did not improve liver histology (although in patients with prior suboptimal response to prednisolone)[121] and information is lacking on its longer-term efficacy. In small randomised controlled trials (RCTs) in adults[122] and in children[123] cyclosporine achieved similar rates of biochemical remission to prednisolone. However, pending further information, induction therapy should remain steroid-based for adults and children.

Of the regimens in the initial randomised trials, prednisolone monotherapy 60 mg/day was associated with more steroid-related adverse effects than, prednisolone 30 mg/day plus azathioprine 50 mg/day.[124 125] A cohort study[43] showed independent associations between non-use of a steroid-sparing agent (SSA) in steroid-treated AIH and higher death/transplant rates. The added benefits of SSA use were confirmed in a meta-analysis of these two studies.[3] Thus, this 'combination' regimen of a steroid (usually prednisolone, but see part 4 below) and a 'steroid-sparing agent' (usually azathioprine, but see part 8 below) remains the standard initial treatment for AIH in adults and children.

What is the best first-use steroid?

Prednisolone has been the first-use steroid in most patients with AIH. Prednisone is identical to prednisolone and is used in North America. Budesonide is an alternative corticosteroid with 90% first-pass liver metabolism in a normal liver, which should minimise systematic side effects.[126] In patients with cirrhosis, intrahepatic shunting reduces efficacy and increases systemic exposure; thus, budesonide should not be used.

In a randomised trial in AIH but without cirrhosis,[127] serum ALT and AST normalisation rates after 6 months were higher and risk of (mainly cosmetic) adverse events was lower in patients receiving budesonide (9 mg/day), compared with prednisone (40 mg/day, dose tapered), both with azathioprine. This trial informed the equal recommendation in the American Association for the Study of Liver Diseases (AASLD) of either budesonide or prednisone as first-use steroid, with no preference expressed.[63 128]

However, limitations of the trial include short duration, failure to include normalisation of serum IgG (slower in the budesonide group) in defining remission, and an unusually low AST/ALT normalisation rate (39%) in those receiving predniso(lo)ne. *In a separate analysis of children in the trial,*[129] *remission rates were almost identical in the two treatment arms, and adverse effects differed only regarding less weight gain in the budesonide group*.

In subsequent observational studies, rates of serum ALT±IgG normalisation rates have either been similar[43 130] or lower[131] in patients receiving budesonide compared with prednisolone. In a further meta-analysis of the one RCT and four cohort studies,[3 102] budesonide (compared with predniso(lo)ne) resulted in (a) similar serum transaminase±IgG normalisation rates after 6 and 12 months and (b) lower rates of cosmetic (but not other) side effects.

In a longer-term cohort study, the incidence of cataracts and fractures was similar in budesonide versus prednisolone treated patients.[132] Finally, in the UK AIH audit[43] 5-year all-cause and liver-related death/transplant rate were not different in patients initially receiving budesonide and prednisolone.

Thus, budesonide has (compared with predniso(lo)ne) a lower risk of cosmetic adverse events; thus, it can be considered in adult patients without cirrhosis or liver failure if these are expected to be problematic. However, it is not clearly more (and possibly less)[131] effective in achieving biochemical response; and data are sparse regarding longer-term efficacy. *Budesonide is not currently recommended in children as a first-line therapy*.[2 133]

Intravenous hydrocortisone can be used when there is concern about oral steroid absorption. Intravenous methylprednisolone has been used in AS-AIH, although it has not been formally compared with prednisolone. Of concern is hepatotoxicity, reported in 6–8% of patients receiving methylprednisolone for multiple sclerosis or Graves' ophthalmopathy.[134 135] About 2% of cases are severe (based on 'Hy's Law')[136] and some have been fatal or required transplantation.[137] While some cases ave features of and may represent coincidental AIH, most have features more suggestive of DILI, and there might be recurrence on re-exposure to methylprednisolone. Some patients have improved on treatment with other steroids, so the hepatotoxicity appears to be methylprednisolone specific.

Steroid monotherapy?

While corticosteroids plus azathioprine is the usually recommended first-line treatment for AIH (figure 2), steroid monotherapy should be considered in these situations:

1. Decompensated cirrhosis. Although not evidence-based, many centres are reticent about adding a steroid-sparing agent. AASLD guidelines[63] advise against.
2. Diagnosis of AIH is uncertain, when substantial improvement of serum transaminases with steroids increases the likelihood of AIH and might enable subsequent SSA introduction with more confidence.
3. Expected short treatment duration—for example, in a non-cirrhotic patient when a suspected drug precipitant has been withdrawn (Section O).
4. Homozygosity for the TPMT deficiency allele, or need for coincidental allopurinol therapy. (remembering that allopurinol might sometimes be beneficial (Section G)). Combined with reluctance to use mycophenolate (eg, in a woman contemplating pregnancy).

Table 7 Adverse effects of corticosteroids in autoimmune hepatitis

Side effect	Frequency (%)		Patient risk factors	Related to dose	Reversible
	Prednisolone	Budesonide			
Weight gain*[127] Average	8–19[86 127] 5.1 kg[129] (children)	1–12 0.2 kg[129] (children)	Not known	Likely	40%[195]
Cushingoid appearance[127 141]	20 (0–52)	10[127] Lower than with prednisolone in children[142]		Yes[3]	Yes[127]
Acne	24 (5–44)	9[127]	Not known	Not known	Yes[127]
Hirsutism	9[146]	3[127]	Not known	Not known	Not known
Muscle weakness[127]	7.3	4.9	Not known	Not known	Not known
New-onset diabetes mellitus[132 462]	9.5.(2–37)[31 33 43 132 140 186 462–464]	0–4	Higher BMI, older age	Yes[3 132 462]	10–50%
Osteoporosis or fracture[132]	9 (0.4–21)	Similar to prednisolone[132]	Bone mineral density, osteoporosis risk score	Yes and duration[132 150]	Bone mineral density increase with bisphosphonates of on switch to budesonide
Serious infection	1.7–2.3-fold increase.[465]; 24%[140] 9% of children[142] (main cause of death)	Not known	Not known	Yes[140 465] (also duration)	May persist[465]
Cataract[132]	5 (0–9)	Lower than prednisolone	Older age	Yes	No
Hypertension	8 (7–9)[33 127 86]	3[127]	Not known	Yes[466]	?
Adrenal insufficiency (see Section J)	37(11–60)[467]†	Case reports but seems rare[258]	Not known	Not known	85% (within 3 years)[467]
Psychosis	1 (0–4)[33]	No reports	Not known	Yes[468]	Yes
Growth retardation++§	18.1[142]	Not known	Worse in boys[142]	Probably.[469 470]	Not known
Mood disorder‡[127]	7.6	9.8	Prior depression?	Untested but likely	Yes
Cognitive problems[141]	22	8		Not known	
Insomnia[127 141]	4.8–8.5	1.0–8.3	Not known	Untested but likely	Yes

*Not defined or quantified
† Based on short Synacthen test.
‡Anxiety, irritability, depression
§Switching from prednisolone to budesonide led to 40% reduction in (mainly cosmetic) AEs
¶++ in children receiving >0.75 mg/kg/day prednisolone, endocrinological advice should be sought.

5. Current or recent cancer, resulting in reluctance to use azathioprine or mycophenolate (Section I).

In these situations, prednisolone is usually preferred. *Steroid monotherapy is not recommended in children*.

What is the optimal initial dose of predniso(lo)ne?

The initial daily dose of predniso(lo)ne ranged from 10 to 60 mg/day in the early AIH trials.[99] Recommended initial dose was 30 mg per day in previous UK and in recent AASLD guidelines,[63] and 1 mg/kg/day in EASL guidelines.[23] We conducted a meta-analysis[3 102] of initial predniso(lo)ne dose in adults with AIH (excluding studies focusing on AS-AIH or on AIH with ALF).[3 102] We found five studies[43 125 138–140] where outcomes were compared in patient subgroups receiving 'low dose' and 'high-dose' prednisolone. Most patients also received azathioprine. Biochemical response rates after 6 and 12 months and all-cause death/transplant rates were not significantly different (despite heterogeneity). However, high-dose predniso(lo)ne was associated with more adverse effects. Other studies[132] also suggest that risks of fractures, and cataracts are related to prednisolone dose.

Therefore, we recommend an initial prednisolone dose of no more than 40 mg/day (or 0.5 mg/kg/day) for adults with AIH, given as a single morning dose. The dose should be reduced over 3 months in 5–10 mg/day increments every 2 weeks, if (as in 90% of cases) serum transaminases fall gradually. Because most steroid adverse effects are dose-dependent (table 7), we recommend reducing the dose to below 20 mg prednisolone as soon as possible. Budesonide dose can also be reduced gradually.

In paediatric patients, a dose of 2 mg/kg/day with a maximum of 60 mg/day is recommended, but in practice there is little additional efficacy and a greater risk of side effects, so a maximum of 40 mg is acceptable. More detailed guidance is available.[2]

Adverse effects (AEs) of steroids

Over 70% of patients with AIH report negative feelings about steroid therapy.[141] Table 7 summarises the main AEs. Steroids have been associated in some studies with lower quality of life scores in AIH (Section L).

Children (especially adolescents) experience similar AEs to adults. Weight gain, growth retardation, decreased bone density and Cushingoid features develop in about 20% of children receiving prolonged steroid therapy.[142]

Steroid-related AEs should be anticipated, and proactively managed. Patients should be reassured that they are not inevitable. Anticipated AE risk might influence choice of steroid and initial dose. Advice on dietary and exercise programmes to minimise weight gain should be given. Management might include reduction in steroid dose as serum transaminases improve, or (in non-cirrhotic patients), changing prednisolone to budesonide.

BONE HEATH

Discrepant values for the prevalence of vitamin D deficiency (serum levels of 25-hydroxyvitamin D <25–30 mmol/L) are reported: 20% of 209 US patients and 80% of 64 Turkish patients with AIH.[143 144] Deficiency was associated with more severe AIH and with poor treatment response. Supplementation in one study was not of benefit.

We suggest optimising oral calcium intake and offering vitamin D supplements to patients starting bisphosphonates for osteopenia or osteoporosis (see below). Calcium supplements might also be considered in all patients with poor dietary calcium intake and those at risk of vitamin D deficiency (including malabsorption and poor sunlight exposure).[145]

In the early AIH trials,[124 146] 5–10% of steroid-treated patients (most aged under 50 years) developed fractures over 2–3 years. In one large cohort study, 15% of patients sustained at least one fracture.[132] In 35% of patients, fractures were vertebral; these are often asymptomatic.

Increased bone resorption is demonstrable within days of starting corticosteroids.[147] Increased fracture risk occurs in patients on prednisolone doses as low as 5–7 mg daily[132 148 149] and with budesonide (at a mean dose of 6 mg daily).[132 149] The increased risk can persist for up to a year after stopping steroids.[149]

The decision to offer bone-protection agents (usually bisphosphonates) is often based on results of a bone mineral density (DEXA) scan. In 219 patients with long-standing AIH[150] the average (age-adjusted) DEXA scores were lower than normal, and prevalence of osteoporosis was 16%. Factors associated with lower bone density included older age, lower BMI, liver fibrosis and high cumulative prednisolone dose. Improvement in bone density was demonstrated in 15 patients after switching from prednisolone to budesonide.[151]

The UK National Osteoporosis Guideline Group (NOGG),[145] https://www.nogg.org.uk/full-guideline advocates a more proactive approach(summarised in figure 3) than previous AIH guidelines to preserving bone health. Prior to starting steroids, they recommend calculating the 10-year risk of major osteoporotic fracture or 'FRAX' score, available online (www.shef.ac.uk/FRAX). The score is an algorithm incorporating parameters associated with fracture risk: age, gender, BMI, smoking, alcohol use, personal or parental fracture history, comorbidities such as rheumatoid arthritis and corticosteroid use.

The score has very high, high, intermediate and low-risk categories, all age-dependent. In very high- or high-risk patients, NOGG recommend starting bisphosphonates along with corticosteroids, rather than awaiting the DEXA scan result. Patients at intermediate risk should have a DEXA scan soon after starting corticosteroids. The scan result is then integrated to give a modified FRAX score. If there is delay (>6 months) in performing a DEXA scan, proactive bisphosphonate should be considered. If the FRAX score is in the low-risk category, neither DEXA nor bisphosphonates are needed.

An alternative approach to bone health is detailed by the Scottish Intercollegiate Network,[152] which uses QF fracture, another online fracture risk estimator.

It remains unclear how this proactive approach to bone protection can be incorporated into management of patients with AIH. Capacity will be centre-specific and additional resources/infrastructure might be required.

Before starting bisphosphonates, patients need advice about potential adverse effects.[149 153 154] Intravenous preparations are preferred in patients with oesophageal varices and in those developing AEs with oral bisphosphonates.[153]

Rare but serious AEs of bisphosphonates include osteonecrosis of the jaw (ONJ, 1 event per 10 000–100 000 patient-year, when given for osteoporosis)[155] and atypical femoral fractures (AFF; 1.7-fold increase, one event per 30 000 patient-years).[149 153 154] Over the first few years of bisphosphonate use, ONJ and AFF numbers are 10–100-fold lower than estimated number of fractures per year saved in high-risk patients. Thereafter, the relative advantages of bisphosphonates might diminish, underlying the importance of steroid withdrawal, when possible, with the potential for also stopping bisphosphonates.

For full details of bisphosphonate-related side effects, cautions and contraindications regarding use, and details of administration, see the British National Formulary https://bnf.nice.org.uk.

In patients not started on bisphosphonates, the need for their use should be reassessed at 2-year intervals.

Steroid-sparing agents (SAs)

Choice of agent

Azathioprine remains the first-line SSA (however see part below on mycophenolate). Information is lacking on other thiopurines (mercaptopurine and thioguanine), although they might have a role as second-line agents (Section G).

The main contraindication to azathioprine use is a very low thiopurine methyl transferase (TPMT) enzyme activity, suggesting homozygosity for the TPMT deficiency gene (see section below on Mycophenolate). These patients need an alternative SSA, the best characterised of which in AIH is mycophenolate (see below and Section H). Compensated cirrhosis in AIH does not contraindicate azathioprine use, even with stable leucopenia (usually due to cirrhosis), although this might complicate blood count monitoring. However, there is reticence regarding use of azathioprine (and other SSAs) in decompensated cirrhosis (see steroid monotherapy above).

Timing and dose of azathioprine; prior TPMT activity measurement

Introduction of azathioprine (and other SSAs) is often delayed after starting steroids, usually by 2 weeks or until serum bilirubin falls below 100 µmol/L).[156] Reasons include awaiting results of TPMT enzyme measurement, doubt about AIH diagnosis and concern about azathioprine hepatotoxicity.[1 23 63] However, in a multicentre cohort,[157] delay in azathioprine introduction of >2 weeks (versus <2 weeks) after starting steroids resulted in similar rates of biochemical remission, adverse effects (including hepatotoxicity) and azathioprine discontinuation. There seems little reason to delay beyond 2 weeks, especially as it takes up to 8 weeks for azathioprine metabolites to reach a steady state.

The azathioprine dose used in the early Mayo Clinic and UK trials was 50–75 mg/day. The dose used in European cohorts and RCTs has usually been weight-based: 1–2 mg/kg per day. In a preliminary cohort study,[158] a 1–2 mg/kg dose was associated with slightly higher remission rate than a fixed 50 mg/day dose, but similar AE rates. We recommend starting at 1 mg/kg/day. Some centres subsequently increase the dose in steps to 2 mg/kg/day as the steroid dose is reduced; however, this is not evidence-based. *In children, azathioprine is usually added once the transaminases are almost normal and can usually be started at 2.0–2.5 mg/kg/day.*

Azathioprine undergoes intracellular activation to form the active 6-thioguanine nucleotides (6-TGNs). Blood levels of 6-TGN are poorly related to azathioprine dose and determined mainly by activity of TPMT, which diverts azathioprine metabolites away from 6-TGN formation and towards inactive metabolites.[156] Thus, low TPMT activity results in higher active

6-TGN metabolite levels.[159] Conversely, high TPMT activity increases levels of other metabolites: some inactive, but some (6-methylmercaptopurine nucleotides) are implicated in azathioprine hepatotoxicity.[160]

TPMT activity is controlled by an autosomal co-do/minant genetic polymorphism. About 1 in 300 people are homozygous for a deficiency mutation and so, have very low TPMT activity.[159 161] Definition of 'very low' is laboratory-specific: usually <2.5 units/mL.[156] Such people develop high 6-TGN levels and are at higher risk of azathioprine adverse events. Routine TPMT measurement (genotype or activity) prior to commencing thiopurine therapy is supported by cost-benefit analyses.[156]

Between 10% and 16% of people are heterozygous for a TPMT deficiency mutation and usually have modestly lower TPMT enzyme activity and higher TGN levels.[156] In meta-analyses incorporating many diseases, carriage of a TPMT mutation was associated with a 3–4-fold higher risk of azathioprine-related adverse events.[160 162 163] In patients with inflammatory bowel disease (IBD),[164] TPMT-guided dose adjustment, was associated with less bone marrow suppression in patients with TPMT mutations, but not with fewer AEs overall.

In patients with AIH, azathioprine doses are usually lower than those used in IBD, and TPMT activity is influenced by factors other than genotype.[159] In most studies, TPMT activity levels and heterozygosity showed no association with azathioprine-related adverse events.[165–168] Nor have TGN levels been unduly elevated in patients developing azathioprine-related leucopenia.[166 169] Thus, the benefits of azathioprine dose modification in heterozygous patients are not established.

We recommend that TPMT genotyping and/or enzyme activity assay be performed prior to commencing treatment in AIH; mainly to detect the 0.3% of patients with homozygous deficiency and thus, at high risk of severe AEs. Enzyme activity is a reasonable index of genotype, and most laboratories set their own ranges for normal (wild), modestly low (heterozygote) and very low (homozygote).

While measurement of TGN levels can also be used to modulate azathioprine dose for maximum efficacy, we think there is insufficient evidence to support doing this routinely (however see, sections G and I) .

Adverse effects (AEs) of azathioprine

Based on pooled study results in 962 patients with AIH,[157 165 168 169] a serious azathioprine-related AE occurred in 16% of patients, usually leading to discontinuation. The main AEs were bone-marrow depression (3%), gastrointestinal symptoms (9%), hepatotoxicity (2%), pancreatitis (1%) and allergic reaction (1.5%). They might be commoner in patients with cirrhosis.[165]

The incidence of azathioprine hepatotoxicity in IBD and other conditions is 0.3–10%[170]; thus, the reported 3% incidence of azathioprine hepatotoxicity in AIH[157 168 169] might be an underestimate. Distinction from a AIH relapse might be difficult. Hepatotoxicity in both IBD and AIH has been associated with high levels of the azathioprine 6-methyl mercaptopurine nucleotides,[169 171] measurement of which might be diagnostically useful.

The best-characterised option in azathioprine-intolerant patients is mycophenolate; discussed in Section H, although steroid monotherapy is an alternative.

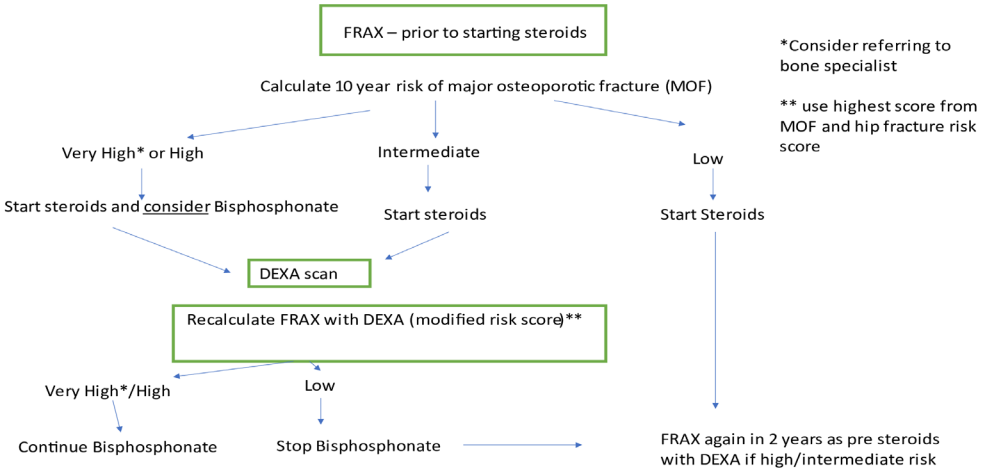
The increased cancer risk possibly associated with immunosuppressive drugs, including azathioprine, is discussed in Section I.

Use of azathioprine and Epstein-Barr virus (EBV) status

About 90% of adults have evidence of prior EBV infection, but only 50–70% of children and adolescents do. As discussed in Section I, immunosuppressive drugs might be associated with increased risk of lymphoproliferative disorders (LPDs). In patients with inflammatory bowel disease (IBD), this risk has been specifically associated with current use of thiopurines. Most LPDs occur in older EBV-positive patients.[172 173]

There is also an increased risk of haemophagocytic lymphohistiocytosis and other LPDs, associated with primary EBV infection in younger (<35) previously EBV-naïve patients taking thiopurines.[174 175] Estimated absolute risk in these patients is 3/1000 patient years.[173] Thus, some[176] IBD guidelines suggest routine testing of EBV status, and advise caution with thiopurine use in EBV-naïve patients.

Few equivalent data are available in AIH. In a recent series of 229 children with AIH or autoimmune sclerosing cholangitis[177] (most receiving either azathioprine (168) or mycophenolate



Notes on Frax score calculation: 1.Nearly all patients with AIH initially receive "high dose" corticosteroids (defined by NOGG as >7.5 mg prednisolone per day for at least 3 months). NOGG recommend that the FRAX scores for these patients should be multiplied by a factor of 1.15{Gregson, Arch. Osteoporosis 2022 17(1) 58} but this multiplier is not needed with prednisolone <7.5 mg/day or budesonide.

2.The risk factors in the FRAX score calculator also include chronic liver disease, based on associations of cirrhosis with fracture risk. {Lupoli, Clin. Endocrinol. 2016 84(1) 30} However, it is doubtful if untreated patients with recently diagnosed AIH and without cirrhosis have lower bone density and therefore, at increased fracture risk. Thus the "chronic liver disease" box should probably be ticked only in patients who have cirrhosis at time of fracture risk assessment.

Figure 3 Summary of suggested bone health strategy for patients on steroids.

(69)), EBV status had been checked at AIH diagnosis in only 10%. Five patients developed symptomatic acute primary EBV infection (four on azathioprine, and one mycophenolate). Liver tests were abnormal in two, and no patients developed LPD pre-transplant. However, of 39 patients who underwent liver transplantation, a further two (who had initially received azathioprine) subsequently developed LPD (EBV-negative patients, EBV-positive donor).

Thiopurines are central to management of AIH and (unlike in IBD) there are limited alternatives (but see Section F below on mycophenolate). Also, lower thiopurine doses are used in AIH than in IBD.

We suggest that testing of EBV status be considered in AIH, and in EBV-negative patients we recommend vigilance for possible detection of primary EBV infection and LPD. We do not think that the available evidence is sufficient to recommend routine avoidance of azathioprine in EBV-negative patients.

Mycophenolate mofetil (MMF) as a first-line agent

Observational studies[178] suggested that MMF (1.5–2.0) g/day, with prednisolone, was well-tolerated and achieved remission (normal serum transaminases and γ-globulins), usually, within 3 months. In follow-up studies[179] and in a recent RCT[180] in 70 patients, MMF (compared with azathioprine) achieved a higher CBR rate after 6 months and caused fewer AEs requiring a change of drug. Meta-analysis of these two studies[3 102] favoured MMF over azathioprine. However, for definitive conclusions, further data are needed. *Mycophenolate mofetil is not currently used as a first-line therapy in children.*

Monitoring of patients during treatment

Monitoring can be done in secondary or primary care if results can be assessed and actioned reliably. (Table 1) Assessments should be more frequent if serum transaminases are not settling or there are treatment-related AEs. Stopping treatment is discussed in Section I.

Initial management of Acute Severe AIH (AS-AIH), AIH with Acute Liver Failure (AIH-ALF) and AIH with Acute on Chronic Liver Failure (AIH with ACLF)

These severe presentations of AIH are described in sections C–E. They represent medical emergencies, and correct management decisions can be life-saving.

AS-AIH

The most important thing is to ensure that the option of urgent liver transplantation is available if the patient does not rapidly improve, either spontaneously or on steroids.[47] This means regular discussion with a transplant centre and usually, transfer of the patient there.

The second issue is whether corticosteroids should be used. There are no randomised trials of therapy for AS-AIH. Management is based on results from cohort studies. These comprise mostly (though not entirely) patients with AS-AIH (no cirrhosis or encephalopathy).[48–51]

Corticosteroids have been used in most patients with AS-AIH, and in four studies were associated with a 37 (31–43)% possibility of death or needing transplant,[48–51] representing, in a meta-analysis, a threefold reduction, compared with those not receiving steroids.[3 102] Patients receiving steroids had less severe liver disease (lower MELD score, less encephalopathy) and had prior exclusion of sepsis. However, the steroid 'effect' was independent of disease severity in the largest cohort.[49] Median prednisolone dose was 40–60 mg/day, but up to 1.5 mg/kg/day. Efficacy seemed unrelated to steroid dose[49 50] or to the mode of administration (intravenous methylprednisolone or oral prednisolone).

The third question is whether and when non-response to steroids is identifiable and transplantation needed. In the above studies, poor response to steroids and death/transplant were associated with higher initial MELD score and/or INR; with presence of encephalopathy, and sometimes[49] with older age. Close monitoring is essential, as rapid liver transplant must be the next option in the absence of clear improvement. The definition of improvement has varied. A score incorporating INR, bilirubin and the change in these parameters over 3 days (SURFASA score) was found to be predictive of liver transplantation or death. Thus, patients with a score of −0.9 had a 75% chance of response to steroids, but those with a score over 1.75 had an 85–100% risk of death or liver transplantation.[50] In the largest reported study (242 patients),[49] the MELD score after 7 days of steroids was the best predictor of outcome, and this report includes a useful nomogram. Preservation of liver volume on CT scan has also been reported[181] as predictive of a good outcome, but confirmation is needed.

Use of second-line agents in patients with AS-AIH not responding to steroids is not routinely recommended, although there are reports of benefit from tacrolimus[182] and ciclosporin.[183]

Some patients presenting initially with AS-AIH then develop encephalopathy, in effect, progressing to AIH with ALF. Progression rate is correlated across studies with median initial MELD score and INR. Also, sepsis develops in about 20% of patients with AS-AIH or AF-AIH. The risk is not obviously increased following steroid treatment but is associated with a higher initial MELD score.

Based on these studies, we suggest that in patients with AS-AIH, an INR greater than 2.5 at presentation represents a good cut-off value, above which steroid therapy is unlikely to result in avoidance of transplant.[48 50 51] A trial of steroids (usually prednisolone 40 mg/day) can be considered in AS-AIH if there is (a) full involvement and agreement of the local transplant centre, (b) exclusion of, or successful treatment of, sepsis, (c) INR<2.5, (d) facilities for close monitoring, ideally in a high-dependency ward.

AIH with ALF

Some cohorts consist mainly of patients presenting with AIH-ALF (including encephalopathy). In these, recovery with steroid treatment is seen in only 9–42% of patients,[49 52 54 184] and no survival benefit was seen with steroids in ALF-AIH in one multicentre cohort.[52] A trial of steroids can be considered in patients presenting with grade 1–2 encephalopathy, especially with lower MELD scores, but all these patients should be managed in a transplant centre.[47]

AIH with ACLF

Although presence of cirrhosis was an exclusion criterion in the initial description of AS-AIH,[48] in some cohorts, about 20% of patients had cirrhosis or 'severe fibrosis' at biopsy and thus, should be classified as AIH with ACLF.[49 50] However, cirrhosis did not seem to be an independent adverse prognostic factor.

In 82 patients with AIH and ACLF (based on a history of prior chronic liver dysfunction; 39% with cirrhosis), 28 (34%) received steroids and showed improved 90-day survival (75% vs 48%, p=0.02) compared with those not

receiving steroids.[46] Patients with advanced age, higher MELD score >27, hepatic encephalopathy grade >3 and fibrosis grade >F3 had a poorer response to steroid therapy. However, in another cohort with AIH and ACLF,[185] all with cirrhosis, only 10 of 29 steroid-treated patients survived without transplant. A MELD score <24 was associated with survival.

Thus, some patients with AIH-ACLF might benefit from corticosteroids. However, diagnosis of ACLF is also a potential mechanism to expedite liver transplantation in the United Kingdom for appropriate candidates.

The management of children is similar to that of adults.

RECOMMENDATIONS SECTION F

1. We recommend immunosuppressive treatment (IST) in most patients with AIH, regardless of symptoms. *Grade of evidence: high. Strength of recommendation: strong.*

2. We recommend that in patients with mild AIH (all of: serum ALT<50 U/L, Ishak necro-inflammatory score <6 and fibrosis stage <2), the decision to offer treatment should be based on a balance of benefits and risks. *Grade of evidence: low. Strength of recommendation: strong.*

3. We recommend that patients starting treatment for AIH should:

(a) Ensure immunisation is up-to-date against: COVID-19, pneumococcus, influenza, shingles, hepatitis A, hepatitis B (if HBV markers absent) and ((if under 25 or if gay, bisexual or men who have sex with men (GBMSM) and under 45), human papillomavirus.

(b) Receive prophylactic nucleotide therapy if HBV surface antigen positive or if core antibody positive and starting rituximab.

(c) Be monitored for HBV reactivation if HBV core antibody positive and receiving other treatments. *Grade of evidence: low. Strength of recommendation: strong.*

4. We recommend that first-line initial therapy should usually comprise a corticosteroid plus azathioprine. *Grade of evidence: high. Strength of recommendation: strong.*

5. Although not routinely recommended over prednisolone, we recommend that budesonide (initially 9 mg/day) be considered in adults without cirrhosis if there is major concern regarding steroid cosmetic adverse effects. *We do not recommend budesonide in children as first-line therapy. Grade of evidence: high. Strength of recommendation: strong.*

6. We recommend that the initial dose of prednisolone be approximately 0.5 mg/kg/day and not usually exceed 40 mg/day, given as one morning dose, *or up to 2 mg/kg in children to a maximum of 40 mg. Grade of evidence: moderate. Strength of recommendation: weak.*

7. We recommend that if the test is readily available, thiopurine methyltransferase (TPMT) enzyme activity be measured before starting azathioprine, to exclude homozygosity for TPMT deficiency. *Grade of evidence: moderate. Strength of recommendation: strong.*

8. We recommend that the standard starting dose of azathioprine be 1 mg/kg day *(2.0–2.5 mg/kg in children*). In patients with modestly reduced TPMT activity, in the heterozygous range, there is insufficient evidence for routine reduction of the initial azathioprine dose. *Grade of evidence: moderate. Strength of recommendation: weak.*

9. We recommend that in patients homozygous for TPMT-deficiency, mycophenolate mofetil can be substituted for azathioprine (with advice on avoiding pregnancy). Wider use of mycophenolate mofetil as a first-line agent awaits its further evaluation. *Grade of evidence: moderate. Strength of recommendation: strong.*

10. We recommend that steroid monotherapy (prednisolone 0.5 mg/day or maximum 40 mg/day, if tolerated) be considered in patients with decompensated cirrhosis, current/recent malignancy, an uncertain AIH diagnosis or a suspected precipitant, with expectation of a short treatment duration. *Grade of evidence: low. Strength of recommendation: weak.*

11. We recommend monitoring (detailed in table 1) of patients on steroids and or thiopurines. This can be done in secondary or primary care if there is a system for accessing and promptly acting on results. Azathioprine should be promptly reduced or stopped if there is significant bone marrow depression and stopped if there are other severe adverse events (eg, pancreatitis). *Grade of evidence: moderate. Strength of recommendation: strong.*

12. We recommend that in most patients, the prednisolone dose be reduced gradually over 1–3 months to 5–10 mg/day (and budesonide to 6 mg/day), guided by the fall in serum transaminases. For dose reduction below 5 mg/day, see Section I. *Grade of evidence: low. Strength of recommendation: strong.*

13. We recommend that as the steroid dose is reduced, the dose of azathioprine can be increased gradually from 1 to 2 mg/kg/day, with appropriate blood count monitoring. *Grade of evidence: low. Strength of recommendation: weak.*

14. We recommend that measurement of azathioprine metabolites is not needed routinely, but can be considered if there is leucopenia, or suspected non-adherence. They can also be useful in patients with an inadequate serum ALT response, to inform whether the dose should be increased (see Section G). *Grade of evidence: low. Strength of recommendation: weak.*

15. We recommend routine supplementation with vitamin D and optimisation of dietary calcium intake in patients receiving bisphosphonates and in those with poor calcium intake and / or risk factors for vitamin D deficiency. *Grade of evidence: low. Strength of recommendation: weak*

16. We recommend consideration of calculating the FRAX (fracture risk) score in adult patients starting steroids. Some older patients will have scores in the 'high-risk' fracture category. In these, consider starting bisphosphonates as soon as feasible, pending a DEXA scan report, which then can modify the risk score and need for treatment. *Grade of evidence: moderate. Strength of recommendation: weak.*

17. We recommend that patients with AS-AIH (INR >1.5 without encephalopathy) receive prednisolone monotherapy 40 mg/day if INR is <2.5 and sepsis has been excluded. They should be managed in close liaison with a transplant centre because of an approximately 35% chance that (despite treatment) they will require early liver transplantation. *Grade of evidence: moderate. Strength of recommendation: strong.*

18. We recommend that patients with AIH and ALF (including encephalopathy) should be referred promptly to a transplant centre). *Grade of evidence: low. Strength of recommendation: strong.*

19. We recommend that patients with AIH and decompensated cirrhosis, and those with jaundice but with MELD score of <27, can (after a negative septic screen) be started on prednisolone, but should be discussed with a transplant centre if the MELD score does not fall progressively. *Grade of evidence: low. Strength of recommendation: strong.*

Section G. Adequate and inadequate treatment responses

Definitions

The term inadequate response is used here generically; specific definitions are given in table 8. Response can be defined biochemically and histologically. The definition of biochemical response has changed with time: achieving serum transaminases of <2 x ULN in the initial randomised trials, then incorporating serum γ-globulin, and finally, requiring normal serum transaminases. Patients with even mild persistent ALT elevations (1–2 x ULN) have higher rates of cirrhosis development[43] and liver-related death/transplantation.[55 186–188]

Recently, the International AIH group (IAIHG) developed consensus definitions (table 8) for response and remission, aiming to achieve harmonisation.[189]

Overall, 45(35-68)% patients achieve complete biochemical response (CBR) within 6 months (CBR-6).[131 187 189–192] These patients have lower liver-related death/transplantation rates than those not achieving CBR-6.[189 190 192] The proportion achieving BR within 12 months rises to 62(45-70)%;[131 187 191 192] these patients also have lower liver death/ transplantation rates[190] and adverse event rates[187] than those not achieving CBR-12. CBR-6 has not yet been shown to superior to CBR-12 in regard to predicted survival[187 189 190 192] (though it may be in regard to subsequent cirrhosis development).[192]

Normalisation of serum IgG (in addition to serum transaminases) seems to confer additional prognostic value in some,[187 190] although not other,[193 194] studies.

The IAIHG also defined non-response (NR): as <50% reduction in serum transaminases after 4 week's treatment. This was seen in 17% of patients.[189] In the validation study, NR was associated with higher liver-related death/transplant rates (21.4% vs 2.4%; p<0.001).[189]

We have here adopted these IAIHG definitions[189] of non-response and of CBR (within 6 months) (table 8). However, their further validation in other (ideally prospective) cohorts is needed, particularly regarding the optimal time for defining biochemical response (6 or 12 months) and the added predictive value of serum IgG normalisation.

Previously, remission has also been defined histologically. Histology response lags behind biochemical response by several months: in the Mayo clinic RCT, only 28% and 50% of patients receiving prednisolone±azathioprine achieved histological remission after 6 and 12 months, respectively.[124] Thus, repeat biopsy to confirm remission is not recommended over the first 2 years.

Histological remission after 2–3 years treatment has been considered the 'gold standard' for assessing remission (usually defined[77] as modified Ishak necro-inflammatory score of <4 (see Section D), and has been the basis for inclusion in randomised trials of therapy to prevent AIH relapse[195–198] (see Section I). Histological remission is also associated with stability or improvement in liver fibrosis[199 200] and in one study, with better long-term survival, compared with those with persisting histological activity.[200]

In three studies,[191 201 202] histological remission was confirmed in only 162 out of 252 patients (64%) who achieved sustained complete biochemical remission after 2–6 years' treatment. However, liver biopsy carries the risk of complications and is subject to potential sampling error. Therapeutically relevant differences in necro-inflammatory score were recently reported between right and left lobe biopsies (obtained at mini-laporoscopy) in 30% of patients with AH.[203] There remains insufficient evidence of the additional use of follow-up biopsy in informing patient management to recommend routine confirmation of histological remission in patients achieving CBR.

However, follow-up liver biopsy is sometimes useful. First, when there is diagnostic uncertainty (eg, where steatosis/steatohepatitis might be causing persistent biochemical abnormalities); although elevation of both ALT and IgG are usually associated with ongoing AIH histological activity.

Second, in patients with cirrhosis at diagnosis, who are less likely to achieve CBR,[189] and have poorer longer-term outcome (see Section I). Also, CBR might be less reliable (compared with the CBR in patients without cirrhosis) in predicting histological remission.[202] Thus, in patients with cirrhosis, the case for confirmation of histological remission might be stronger.

Management of inadequate response

If treatment response is adequate (ie, CBR is attained), corticosteroids should be phased out gradually (see Section I). The management of patients who meet the definitions of inadequate response is summarised in table 9. There is no prescriptive evidence-based algorithm for all scenarios. Decisions might also be guided by disease activity or severity. For example, in someone not achieving CBR-6, the presence of raised serum transaminases (ie, not just serum IgG), the presence of cirrhosis at diagnosis or evidence of its development on transient elastography after 6 months (Section I) might all incline towards deciding on an earlier change in treatment.

For patients with AS-AIH, there should be discussion with a transplant centre, and inadequate response to steroids after 3–7 days should prompt transfer, if not done earlier (Section F).

For patients meeting other definitions of inadequate response, the strategy should be to achieve serum ALT, AST and IgG levels as low as, and for as much of the time as possible. While also keeping treatment side effects to a minimum. The need for a second clinical opinion should be considered. Strategies (table 9) include:

a. Diagnosis review: considering alternative diagnoses and co-existing liver disease, such as drug-induced liver injury (Sections E,O), a variant syndrome (Section N) or MASLD (Section E).
b. Medication adherence review (Section L).
c. Optimisation of treatment. Consider whether the steroid dose is adequate or whether it has been reduced too quickly. If patients have not responded to budesonide consider changing to prednisolone. It takes up to 8 weeks for azathioprine metabolites to reach a steady state, and in some patients, a slower reduction (even an increase) in prednisolone might be needed.
d. Re-institute (or maintain) low-dose corticosteroids. Although phasing out of steroids should be attempted after attaining CBR (Section I), this is not always achievable, and steroids are often continued for much longer, with the dose titrated to maintain normal serum transaminases and IgG, if tolerated. Budesonide is no more (and possibly less) effective in this regard[3 102] but might be better tolerated than prednisolone, and so, can be used in patients without cirrhosis.
e. Change to a second-/third-line agent (Section H), There is insufficient evidence to support routine change to a second-/third-line agent in patients with NR after 4 weeks or who do not achieve CBR after 6 months as defined in table 8. In

Table 8 Definitions of response

Term	Definition
Biochemical remission	Normal serum transaminases and IgG
Biochemical response (BR)	Achievement of biochemical remission
Complete biochemical response (CBR)–6	Achievement of biochemical remission within 6 months of starting treatment (and confirmed 2–4 weeks later)
Insufficient response	Failure to achieve complete biochemical response
Complete biochemical response (CBR)–12	Normalisation of serum transaminases and IgG within 12 months of starting treatment (and confirmed 2–4 weeks later)
Non-response (NR)	<50% decrease in serum transaminases within 4 weeks of treatment initiation
Histological remission	Modified Ishak[77] hepatitis activity index (mHAI) <4/18
Treatment intolerance	Any adverse event or perceived side effect felt to be treatment-related, as assessed by the treating physician or patient, leading to drug discontinuation

a well patient without cirrhosis and without treatment AEs, the steroid- and azathioprine-based regimen (although optimised) can be continued for a further 6 months. However, in patients with cirrhosis at diagnosis or developing cirrhosis (repeat biopsy, elastography or portal hypertension), the argument for a second/third agent is stronger. In such patients, consider the need for an expert opinion.

f. Thiopurine therapy can also be optimised. A meta-analysis of seven studies in AIH found a correlation between TGN values and being in biochemical remission.[161] TGN levels of >220 pmol/8×10^8 red blood cells have been associated with being in remission, with a sensitivity of 83% and a specificity of 62%.[169] However, many patients achieve remission with lower TGN levels.[169 204] Measurement of azathioprine metabolites can also help distinguish true non-response from poor adherence.

g. Other patients have a combination of low TGN and high 6-MMP levels. Allopurinol inhibits xanthine oxidase, which converts 6-mercaptopurine (the first metabolite of azathioprine) to inactive metabolites and might also reduce TPMT activity.[205] Thus, allopurinol co-administration (with reduced dose of azathioprine) increases 6-TGN and reduces 6-MMP metabolite levels and can thus potentially increase efficacy (and toxicity) of azathioprine.[205] In a series of eight patients (five with inadequate response, three with azathioprine intolerance),[206] azathioprine metabolite levels changed as predicted, and most patients achieved remission or restoration of tolerance. One developed reversible neutropenia. Recently[207] experience with allopurinol addition has been reported in 36 patients responding inadequately to standard treatment, with an overall fall in serum ALT and CBR achieved in 76%.[205–207]

The management approach to inadequate treatment response in children is similar to that in adults.

RECOMMENDATIONS SECTION G

1. Confirmed normalisation of serum ALT/AST and serum IgG should be the aim of treatment. *Grade of evidence: moderate. Strength of recommendation: strong.*

2. We recommend that response to treatment be assessed at the following time points, with inadequate response being defined as:

(a) After 1 month: <50% decrease in ALT/AST

(b) After 6 months: failure of normalisation of ALT/AST and IgG. *Grade of evidence: moderate. Strength of recommendation strong.*

3. In patients with inadequate response, we suggest review of diagnosis and assessment of adherence to medication, followed by considering changes to steroid regime and also to azathioprine regimens, to achieve TGN levels in the therapeutic range. *Grade of evidence: low. Strength of recommendation: strong.*

4. Liver biopsy to confirm histological remission in those with complete biochemical remission is not routinely required, although it might sometimes be useful. *Grade of evidence: low. Strength of recommendation: weak*

Section H. Second- and third-line treatments

Overview

The evidence base for immunosuppressive therapy beyond azathioprine and prednisolone in AIH consists of small retrospective heterogeneous case series (table 10). The likelihood of response to second-/third-line agents is higher for those who are switched due to azathioprine intolerance rather than due to inadequate response (see definitions in table 8).

Choice of second-/third-line therapies is individualised, requiring consideration of:

- Adherence to first-line therapy.
- Reason for first-line treatment failure (intolerance or inadequate response).
- Disease duration, and (if biopsy repeated) inflammation and fibrosis severity.
- Frailty and comorbidity (infection risk, cardiovascular or renal disease).
- Potential for pregnancy.
- Patient choice.

This complexity highlights the importance of clinician experience, networking and collaboration.

First, ensure that first-line therapy has been optimised (Section G and table 9). Second, the risks, benefits of second-/third-line agents, including acknowledgement of their limited evidence base, should be discussed with the patient. Use of two to three immunosuppressive drugs might be required. However, the need for ongoing treatment should be regularly re-assessed, and the goal should be to maintain remission using one agent.

Budesonide

As well as its use as a first-line agent (Section F), budesonide might have a role as an alternative steroid in non-cirrhotic patients who have significant AEs with prednisolone (table 10).[126] In 60 prednisolone-treated patients[151] switched to budesonide (due to prednisolone side effects (n=30) or prednisolone dependence (n=30)), the biochemical response rate was 70% after 12 months. However, 15 patients had to restart prednisolone, either because of disease flares or AEs. There is no evidence to support budesonide substitution in

Table 9 Implications and management options in patients meeting various definitions of inadequate response. Which of these measures is introduced and at what stage, should be an individualised and response-guided decision

AIH type	Response	Time treated	Not met (%)	Not met: Implications		Not met: Managementeloptions (o: not recommended; +, ++, +++, ++++ reflect increasing recommendation strength)				
				Fibrosis progression	Risk of death/ transplant or adverse liver outcomes	Reconsider diagnosis (Section D) and drug adherence (Section L)	Budesonide: change to prednisolone. Prednisolone: increase or maintain dose*	Increase AZA dose, check metabolites† ±add allopurinol	second/3rd line agent (Section I)	Refer for transplantation (Section K)
Acute severe	Fall in MELD score	3–7 day	30–40	?	>70% (liver)[49 50]	+++				++++
Any	>50% ALT fall	1 month	17[189]	?	8-fold higher (liver)[189]	++	++	++	+	+
Any	CBR+	6 months	45–68[189 190]	worse[201]	Higher (7.5% vs 0% (liver))[189]	+++	++	+	+	+
Any	CBR+	12 months	45–70[131 187 191 192]	?	3–4 fold higher (all-cause)[187]	+++	+	+++	+++	+
Any	Histological remission	24–36 months	50–75‡[191 200 201]	worse[191 200]	3-fold higher (all-cause)[200]	+++	++	+++	+++	+

+ Serum AST, ALT and IgG in normal range.
*Alternatively, change budesonide to prednisolone, or prednisolone to budesonide (if adherence issues).
†Takes 8 weeks to reach steady-state levels.
‡Of patients in biochemical remission.
ALT, alanine transaminase; AST, aspartate aminotransferase; AZA, azathioprine; CBR, complete biochemical response.

patients with inadequate response to prednisolone (assuming adequate adherence).

Mycophenolate mofetil (MMF)/mycophenolic acid

When azathioprine is stopped due to intolerance, substitution with MMF (continuing steroid therapy, if appropriate) is the best-characterised strategy.[208]

In a systematic review of 14 studies including almost 400 patients, pooled biochemical response rate on MMF was 82% in azathioprine-intolerant patients, much higher than the 32% in azathioprine inadequate responders.[208] MMF was usually well-tolerated, with pooled adverse events and discontinuation rates of 15% and 8%, respectively. The necro-inflammatory score also falls on MMF, and histological remission and 5-year survival rates were not different from those seen with azathioprine continuation (in tolerant patients).[188]

Given its lower efficacy (compared with that in azathioprine-intolerant patients), use of MMF in patients with inadequate response to azathioprine might be questioned. Nevertheless, the AASLD Guidelines[63] recommend MMF in this situation over tacrolimus (see below) because of the perceived lower medium-term toxicity of MMF, compared to calcineurin inhibitors (see contraindication in pregnancy below).

6-Mercaptopurine (6-MP) and thioguanine

In 49 azathioprine-intolerant patients from two studies,[209 210] thioguanine was tolerated in 40 and 36 achieved complete biochemical response. 6-Mercaptopurine was tolerated in 18 of 33 azathioprine-intolerant patients in two pooled studies,[168 211] with 8/15 informative patients having a complete biochemical response.

Data in azathioprine non-responders are sparse. Thioguanine seems tolerated and achieved improvement in serum transaminases in seven out of seven patients, but complete remission in only two.[209 210] Given the small evidence base, we think these agents have a limited role in AIH.

Calcineurin inhibitors (CNIs)

Tacrolimus (TAC) and ciclosporin prevent transcription of cytokine genes, particularly interleukin-2 (IL2), with an inhibitory effect on CD4+T helper cells. Studies of CNIs in AIH (see table 11) have been mostly in patients with inadequate response to, rather than intolerance of, standard treatment. They are small, retrospective, and usually lack information on histological response and transplant-free survival.

In a meta-analysis[212] of tacrolimus in AIH (162 adult patients in seven studies, six as a second-line agent), there was heterogeneity, because some studies combined results in patients intolerant of first-line therapy with those unresponsive to first-line therapy. Overall, 75% achieved biochemical response and renal function was stable in most patients. However, tacrolimus was discontinued in 17% of patients. Of 30 (18.5%) patients who underwent liver biopsy, 25 achieved histological remission. There was also improvement in hepatic inflammation and fibrosis in nine patients with steroid-refractory AIH without renal impairment, using trough levels <6.0 ng/mL.[213] Biochemical improvement with tacrolimus was also demonstrated in seven of nine patients with new-onset icteric AIH that was unresponsive to corticosteroids.[182]

In the largest individual study of tacrolimus as second-line therapy[214] (80 patients), complete biochemical response (CBR) rate in patients who were intolerant of first-line therapy was 94%, (similar to 92% seen with MMF in intolerant patients).

Table 10 Use of second- and third-line therapies in autoimmune hepatitis

Agent	
Budesonide[126]	Avoid in cirrhosis, acute severe AIH, acute liver failure, or if failing to achieve remission with prednisolone (unless due to poor adherence)[151 471]
Mycophenolate mofetil/ mycophenolic acid[208]	Better outcomes in patients with azathioprine intolerance (compared with those with inadequate response) Consider before tacrolimus, given better side-effect profile Highly teratogenic Otherwise well-tolerated and safe; most adverse effects are gastrointestinal (reduced with mycophenolic acid)
Calcineurin inhibitors	Small open studies mostly in inadequately responding AIH and lacking hard outcome data. Biochemical and histological improvement with tacrolimus in most patients[212] *Side effects* include weight gain,[472] dyslipidaemia,[473] hypertension,[474] insulin resistance,[475] renal impairment,[476] neurotoxicity[477] and increased malignancy risk[478] Tacrolimus discontinued in 17%[212] *Schedule*: ERN suggests 0.1 mg/kg twice daily, or prolonged-release formulation of tacrolimus in lower doses, with target trough levels <8 ng/mL[479] Once-daily preparation reduces tablet burden, with similar or less adverse effects[480] Biochemical response in case series with ciclosporin, but frequent side effects[215]
Rituximab	Case reports/series demonstrate sustained biological remission and improved histology[217–219] Prior to administration, check HBV (sAg and cAb), HCV and HIV status. If either HBV aAg or cAb positive, give anti-HBV prophylaxis (Section F) Need annual influenza and 5-yearly pneumococcal vaccinations[481] Ideally administer vaccines 4 weeks before starting or 6 months after last dose, and avoid live vaccines[482] Avoid in patients with severe heart failure or uncontrolled cardiac disease[483] Dosing regimen - 1000 mg at week 0 and 2; consider repeat treatment cycles approximately every 6 months A slow rate of first infusion and pre-medication with paracetamol, antihistamine and methylprednisolone result in fewer infusion-related reactions (IRRs), including hypertension, hypotension, nausea, rash, fever, urticaria, angioedema, bronchospasm and anaphylaxis[223–225 484] Risk of opportunistic infection and progressive multifocal leukoencephalopathy (PML)[223–229]
Infliximab	Small series suggests effectiveness as rescue therapy,[233] but high infection rate No long-term efficacy data Seems safe in early pregnancy but consider stopping after 30 weeks to limit fetal exposure[244 245] Infliximab might trigger autoimmune-like hepatitis (see Section O)

ERN, European Reference Network.

In contrast, in patients non-responsive to first-line therapy, tacrolimus achieved a CBR rate of 56%, compared with 34% achieved with MMF.

Specific guidance for tacrolimus use in AIH is not evidence-based. However, table 10 summarises the main side effects and a regimen based on a recent statement from the European Reference Network (ERN) and IAIHG.

There are limited data on the use of ciclosporin in management of AIH in adults. In small case series there was a high biochemical response rate (≥80%), although with high AE rates.[215] However, following liver transplantation, a lower rate of de novo diabetes is reported with ciclosporin than with tacrolimus.[216]

Rituximab

Rituximab is an anti-CD20 monoclonal antibody that depletes B cells and is widely used in autoimmune conditions. In three patients with prednisolone-refractory AIH,[217] rituximab achieved normal serum ALT within 6 months in all, and histological improvement in two. A multicentre case series (22 patients) showed biochemical improvement (sustained for up to 2 years) and freedom from AIH flare after 2 years without serious AEs in 71%.[218] A recent Spanish registry study[219] of 35 patients with AIH receiving rituximab reported complete remission in 89% overall (86% with prior inadequate response to standard therapy). Prednisolone could be reduced from (median) 20 mg to 5 mg/day and stopped in 47%.

Rituximab is not licensed for use in AIH, and approval and funding rules will be centre-specific. Patients need informing that the evidence for its efficacy is limited, and that safety experience comes from other diseases.[220 221]

For a suggested infusion regimen, see table 10. The usefulness of CD20+B cell surveillance is not established but might help to time subsequent infusions rather than waiting for AIH relapse.

Hypogammaglobulinemia occurs in up to 38% of patients receiving rituximab[222] and contributes to infection risk: 94 per 100 patient years in rheumatoid arthritis (RA) and 3–19%[223–226] in other conditions. For viral screening precautions (see table 8).

Progressive multifocal leukoencephalopathy (PML) following rituximab is rare,[227–229] with rates of 2.6 per 10^5 patients with RA and <1 per 10 000 patients with polyangiitis. Risk factors include other immune disorders, malignancy and immune-modulating treatments.[229 230] Although data are limited, gender, age, previous medications and underlying disease seem not to affect survival.[231 232]

There is an ongoing RCT evaluating ianalumab (VAY736), an anti-B-cell activating factor receptor human IgG1 monoclonal antibody, in patients unresponsive to, or intolerant of, corticosteroids and azathioprine (NCT03217422).

Infliximab

There are isolated case reports and one small case series[233] of infliximab use in AIH in patients either intolerant of, or unresponsive to, first-line therapy. Caution is needed, as anti-tumour necrosis factor (anti-TNF) therapy can also trigger autoimmune-like hepatitis (see Section O).

Antimicrobial prophylaxis

Following liver transplantation, patients are at risk of opportunistic infection, and prophylactic antimicrobial agents seem to improve survival.[234 235] Infection risk decreases as IST is weaned. Similar considerations apply to patients with AIH receiving triple IST. Although not evidence-based, we recommend anti-bacterial and antiviral prophylaxis for patients receiving triple IST, with prednisolone doses ≥10 mg/day. For example, co-trimoxazole 480 mg daily and acyclovir 200 mg three times a day (local practices will vary).

What are the endpoints of second/third-line treatment?

The end point is ideally, biochemical remission, but in patients for whom first-line therapy fails, this is not always attainable. Another important endpoint is reduction or withdrawal of corticosteroids, given their longer-term AEs (table 7 and Section I).

Safety in pregnancy

AIH is typically quiescent in pregnancy, thus second-/third-line agents are rarely needed then. However, consideration of future pregnancy is relevant (for both women and men).

MMF is highly teratogenic[236 237] and should not be used in either women or men who are planning to conceive and/or who are not using highly effective contraception. Women receiving MMF should be advised to use contraception (two methods) during treatment and for 6 weeks after discontinuation. Male patients (and their female partners) should use effective contraception during treatment and for 90 days after stopping.

Tacrolimus appears to be safe in pregnancy (data largely extrapolated from transplant populations).[238] Rheumatology guidelines suggest that rituximab be stopped 6 months before conception, although limited evidence suggests that it is not teratogenic. Neonatal B cell depletion is seen after its use in the second and third trimester, and data are lacking regarding rituximab use during breastfeeding.[239–243]

While data in AIH are lacking, extrapolation (largely from IBD populations) suggests that infliximab is safe in pregnancy.[244 245] However, infliximab crosses the placenta in the second trimester and requires consideration of discontinuation later in pregnancy.[246] Thus, in women who are planning pregnancy, other options should be considered.

Children

Most experience with second-line therapy is with mycophenolate mofetil (MMF), tacrolimus and cyclosporin. The dose of MMF is 2×500 mg twice daily. It is better tolerated than azathioprine, but (given its teratogenicity), is best avoided in adolescent girls. Tacrolimus achieves remission in about 75% of cases within 6 months and is safe in children. The dose needs to be titrated to achieve good trough levels to reduce renal or other side effects. Cyclosporin, although effective, is rarely used in children now because of adverse effects.

Conclusion

The limited evidence supporting second-/third-line treatments in AIH precluded firm recommendations. We emphasise the importance of a personalised approach, clinician experience and network approaches. Second/third-line treatments are a key area for collaborative research.

RECOMMENDATIONS SECTION H

1. We recommend budesonide as an option in non-cirrhotic adult patients with significant prednisolone-associated AEs. *Grade of evidence: moderate. Strength of recommendation: weak.*

2. We recommend mycophenolate mofetil (MMF) as an option in those who are intolerant of azathioprine, and who are aking active steps not conceive. *Grade of evidence: moderate. Strength of recommendation: weak.*

3. We recommend that in patients responding inadequately to azathioprine despite treatment optimisation, tacrolimus might be more effective as a rescue therapy, but MMF can also be considered owing to its better side-effect profile. *Grade of evidence: low. Strength of recommendation: weak.*

4. We recommend that second/third-line therapies, other than MMF and tacrolimus, require specific expertise: specialist input should be sought prior to their use. *Grade of evidence: low. Strength of recommendation: strong.*

Section I. Longer-term management

AIH is usually a lifelong disease, which (in the absence of a clear precipitant) rarely disappears, and which many patients will live with for several decades. Although occasional patients have been labelled as 'burnt-out' AIH, the rate of long-term spontaneous disease remission seems low.[188] Thus, follow-up should be lifelong, with the aims of:

1. Limiting progression of liver injury by minimising relapse rate and fibrosis progression.
2. Maximising patient well-being: minimising adverse treatment effects and optimising quality of life (Section L).

Monitoring

Patients should continue to have a consultation, with recent blood test results available (table 1); at least every 6 months and more frequently, if symptomatic or not in remission. Some consultations can be remote.

De novo cirrhosis develops despite treatment over several years in 14 (6–40)% of patients with AIH[44] (Section J) and is independently predictive of poor outcomes. Prevention of fibrosis progression is an important aim of long-term treatment. Its assessment by repeated liver biopsy is unappealing to most patients. The best studied non-invasive modality is transient elastography. Its accuracy against liver biopsy is established in chronic viral hepatitis and MASLD. Cross-sectional studies in patients with AIH[247–250] also suggest reasonable accuracy of transient elastography in comparison with liver biopsy in patients after >6 months' treatment. Accuracy is lower in patients starting treatment because liver inflammation artificially elevates the score.[250] Combined liver and spleen stiffness measurement by two-dimensional shear wave elastography has also been validated against histology in AIH.[251]

Parameters based on standard blood test results (including Fibrosis-4, AST to Platelet Ratio Index, and Non-Alcoholic Fatty Liver Disease fibrosis scores) have also been developed for assessing fibrosis in viral hepatitis and MASLD. However, they appear to be of limited value in AIH.[252]

Although non-invasive fibrosis monitoring in AIH awaits firm evidence, it is a rational strategy, especially in patients with an inadequate early treatment response or who have relapsed. Demonstration of de novo cirrhosis development would also inform monitoring for cirrhosis complications. Although 2–3 yearly transient elastography seems reasonable, the optimal interval is unknown, and practice might be limited by local resources.

Management of patients attaining complete biochemical response (CBR-6)

CBR within 6 months (CBR-6) does not indicate histological remission; this can take 2–3 years.[124 125] However, as discussed in Section G, patients who achieve CBR within 6 months have lower rates of subsequent liver death/transplantation and liver adverse events respectively than patients who do not.[187 189 190 192] Thus CBR-6, especially if sustained, seems an adequate early treatment outcome (at least in patients without cirrhosis), without need for routine confirmation of subsequent histological remission (Section G). Confirmation of fibrosis stability

or improvement with repeated non-invasive testing, provides further evidence of a favourable response.

Stopping steroids

Previous UK guidelines[1] recommended routine steroid treatment for at least 2 years (because of the expected time needed to achieve histological remission).[124 125] However, given the good outcomes associated with CBR-6 the question of steroid duration needs reconsideration.

In a multicentre audit,[43] lower death/transplant rates were associated with continuing steroids for more than 6 months, but not more than 12 or 24 months, nor with continuing steroids beyond 3 months after attaining normal serum ALT levels. Thus (while more information is needed), the benefits of continuing steroid therapy beyond attainment of CBR are unclear.

Also, there is increasing concern about the longer-term adverse effects of continuing corticosteroids. The prevalence of diabetes[253] and of hepatic steatosis[85 87] in AIH increases with time after AIH diagnosis and they are both associated with prednisolone dose. Some registry studies[254], though not others [255], report that patients with AIH are at increased risk of vascular disease, which in studies of other conditions, has shown associations with steroid use.[256]

Prolonged use of steroids is still common practice. In a large UK prevalent AIH survey,[257] 55% of patients were receiving 'long-term' prednisolone treatment, 14% in doses over 10 mg/day. However, in a recent US study[86] only 56% of patients remained on steroids 1 year after starting treatment. This might reflect an emerging trend towards earlier steroid withdrawal.

Thus, in adults, if CBR is confirmed by repeat testing after 2–4 weeks, steroids can be slowly withdrawn, usually over about 3 months and using the strategy in table 11.

However in children low-dose steroids should be continued, and stopped only after discussion with a specialist centre.

Patients should continue to be monitored for:

Joint pains: reported in about half of patients during steroid withdrawal; these usually respond to paracetamol or non-steroidal anti-inflammatory drugs.[195]

Adrenocortical insufficiency (AI):[258 259] because of glucocorticoid suppression of the hypothalamic-pituitary axis. AI following steroid withdrawal has been highlighted as an underdiagnosed problem, although its clinical significance remains uncertain.

Many patients with chronic inflammatory diseases including AIH, receive corticosteroids for months or years. In a review of such patients, 37 (13–63)%[260] had 'biochemical' AI while on, or shortly after stopping steroids, suggested by low serum cortisol levels 30 min after receiving adrenocorticotrophic hormone: the short Synacthen test (SST). The variation in biochemical AI prevalence is unexplained, although it is weakly related to mean steroid dose and duration.[260] AI is less likely if prednisolone is taken as a single morning dose. AI has also been documented after oral budesonide[258] but seems rarer. On repeat testing after further time off steroids, AI prevalence falls: to 23% after 1 year and 15% after 3 years.[261] No data are available for patients with AIH.

The clinical significance of biochemical AI is unclear. Since there is no mineralocorticoid deficiency, corticosteroid-related AI differs in presentation from primary Addison's disease. Symptoms are vague, but include malaise, dizziness, faintness, fatigue, depression, arthralgia, myalgia, hypoglycaemia and hyponatraemia.

Under conditions of stress, (severe infection, major trauma, psychological upset) some patients with AI develop adrenal crisis. Patients with AI of pituitary origin are admitted to hospital more often than control groups.[262] In a Danish registry study,[263] the incidence of hospital attendance for patients with symptoms suggesting AI (hypotension, GI upset, hypoglycaemia and hyponatraemia, but not, presentations unrelated to AI) was 1.5–2.5-fold increased, over 7 months after stopping steroids, compared with periods before and after this. Many patients were not diagnosed with AI even after they presented thus. However, the absolute incidence of such events was low (peak value 2.8/1000 patients).

On balance, there is currently insufficient evidence to support a firm recommendation for routine screening for AI in steroid-treated patients with AIH. However, we suggest that:

(i) Steroids be tapered slowly and testing for AI be considered during/following steroid withdrawal, as detailed in table 11.[258]

(ii) Patients receiving corticosteroids receive education on adrenal crises, and are given NHS steroid emergency cards, which include advice on so-called 'sick-day rules'.[264] They should be advised to follow the guidance on the cards for 2 years after stopping steroids and should continue to receive hydrocortisone cover in any severe acute illness.

(iii) Endocrinological advice be sought for patents with suspected or proven AI.

AIH relapse

Management following attainment of CBR is based first (although not solely) on relapse prevention.

Definition and frequency

Relapse has been defined variably as: serum ALT (±AST) more than once, twice or three times the upper limit of normal (ULN).[265 266] Definition of the initial remission is also variably defined, as less than once or twice the ULN, and sometimes but not always, requiring confirmation of histological remission.

Given this variation, relapse rates unsurprisingly, have varied: 74% (25%–100%) overall, and 62% (36%–67%) over 12 months following treatment withdrawal.[265] Meaningful pooling of results has not been possible. Most relapses occur within the first year, but 10% have been reported 4–22 years after treatment withdrawal.

Higher relapse rate[265] has been associated with (a) higher serum transaminases (even within the normal range) and serum IgG, either on stopping treatment, or at presentation, (b) longer time to achieve initial remission, (c) need for combination treatment, (d) absence of a trigger (viral or drug) for AIH and (e) psychological stress. Associations with gender, age, antibody status, fibrosis and inflammation severity and treatment duration have been absent or inconsistent, although larger studies do suggest an association with younger age.

Prevention

Continuing therapy in patients achieving complete biochemical (±histological) remission (so-called 'maintenance therapy') reduces the risk of relapse. Stopping prednisolone but continuing azathioprine alone (at an increased dose of 2 mg/kg/day) reduced relapse rate to zero over 12 months in a second RCT[197] and to 17% over 5 years in a follow-up observational study.[195] In one RCT[198] of 61 patients who achieved biochemical and histological remission and had prednisolone and azathioprine withdrawn,

Table 11 Suggested strategy for corticosteroid withdrawal (adapted from Prete and Bancos[258] figure 3)

Steroid	Dose (mg/day)	Reduction strategy*	Pituitary/adrenal axis testing†	Sick-day rules[264]
Prednisolone	20–40	5 mg/day weekly	If AI suspected	Yes
	10–20	1–2.5 mg/day weekly	If AI suspected	Yes
	5–10	1 mg/day weekly	If AI suspected	Yes
	0–5	1 mg/day 1–2 weekly*	After 1–2 weeks of 5 mg/day consider routine AM cortisol+; SST if AI suspected*	Yes
Budesonide	3–9	3 mg/day 2-weekly	If AI suspected	Yes

*Slow rate of reduction if any symptoms develop.
†Do not do until prednisolone dose is <5 mg/day. Prednisolone needs to be stopped for 24 hours prior to testing. The screening test is a morning (0830-0930) serum cortisol. A value >270 nmol/L makes AI unlikely (Sagar Clin. Endocrinol. 2021; 94:36, Woods Eur. J. Endocrinol. 2015; 173:633) and steroids can be stopped; in the remainder a Short Synacthen test (SST) is needed.
AI, adrenal insufficiency; SST, short Synacthen test.

chloroquine (compared with placebo) reduced the 3-year relapse rate from 80% to 41%. However, adverse effects of chloroquine occurred in 17/31 patients, resulting in drug interruption in 6.

Thus, standard maintenance therapy for AIH remains azathioprine 2 mg/kg/day. This is now commonly used in patients without confirmed histological remission. It might be continued for many years, although in practice the dose is sometimes gradually reduced to 1 mg/kg/day. As discussed in Section G, thiopurine therapy can be optimised to achieve metabolite levels, which have been associated with lower serum ALT levels, improved likelihood of remission and lower risk of relapse.[161 169 204]

Many patients in clinical practice, also receive small doses (<10 mg/day) of prednisolone, and others receive prednisolone monotherapy; usually because attempts to phase this out have resulted in relapse. A randomised trial[196] showed prednisolone monotherapy to be only moderately effective in preventing relapse, but small doses can be useful in patients in whom there is reluctance to use azathioprine (for example, cancer, see below).

Neither budesonide or mycophenolate have been evaluated regarding relapse prevention, but their use here is rational in patients poorly tolerant of prednisolone and azathioprine respectively.

Presentation and management

Relapse of AIH usually presents as an asymptomatic flare in serum transaminases on monitoring. In well patients without cirrhosis, it is reasonable to repeat the tests after 1–2 weeks before changing treatment. However, in patients with cirrhosis, relapse has been associated with hospital admission and occasionally with death.[267]

Serum IgG is less often elevated than in initial presentation of AIH. In one study,[266] median serum IgG on relapse was 15.4 (11–22) g/dL suggesting normal levels in over half. If the presentation is atypical, (including for example, a prodromal illness) hepatotropic viruses (box 1) should be tested for, ultrasound scan performed and drug toxicity considered. In clinically typical cases, liver biopsy usually confirms AIH and is not necessary routinely.

On re-treatment with prednisolone serum transaminases normalise in over 90% of patients.[265] In the randomised trial of prednisolone versus budesonide,[127] some patients had relapse (rather than first presentation) of AIH, suggesting that budesonide is also effective in treating AIH relapse.

As with initial induction treatment, it is reasonable to continue steroids until CBR is achieved on two occasions.

There is no evidence that one relapse is associated with a worse outcome. However, after re-achieving CBR, there is a stronger case for then continuing azathioprine (or mycophenolate) in maintenance doses. In two studies, rates of second relapse after stopping treatment were 62% (over 1–33 years)[268] and 100% (over 0–5 years).[266] Patients who had two or more relapses, or more than four relapses per decade, were more likely to die or to need liver transplantation than were non-relapsers.[265] Development of cirrhosis is also associated with repeated relapse.[43 55 268]

In children who relapse, it is important to ensure the dosage is correct for their height and weight.

Consequences of long-term drug treatment of AIH

Aside from the inconvenience of blood monitoring, and ongoing adverse effects (Section F), these might also include a modestly increased risk of cancer.

In eight studies,[269–276] the risk of any malignancy after (but not before)[277] a diagnosis of AIH was (median (range) 1.7 (1.4–3.0)-fold increased, compared with population controls. Extrahepatic cancer risk was 1.3–2.7-fold increased, though much less than the 10–40-fold increased risk of hepatobiliary cancer. Risk is increased for some specific cancers, including non-melanoma skin cancer (NMSC) (2.95 (1.57–28.0)), lymphoproliferative cancer (3.3 (1.7–5.2)) and colorectal cancer (2.1 (1.37–3.1) but not for others, such as breast cancer (0.91 (0.6–1.27)). This argues against an artefactual increase in cancer diagnosis, from regular hospital attendance.

Increased cancer risk is probably, related partly to immunosuppressive therapy (IST).[278] Following solid organ transplant and long-term IST, the risk of NMSC in national database studies[279 280] increased by 14–127-fold and that of other cancers by 2.1–2.4-fold, though again, not of breast cancer. In a large case–control study of liver transplanted patients, an independent association was noted between cancer development (or recurrence) and cumulative tacrolimus dose.[281] In a recent meta-analysis of patients following solid organ transplantation, rates of all cancers, non-melanoma skin cancer and lymphoma were lower in those taking mycophenolate than in those taking azathioprine.[282] A national registry study of AIH[275] found a weak association between cancer risk in AIH and duration of IST in general, and with duration of azathioprine, but not of prednisolone.

A separate question is whether IST adversely influences the course of cancer and thus, whether it is safe to continue with its use in patients with cancer. Evidence is inconclusive. In the CESAME study of patients with IBD and a history of cancer, development of new or recurrent cancer was not increased in patients receiving IST (usually thiopurines).[283] Studies in patients with RA and prior cancer (at least 3 years previously) suggest similar rates of new or recurrent cancer in patients receiving biological agents as those on standard IST.[284] In a study of liver transplanted patients,[281] reducing or stopping tacrolimus after cancer diagnosis was not associated with improved outcome.

However, there remain theoretical concerns about the potential of IST to impair the immune response to cancer. Thus, in a

Table 12 Parameters influencing a decision to stop immunosuppressive (IS) treatment in patients with AIH who have been in CBR, sustained over 12 months

Parameter	Favours stopping IS	Reason
Age>40 years (larger studies)	Yes	Lower relapse rate*
AIH precipitant (drug, vaccine, infection)	Yes	
Sustained CBR	Yes	
Serum ALT low-normal	Yes	
Previous relapse	No	Second relapse: might worsen outcome
Cirrhosis	No	Might decompensate with relapse
Recent cancer (< 3 years)	Yes	IS might aid tumour growth
Remote cancer (>3 years)	Maybe not	No clear evidence
Patient wants to stop	Yes	

*See relapse risk factors, above.

patient with current or recent cancer, it is usually recommended that IST be stopped, if possible and if not, reduced to the lowest level needed to control AIH. The decision might be influenced by the type of cancer. Thus, it might be reasonable to continue IST in someone with AIH who develops NMSC, but less so, after development of melanoma.

Stopping azathioprine (or other steroid sparing agent)

Stopping all IST is often recommended after 2–3 years, including at least 1 year of sustained CBR.[23] A decision should be based on a balance of the risks and benefits, and ultimately determined by informed patient preference.

Criteria influencing the decision are summarised in table 12 In submission. Withdrawal should proceed with caution (if at all) in patients with cirrhosis, in whom the risk of AIH relapse is not increased, but its consequences might be more serious.

Is liver biopsy necessary before stopping treatment?

EASL guidelines[23] recommend a liver biopsy prior to a decision to withdraw treatment. However, this is not yet evidence based. In 25–60% of patients with sustained CBR, there is persistent histological activity (necro-inflammatory score >3),[200 201 250 285] As such persistent activity might have adverse prognostic implications,[200] there is a rationale for continuing (and perhaps, altering) treatment in such patients, if tolerated. However, whether such alterations will achieve histological remission and/or improve outcome is not known.

Other indications for repeat biopsy include assessment of fibrosis severity (especially when non-invasive testing is inconclusive) and diagnosis of co-existing steatohepatitis. Biopsy is of limited use in predicting relapse[266 285 286]; absence of plasma cells in the portal tracts[287 288] predicts a low relapse rate, but the necro-inflammatory score does not.

Thus, we do not think that there is adequate evidence to recommend routine liver biopsy prior to attempted withdrawal of IST therapy in adult patients with CBR and stable fibrosis on non-invasive testing, although it might be useful in some patients.

Follow-up

After stopping treatment, patients should be followed up as for patients receiving treatment (Section F, table 1). Fibrosis severity should be assessed non-invasively at treatment withdrawal and 2–3 yearly thereafter. When these tests suggest progressive fibrosis, repeat liver biopsy should be considered: especially if serum transaminases and/or IgG are raised. If biopsy shows more than minimal hepatitis, re-institution of treatment should be considered, given the associations between fibrosis progression, persisting inflammation and poorer outcome.

Relapses should also be monitored for and treated, and the need for maintenance therapy then reconsidered, as detailed in table 11. In patients who (despite initially attaining CBR) relapse while on azathioprine maintenance therapy, there is a case (after re-attaining CBR with steroid-based therapy) for changing the regimen to mycophenolate, or (if cirrhosis is absent) budesonide.

While patients on long-term maintenance immunosuppressive treatment have an increased risk of skin cancer, the benefits of routine screening for this are not established and resources might not allow it in many centres. However, patients should be advised to minimise exposure to sunlight and to be vigilant for, and seek medical advice about, newly developing and persisting skin lesions. Women should also be encouraged to undergo regular cervical cancer screening.

RECOMMENDATIONS SECTION I

1. We recommend long-term follow-up, as AIH is usually a lifelong condition. *Grade of evidence: moderate. Strength of recommendation: strong.*

2. We recommend consideration of non-invasive imaging assessment of fibrosis, at 2–3 year intervals. *Grade of evidence: weak. Strength of recommendation: low.*

3. We recommend that, in adults achieving complete biochemical response (CBR) after 6 months and repeated testing 2–4 weeks later, steroids be withdrawn slowly. This can be over 3 months in adults. *In children low-dose steroids should be continued and stopped only after discussion with a specialist centre. Grade of evidence: low. Strength of recommendation: strong.*

4. We recommend consideration of checking endogenous adrenal function with a morning serum cortisol. Low values necessitate a short Synacthen test, and endocrinological advice. *Grade of evidence: weak. Strength of recommendation: low.*

5. We recommend in patients with sustained CBR over 3–4 years, consideration of withdrawing azathioprine (or other steroid-sparing agent) if many of the criteria in table 12 are met. Withdrawal can be completed in one step, with ongoing monitoring for relapse and for fibrosis progression. *Grade of evidence: low. Strength of recommendation: weak.*

6. We do not recommend routine liver biopsy in adults before treatment withdrawal, but it might be useful in some patients. *Grade of evidence: weak. Strength of recommendation: low.*

7. AIH relapse is usually signalled by a rise in serum ALT/AST with a variable rise in serum IgG. We recommend that other potential causes (including viral) should be excluded, but that

liver biopsy is usually not needed for confirmation. *Grade of evidence: weak. Strength of recommendation: weak.*

8. We recommend that relapse usually be treated by restarting prednisolone. If cirrhosis is absent, budesonide is a potential alternative. Azathioprine (or another steroid-sparing agent) should also be restarted, if not already being taking. *Grade of evidence: moderate. Strength of recommendation: strong.*

9. We recommend that prednisolone be again withdrawn slowly, when CBR is re-attained after a relapse, confirmed. However, there is a stronger case for continuing maintenance treatment with a steroid-sparing agent long term. *Grade of evidence: high. Strength of recommendation: strong.*

10. We recommend that women on long-term immunosuppressive therapy be encouraged to undergo regular cervical screening in line with national guidelines and to have HPV vaccination (if under 25 or if GBMSM and under 45). Also, that patients minimise exposure to sunlight and be vigilant and seek medical advice regarding newly developing and persisting skin lesions.

11. We recommend that some patients, such as those with decompensated cirrhosis, and those responding suboptimally to therapy, be informed (if potentially eligible) that there is a small chance that they might eventually need liver transplantation. *Grade of evidence: low. Strength of recommendation: weak.*

12. We recommend that all patients be advised to adopt a healthy lifestyle (adequate nutrition, non-smoking, low to moderate alcohol intake, physical activity, maintenance of healthy BMI). *Grade of evidence: moderate. Strength of recommendation: strong.*

13. We recommend that patients with cirrhosis (documented at any time) be monitored for complications, including hepatocellular carcinoma and portal hypertension as per generic cirrhosis guidelines. *Grade of evidence: low. Strength of recommendation: strong.*

14. We recommend individualised end-of life care for patients with advanced liver disease who are unsuitable for transplant. *Grade of evidence: low. Strength of recommendation: strong.*

Section J. Long-term outcome of AIH

In about half of patients with AIH, fibrosis stage improves with treatment, especially if histological remission is achieved. In about 20%, fibrosis progresses.[199–201] Fibrosis, assessed using transient elastography also improves with treatment in patients who achieve CBR.[201]

De novo cirrhosis develops despite treatment in 14 (6–40%) of patients[44] and is associated with delayed normalisation of serum transaminases,[43 55] multiple relapses[55] and need for enhanced immunosuppressive therapy.[257] De-novo cirrhosis (like cirrhosis at diagnosis) is an adverse prognostic indicator.[44]

Hepatocellular carcinoma (HCC) in AIH

The pooled annual HCC incidence over 25 studies was 0.3% in AIH overall and 1% in patients with cirrhosis[289]; similar to HCC incidence in cirrhosis related to NAFLD but lower than in cirrhosis related to hepatitis B and C, and to alcohol-related liver disease.[290] Lower annual rates (0.14% overall and about 0.5% in cirrhosis) were reported recently in a (mainly European) multicentre cohort.[291]

Annual percentage incidence rates were higher in Asia (0.5% than in North America, Australia and Europe 0.2–0.4%). In Europe[292] nearly all patients who develop HCC have cirrhosis[289] but in Japan, cirrhosis was present in only 58%.[293] HCC in AIH is also associated with older age, male gender, number of relapses and alcohol excess.[289]

The annual incidence of HCC in AIH-related cirrhosis (0.5–1%) falls below the 1.5% per year threshold advocated in AASLD[290] and EASL[294] guidelines as being cost effective for HCC screening. However, these are based on health economic studies predating development of effective therapies for HCC. A recent analysis[295] incorporating potential harms as well as benefits, suggests that HCC surveillance is cost-effective if incidence exceeds 0.4%, which it does in AIH-related cirrhosis. Thus, surveillance should be considered for all cirrhotic patients with AIH.

Mortality of AIH

The median (range) rates for all-cause and liver-related death/transplant are 11.5 (2–23)% and 6 (0–17)% after 10 years, and 32 (18–53)% and 16 (6–26)% after 20 years' follow-up.[44] Reasons for variation include differences in age at diagnosis and possibly, inadvertent case selection.[188] After 20 years' follow-up, subsequent relapse, cirrhosis development and liver-related mortality rates were similar to those in patients followed up from first diagnosis.[188]

Mortality in AIH exceeds that in the general population, with an overall median standardised mortality ratio (SMR) of 1.72. Excess mortality results from liver disease, accounting for a third of all deaths or transplants. SMR values in AIH, excluding liver-related deaths and transplants, are usually near unity.[44] However, AIH registry studies suggest increases in deaths due to cancer[5] and to cardiovascular disease,[254]possibly related to immunosuppressive therapy (Section I).

No obvious differences are evident, between different continents. However, studies from the USA and Europe suggest that people of Afro-Caribbean origin present with more severe disease and have lower transplant-free survival than Caucasian patients.[41]

Transplant-free survival is over 90% in patients with acute AIH with jaundice,[54 182] 66% in AS AIH and 32% if ALF is also present (Sections C and F). In most studies in adults, cirrhosis or decompensation at presentation are adverse prognostic parameters.[44] In contrast, higher pre-treatment serum transaminases predict lower mortality.[45 186 188] Other adverse prognostic factors include co-existence of PSC[296] and social deprivation.[5]

RECOMMENDATIONS SECTION J

1. We recommend HCC surveillance with 6-monthly ultrasound in all patients with AIH and cirrhosis, unless not felt appropriate due to frailty or comorbidity. *Grade of evidence: low. Strength of recommendation: strong.*

Section K. Liver transplantation (LT) for AIH

LT remains an effective treatment for patients with AIH with decompensated cirrhosis, liver cancer and fulminant liver failure.[48 297] In adults and children, AIH is the indication for LT in 3–5% of transplant recipients in Europe.[298]

Early referral to a transplant centre assessment is recommended for patients with AIH with cirrhosis and persistent hyperbilirubinaemia, abnormal coagulation indices or low serum albumin. Indications for LT include decompensation (ascites, jaundice, spontaneous bacterial peritonitis, variceal bleed, and hepatic encephalopathy). The United Kingdom model for End-Stage Liver Disease (UKELD) scoring system predicts outcome in patients with chronic liver disease; a score of 49 and above confirms eligibility for LT.

Urgent liver transplantation is an option for patients with AIH presenting with AS-AIH, ALF and acute on chronic liver failure (ACLF).[299 300] See sections C and F.

In a multicentre registry study,[298] patient survival following LT for AIH was 79%, 71% and 60%, and graft survival was 73%, 63% and 51% after 5, 10, and 15 years of follow-up, respectively. These outcomes were worse than in patients receiving a transplant for PBC or PSC. The cause is unclear; however, following listing, patients with AIH wait longer for transplant, than those with PBC or PSC.[301] Death and graft loss following LT for AIH have also been related to infection, particularly fungal infection.[298] Immunosuppression might contribute to this. Also, patients with AIH who received a living donor liver transplant had reduced survival, compared with those receiving donation after brain death. This was mainly due to infection and biliary complications.

Memory T and B lymphocytes which initially led to AIH remain in the circulation[302] and migration of these lymphocytes to liver allograft might result in post-transplant recurrence of AIH[303] (see figure 1). Recurrence rates of 20% and 31% over 5 and 10 years, respectively, have been reported,[303] with resulting increased graft loss and reduced survival. Long-term low-dose prednisolone, in combination with other immunosuppression agents, has in some studies, reduced AIH recurrence.[304] However, a recent meta-analysis[128] did not support continued use of prednisolone after transplantation.

Indications for LT in children are similar to those in adults. Approximately 20% of children with AIH require transplantation.[305] *The UKELD scoring system is useful for prioritising children >12 years, but in younger children the Paediatric End-Stage Liver Disease Score (PELD) score is used.*[306]

RECOMMENDATIONS SECTION K

1. We recommend early referral to a liver transplant centre for patients with AIH with cirrhosis and who have persistent impaired synthetic function: prolonged blood clotting, low serum albumin or symptoms of decompensation (ascites, spontaneous bacterial peritonitis, variceal bleed, encephalopathy). *Grade of evidence: moderate. Strength of recommendation: strong.*

2. We recommend early discussion with a liver transplant centre for patients who present with AS AIH (jaundice and coagulopathy) and with AS AIH with ALF (also including hepatic encephalopathy). Grade of evidence: moderate. Strength of recommendation: strong.

Section L. Patient perspectives in AIH

Suboptimal adherence

Non-adherence to medication is common in chronic diseases and might prejudice outcomes,[307] especially in adolescent patients.[308] In a UK AIH survey, 36% of patients admitted to missing treatment doses regularly.[141] In children, adherence rates were 28–94%.[309] Serial TGN metabolite levels in patients prescribed stable doses of azathioprine showed significant fluctuation,[169] suggesting incomplete adherence. Low or undetectable TGN and 6-MMP levels (see Sections F I) suggest suboptimal adherence.

Several factors affect medication adherence.[310] AIH might be asymptomatic, and patients might not understand the need for treatment. In the UK survey, 66% of patients with AIH had experienced treatment-associated AEs.[141] Reduced adherence might also be related to suboptimal patient empowerment and health literacy,[311] social deprivation,[312] non-response to treatment, anxiety and depression.[307 313]

Clinicians need to ask patients about non-adherence[314] and when the issue does arise, avoid blame and stigmatisation.[307] Patients often have good reasons for non-adherence, which should be explored non-confrontationally.[307 311]

Outpatient sessions from specialist nurses and pharmacists can improve adherence.[315–317] Social support from friends and family, patient organisations and support groups can also help.

Almost half of patients with AIH reported taking a complementary medication.[318] Adverse effects were uncommon, and use was usually associated with increased well-being.

Empowering patients

Patient empowerment is a UK government priority. Successful strategies exist for patients with diabetes, hypertension and chronic lung disease.[319–321]

The UK-AIH patient survey highlighted issues with stigmatisation, need for empowerment and lack of support networks.[141] Patients frequently described receiving insufficient knowledge about AIH from non-specialists.

Nurse specialists (in clinic or via telephone advice line) provide an excellent point of patient contact, and can answer questions, field problems, safety-net and facilitate consultant access when needed. Patients also need practical advice about employment, travel, insurance and family planning.

Patient education should include information leaflets (many are available and there is scope for harmonisation), and signposting to organisations such as the British Liver Trust and AIH Support. In the UK patient survey, 74% of patients rated highly the help that these groups provide.[141] The European Research Network patients website: ERN RARE-LIVER also offers patient information on AIH

Access by patients to their medical records and blood results might also improve patient engagement and confidence.[322 323] Many patients support having such access,[324] although it might make other patients anxious.[323] If information is accessible, patients need sufficient education to interpret it. Internet based apps are widely used[325] and are particularly helpful for younger patients.[326]

Since the COVID-19 pandemic, many consultations have become remote. Advantages include convenience and equity of access to care. Data from cardiac services suggest that remote video (vs face-to-face) consultations do not result in more emergency admissions, or harm patients.[325] Indeed tele-health interventions might improve clinical outcomes and decrease inpatient stays, while maintaining patient satisfaction.[327 328] However, such strategies require governance structures and adequate staffing. Many patients still wish to see an 'expert clinician' face-to-face.

AIH and quality of life

Both AIH and its treatments affect health-related quality of life. This remains a key area for further research.[329] Some patients with AIH experience poorer physical and general health[330] and higher levels of fatigue,[141 330] anxiety and depression, some of which relate to worry about long-term prognosis.[331] In a recent qualitative study,[332] patients with AIH commonly reported severe fatigue, sleep disturbance, 'brain fog', anxiety, depression and disrupted social and working lives. Factors associated with poorer health utility include failure to achieve remission and taking corticosteroids.[329] *In children, the presence of symptoms, extrahepatic autoimmune conditions and need for medications had a negative impact on QoL scores.*[333]

Clinicians need to acknowledge the importance of HRQoL for patients. Generic QoL assessments should form part of patient

assessment. Development of an AIH-specific patient reported outcome measure is a research priority.

Patient perspectives

1. We recommend that more attention be focused on quality of life in AIH, with a holistic approach to adherence issues and consideration of formal monitoring of HRQoL and of medication adverse effects. *Grade of evidence: moderate. Strength of recommendation: strong.*

Section M. Pregnancy in AIH

Overview

Fertility in women with AIH seems to be normal.[334] Miscarriage rates (spontaneous loss of pregnancy before 20–24 weeks of gestation) of 42% and 26% are reported in women with AIH with and without cirrhosis.[335]

A meta-analysis of 14 studies (1556 gestations in 1452 patients with AIH) indicated increased risks (compared with those without AIH) of gestational diabetes mellitus in pregnancy (OR=5.73), premature birth (OR=2.2), small for gestation age births (OR=2.48), and a threefold risk of low birth weight.[336] Another meta-analysis[337] confirmed the increased risk of prematurity and gestational diabetes mellitus. Both meta-analyses noted an increased risk of stillbirth (about threefold), but this was not statistically significant. Neither found an increase in fetal malformations. The risk of pregnancy complications was further increased in patients with portal hypertension and in those not in remission prior to conception.[337] However, no significant relationship was observed between maternal or fetal complications and use (or not) of therapy (prednisolone and azathioprine).[336 337]

Data from two large US studies[338 339] (not included in the above meta-analyses) showed higher rates of gestational diabetes in AIH compared with those without liver disease. One (but not the other) also reported higher rates of gestational hypertension, pre-eclampsia, eclampsia and haemolysis, elevated liver enzymes and low platelets (HELLP syndrome). In patients with conditions at high risk of such complications (which includes autoimmune diseases), RCTs[340] and a meta-analysis[341] support use of aspirin 75–150 mg daily from week 12 of gestation (and ideally before week 16) to reduce the risk of pre-term pre-eclampsia . We therefore recommended consideration of low-dose aspirin to reduce hypertension-related complications in pregnancy in AIH.

Smaller case series suggest that the presence of anti-SLA/LP and anti-Ro/SSA antibodies are associated with maternal complications.[335 342] In this high-risk cohort, rates of disease flare (loss of biochemical remission), were reported in 21%, with postpartum loss of biochemical response occurring in 52% of patients. This underlines the need for close monitoring both during pregnancy and in the 3 to 6 months following delivery.

Most patients with AIH remain in biochemical remission throughout their pregnancy supporting the concept of tolerance in pregnancy in AIH. In a study from King's College Hospital, 81 pregnancies were reported in 53 women (41% with cirrhosis).[343] At conception, 75% were on treatment; of these, 74% had been on stable regimens for over a year. The live birth rate was 59/81 (73%), and 11% of infants needed admission to the special care baby unit. For mothers with cirrhosis, the live birth rate was lower, and the need for the special care baby units was higher. Maternal therapy for AIH showed no association with live birth rate, termination rate, miscarriage rate or gestation duration. In all large series and in meta-analyses,[336 344] there is no apparent relationship between the use of azathioprine in pregnancy and adverse outcomes. Therefore, continuation of therapy during pregnancy is justified.

For women with type 2 AIH, recent data suggest that the outcomes in pregnancy are worse than for patients with type 1 AIH: with premature birth rate of 67% vs 19% and also a higher likelihood of loss of remission post partum (100% vs 48%). Medication non-adherence was associated with almost doubling the risk of prematurity and an increased risk of flare in disease activity following delivery.[345]

Management of cirrhotic patients with AIH should be discussed with a specialist centre for timing and frequency of upper GI endoscopy to treat varices (second trimester), US liver and echocardiogram (to exclude portopulmonary hypertension during second trimester) and MRI pelvic (third trimester—to exclude pelvic varices) throughout the pregnancy. Obstetric-liver combined management is essential to improve maternal and fatal outcome. Pregnancy in patients with AIH post-transplant should be discussed with the transplant centre.

Pre-pregnancy counselling

Planned pregnancy in patients with AIH enables medication review, discussion of outcomes for mother and baby, assessment of portal hypertension in patients with cirrhosis, delivery plan, review of breastfeeding and contraception advice. In patients with cirrhosis, pre-pregnancy counselling seems to result in improved acceptance of screening endoscopy pre-pregnancy.[345]

Mycophenolate mofetil is teratogenic[236 237] and therefore, should be stopped 12 weeks before conception. In contrast, azathioprine [336 337 344] and tacrolimus, prednisolone and budesonide[346] appear safe in pregnancy and also, during breastfeeding.

AIH presenting in pregnancy and peripartum

AIH presenting in pregnancy or within 3 months postpartum is rare but can be serious.[343 347] Diagnosis is as in non-pregnant women, but liver biopsy (although not contraindicated) might be challenging. Most biopsied patients were unaware of their pregnancies. If a new diagnosis is made in pregnancy, first-line treatment (Section F) should be started.

RECOMMENDATIONS SECTION M

1. We recommend that treatment of AIH during pregnancy, with corticosteroids (prednisolone/budesonide) with or without thiopurines, should be continued throughout the pregnancy. For newly diagnosed patients, treatment should be given as for non-pregnant women (apart from not using mycophenolate). Treatment is associated with better maternal and fetal outcomes. *Grade of evidence: moderate. Strength of recommendation: strong.*
2. Although pregnancy in AIH is not usually associated with loss of remission, this might occur post partum. Thus, we recommend that immunosuppressive therapy should be continued, and close follow-up undertaken for 3 months post partum and thereafter. *Grade of evidence: low. Strength of recommendation: strong.*
3. We recommend that patients with AIH who become pregnant should be advised that they may have increased rates of gestational diabetes, hypertensive disorders of pregnancy, preterm birth, and fetal growth restriction, and so, will need close obstetric surveillance and consideration of aspirin therapy (100 mg/day, started in the first trimester for pre-eclampsia prevention). There are no restrictions on

breastfeeding in patients with AIH. *Grade of evidence: high. Strength of recommendation: strong.*

Section N. Variant syndromes

Introduction and nomenclature

AIH variant syndrome usually refers to co-existence of features of both AIH and either primary biliary cholangitis (PBC) or primary sclerosing cholangitis (PSC). [348 349 350] The nomenclature used sometimes refers to this clinical situation as overlap syndromes. Consensus diagnostic criteria are lacking, owing to patients lying on a spectrum between the individual diseases in regard to biochemical, immunological and histological features; one disease might be dominant.[348 351–354] These diseases can present concurrently[355 356] or sequentially, sometimes even years later.

They are important to recognise, as treatment and outcome differ from those in patients with pure PBC or PSC. Liver biopsy is a key investigation, and expert histopathological review is important. Serial biopsies are sometimes needed.[357] Variant syndromes often present a management dilemma. Due to their rarity, no clinical trials have been performed (or are foreseeable). Thus, recommendations rely on expert opinion and small case series.

PBC and AIH variant syndrome

Overlapping features

Of patients with AIH, about 10% each have pruritus, raised serum alkaline phosphatase and serum anti-mitochondrial antibodies (AMA).[348 349 358–360] Also, 7–25% have coincidental biliary injury (some with destructive bile duct lesions) on liver biopsy, characteristic of PBC.[349 361]

The presence of one such feature would not usually in itself undermine a diagnosis of AIH. Also, patients with PBC, with marked interface hepatitis, exist without these being true variant syndromes.[362] However, the more features that are present, the more robust the designation of an AIH-PBC variant syndrome. Features can also evolve. Patients with AIH who were positive for AMA are more likely than AMA-negative patients to develop bile duct damage on follow-up biopsy.[360]

Conversely, interface hepatitis, (classically associated with, though not specific for, AIH, see table 3), is present in up to 50% of patients with PBC and might be severe in 10%.[361 362] These patients are more likely to develop progressive fibrosis.

Diagnostic criteria and prevalence

Given these features, diagnosis of AIH-PBC variant syndrome is challenging and cannot reliably be made using the IAIHG scoring systems for AIH.[70 95 363] Specific diagnostic criteria have been developed but remain arbitrary as there is no gold standard against which to validate them. For example, the 'Paris' criteria include at least two of three 'typical' criteria for both PBC and for AIH.

For PBC:

- Serum ALP >2× or γ-GGT >5× upper limit of normal (ULN) values.
- Positive antimitochondrial antibodies (AMA).
- Liver biopsy showing florid bile duct lesions.

For AIH:

- Serum ALT at least 5× ULN.
- Serum immunoglobulin G (IgG) levels at least 2× ULN.
- Positive anti-smooth muscle antibodies (ASMA).
- Liver biopsy showing moderate or severe interface activity.

These criteria have sensitivity and specificity of 92% and 97%, respectively, in cohorts considered to have a 'clinical' diagnosis of both AIH and PBC.[364 365] EASL have endorsed them,[23] but have made the requirement for interface hepatitis (ie, extending into the lobule) more explicit. They might not identify patients with milder cholestatic abnormalities.[349 366] Using the Paris criteria, 9–14% of patients with PBC also had AIH.[351 364 367 368]

A new scoring system to identify patients with PBC/AIH overlap reports a sensitivity of 98.5% and specificity of 92.8%, but this requires further validation.[369]

Treatment

Arguably more important than precise diagnostic categorisation is careful decision making about the need for immunosuppression. It is often reasonable to treat the predominant component first, and assess response.[348] UDCA alone (in doses for classic PBC) might be sufficient for patients with predominantly biliary changes.[350 368] However, in patients without improvement in liver biochemistry, a trial of prednisolone for the AIH component of disease should be considered.

One study[367] (but not another)[370] suggested that initial treatment with UDCA plus immunosuppression was associated with higher biochemical response rates and less fibrosis progression. A meta-analysis on this question[371] is limited by imprecise definitions. However, patients with 'severe' interface hepatitis[370] seem to have a poor response to UDCA alone and might benefit from initial combination treatment. Also, in classic PBC, severe lymphocytic piecemeal necrosis is associated with fibrosis progression and might not improve with UDCA alone.[372] Successful withdrawal of immunosuppression might be more common in PBC/AIH overlap than in classic AIH,[370] although follow-up time in this study was short. Potential adverse effects should be discussed with patients, acknowledging the lack of a firm evidence base. Finally, regular review of the benefits of ongoing immunosuppression is required to avoid unnecessary exposure.

Prognosis

Prognosis in PBC/AIH overlap is worse than in PBC or AIH alone, partly because fibrosis is often more severe at presentation.[351 373–375] However, all data come from before the widespread use of second-line therapies in PBC, the impact of which is unclear.

PSC and AIH variant syndromes

Overlapping features

Antinuclear antibodies and anti-smooth muscle antibodies can be seen in up to 80% of patients with otherwise typical PSC.[97 376–378]

Prevalence of inflammatory bowel disease (IBD) in PSC/AIH overlap varies (13–89%) but seems to be lower than in classic PSC and higher than in classic AIH.[379–381]

Radiology and histology

As discussed above, up to a quarter of patients with otherwise typical AIH show bile duct abnormalities on biopsy. Also, 2–10% have MRCP abnormalities consistent with cholangiopathy.[380 382 383] This rises to 42% if IBD is also present.[349 384]

Such radiological changes might develop later in the disease course, while small duct changes (only evident histologically) can exist without radiographic abnormalities.[380 383]

Patients with PSC/AIH variant might have concentric periductal ('onion skin') fibrosis but biliary features are patchy and can be absent despite obvious cholangiopathy on imaging.

Diagnostic criteria and prevalence

PSC/AIH variant syndromes lack consensus diagnostic criteria but encompass biochemical and histological features of AIH[95] along with cholangiographic features of PSC and/or the 'onion skinning' periductal fibrosis seen on histology in small duct PSC.[349] As with PBC/AIH variant, IAIHG scoring systems are unreliable for diagnosing PSC/AIH variant syndrome.[95 377 385]

Biliary abnormalities on liver biopsies of patients with otherwise typical AIH do not in themselves undermine the diagnosis. However, MRCP should be considered[361] when additional features are present, including (a) younger age at diagnosis, (b) male gender,[296 355 380] (c) inflammatory bowel disease, (d) pruritus, (e) cholestatic liver blood tests and/or (f) poor response to corticosteroids.

Estimates of the prevalence of PSC/AIH variant syndrome range from 1.7% to 14.0% of patients with AIH[296 348 380 383] and 1.4% to 17.0% of patients with PSC.[363 377 379 386 387]

PSC might be diagnosed contemporaneously or sequentially (sometimes years after the primary diagnosis).[355 356 379 381] Patients might also develop a more classic PSC-like phenotype, with strictures becoming the predominant feature, rather than inflammation.[355]

Treatment

Evidence of long-term benefit with UDCA in classic PSC remains lacking.[388] Combination therapy for PSC/AIH variant syndrome with UDCA and immunosuppression might achieve biochemical response, although this is slower than in AIH alone, and poorer in those with small duct cholangiopathy.[296 355 356 377 379 389 390] Patients with higher serum transaminases might respond better to corticosteroids than those with prominent cholestasis.[391] Liver biopsy might show improvement in inflammation but not in the cholangiopathy.[392] Studies in overlap syndromes used varying treatment regimens so synthesis is difficult. As the disease phenotype might evolve over time, the need for immunosuppression needs regular review.

Prognosis

Based on small observational studies, patients with PSC/AIH variant syndrome are, in general, less likely to respond to immunosuppression than those with classic AIH[296 384 393] and more likely to die or require liver transplantation.[190 296 190 296 356 380] However, their survival is still better than for patients with classic PSC.[355 379 380 389 390] Patients responding adequately to immunosuppression might have improved survival.[355 391] Disease recurrence post-transplant appears to be higher in patients transplanted for variant syndromes rather than for a single autoimmune liver disease.[394]

IgG4-related disease (IgG4-RD)

IgG4-RD is a multisystem disorder.[395] It can present as a cholangiopathy,[396] and might simulate PSC, but unlike PSC, it is classically very steroid-responsive. There might be a distinct variant of IgG4-associated AIH where liver histology (while meeting AIH diagnostic criteria) shows prominent IgG4-positive plasma cells.[397–400] Serum IgG4 levels might also be elevated, but this might suggest other organ involvement.[401] High serum IgG4 levels[397] and large numbers of IgG4-positive plasma cells on histology predict a better response to corticosteroids and azathioprine, similar to that seen in classic AIH.[399 400] It is currently unclear whether IgG4-AIH is a distinct entity or a manifestation of a multisystem pathology.

Paediatric patients

AIH/PSC overlap in children differs from that in adults. The terms autoimmune sclerosing cholangitis (ASC) and juvenile sclerosing cholangitis are often used.[402] *Sclerosing cholangitis might also be a feature of inherited conditions, including primary and secondary immune deficiencies, sickle cell disease or cystic fibrosis. ASC is associated with IBD in 45% of cases, and there is a higher presence of pANCA than in classic AIH However, 90% of patients with ASC also have high IgG levels.*[392]

As in adults, diagnostic uncertainty is common. A scoring system for juvenile autoimmune liver disease has been proposed but remains unvalidated.[2] *It generates weighted scores for both AIH and ASC, with ASC scores influenced by cholangiography and pANCA positivity. Many children with ASC respond to immunosuppression. In those with biliary features, UDCA is often added. Discussions surrounding paediatric overlap syndromes continue.*[403 404]

The ESPGHAN position paper and paediatric guideline recommends that cholangiography (MRCP) be performed in all children with biliary features on biochemistry or histology.[2]

RECOMMENDATIONS SECTION N

1. We recommend liver biopsy (unless contraindicated) when after non-invasive-workup (including MRCP) an overlap syndrome is being considered. *Grade of evidence: moderate. Strength of recommendation: strong.*

2. We recommend that interface hepatitis on liver biopsy be considered a prerequisite for a diagnosis of PBC/AIH overlap syndrome to be considered. *Grade of evidence: low. Strength of recommendation: strong.*

3. We recommend that a variant syndrome be considered and a biopsy performed if feasible in patients with clinical features of PBC or PSC but who have marked elevation of serum transaminases or IgG and/or serology that could be compatible with AIH. *Grade of evidence: moderate. Strength of recommendation: strong.*

4. We recommend that concurrent PBC be considered in patients with cholestatic pruritus, cholestatic liver blood tests and/or relevant autoantibodies in addition to the typical transaminitis of AIH. *Grade of evidence: moderate. Strength of recommendation: strong.*

5. We recommend that a PSC/AIH variant syndrome be considered and an MRCP performed in all children, and in adults with otherwise typical AIH who have biliary changes on biopsy, cholestatic liver blood tests, pruritus, suboptimal response to immune suppression, inflammatory bowel disease or subsequent development of any of those features. *Grade of evidence: low. Strength of recommendation: strong.*

6. We recommend that the revised and simplified IAIHG scoring systems not be used for diagnosis of variant syndromes. The Paris criteria (see Section N) can be used, but do not identify all patients. *Grade of evidence: moderate. Strength of recommendation: strong.*

7. We recommend that when the two components of a variant syndrome present simultaneously but one is predominant, this be the first treatment target—for example, UDCA if cholestatic

Table 13 Drugs implicated in causing autoimmune hepatitis or autoimmune-like hepatitis

Drug	Number of cases	Latency (months)	% Raised serum IgG	% ANA+ve	% Spontaneous resolution	Relapse after steroid withdrawal
Nitrofurantoin[405]	>49*	24 (8–36)	>50	80	NK	0
Minocycline[405]	>25*	12 (9–36)	100	80	NK	0
Anti-TNF drugs[412]	39	2.8 (0.5–6)	33–64	67–93	55	1 (adalimumab)
Interferon[413]	37	2 (0.5–32)	70	78	NK	0
Statins[413 485]	24	4 (1.5–62)	68	90	NK	7 (various)
Diclofenac[413]	7	2 (1.5–4)	0	86	NK	0
Methylprednisolone[413]	16	1 (0.5–1.8)	0	94	NK	0
Methyldopa[420]	6	90%<6	50	40	NK	NK
Hydralazine[420]	3	86%<6	28	56	NK	NK
Khat[413]	11	NK	90	30	NK	NK
Tinospora cordifolia[413]	8	2.6 (0.75–7)	70	62	NK	NK

*Numbers in cited references only- likely to be an underestimate.
ANA, antinuclear antibody; NK, not known; TNF, tumour necrosis factor.

features predominate. *Grade of evidence: low. Strength of recommendation: strong.*

8. We recommend that combination therapy with UDCA and immune suppression (prednisolone and azathioprine as used in classic AIH) might give the best rates of biochemical response, with less fibrosis progression. *Grade of evidence: low. Strength of recommendation: strong.*

9. We recommend that patients with an overlap syndrome who have severe interface hepatitis and/or bridging necrosis on liver biopsy should be given immunosuppression at diagnosis. *Grade of evidence: moderate. Strength of recommendation: strong*

10. We recommend that if a trial of immunosuppression is given, there be (a) early review of clinical response, to avoid unnecessary long-term treatment, (b) regular re-evaluation, as the disease phenotype might change over time. *Grade of evidence: low. Strength of recommendation: strong.*

Section O. Drug-related autoimmune-like hepatitis (DI-AILH)

Association of AIH and ingestion of a drug might be coincidental. However, evidence supports a causal association of an AIH-like disease with some drugs (table 13). In 9 (6–18)% patients in AIH cohorts, the disease is 'drug-related'.[32 405–408] In large drug-induced liver injury (DILI) registries, the injury meets the diagnostic criteria for AIH in 16 (3–37)% of patients.[409 410] These cases are now called drug-induced autoimmune-like hepatitis (DI-AILH).[411] The best-established implicated drugs are nitrofurantoin, minocycline, methyldopa, hydralazine, and anti-TNF agents[412] (mainly infliximab but also adalimumab). A recent review[413] also implicated interferons, statins (most commonly atorvastatin), imatinib, diclofenac, methylprednisolone and the complementary/recreational drugs khat and tinospora cordifolia. AIH has been associated with a second episode of DILI following exposure to a different drug.[414 415]

Evidence for a causal relationship between a drug and AILH includes first, reports of several cases. Second, a temporal association, although this might be weak, in that latency (time on the drug prior to AILH presentation) is often longer than that for most cases of DILI (when latency uncommonly exceeds 3 months). Third, liver tests might resolve on withdrawal of the drug alone,[413 416–418] although such cases are relatively few, because usually, corticosteroids are started simultaneously. Fourth, DI-AILH is usually associated with only mild fibrosis and very rarely with cirrhosis, in contrast to idiopathic AIH.[80] Finally, DI-ALIH (unlike 'idiopathic' AIH[266] rarely relapses spontaneously after withdrawal of steroids.

One possible exception is AIH related to statins, which relapsed spontaneously in 7 of 24 cases after steroid withdrawal.[413] This might represent statins precipitating 'idiopathic' AIH. However, given the frequency of statin use, these could also represent coincidental AIH.

There are reports of patients with DILI related to anti-TNF agents,[418] diclofenac and statins[419] being switched (after resolution of the liver injury) to a different drug within the same class, without subsequent relapse. Re-exposure to the initially implicated drug can be hazardous, is rarely justified, and never so if alternatives exist.

Not all liver injury related to these agents is like AIH. Serum antinuclear antibody is raised in the serum of 40–80% of cases of DILI related to nitrofurantoin, minocycline, methyldopa, hydralazine, anti-TNF agents and statins,[413 418–421] but also in 10% of unselected patients with DILI.[420 422] In DILI related to the above drugs, serum IgG is found in 25–40% of cases,[418] and liver biopsy usually shows interface hepatitis and/or lobular hepatitis. However, changes suggesting AIH, such as plasma call prominence, are inconsistent.[420] In 20–35% of cases, DILI and AIH cannot be reliably distinguished on histology.[79 420 423 424]

In (mainly infliximab associated) DI-AILH,[417] 20–33% patients improved on withdrawal of the suspected drug, but without steroids. However, in most studies (in addition to drug withdrawal), patients received steroids. Given the diagnostic difficulties, so also do many patients with DILI due to the above agents, but without features allowing a firm diagnosis of AIH. Normalisation of serum transaminases either spontaneously[413 418] or on steroids occurs in most cases, usually within a few months. The rate of fall seems more rapid than in idiopathic AIH.[423] However, some patients with DI-AILH present with ALF, up to 14% require liver transplantation.[425] Interestingly, the response to steroids might be similar in both patients with and without 'autoimmune' features.[423]

In DILI related to the use of immune checkpoint inhibitors (ICIs),[426] ANA is present in about half of patients. However, usually serum IgG is normal and liver histology does not suggest AIH. Thus, we do not consider ICI-related hepatitis as AIH. Oncology guidelines initially recommended high-dose (1–2 mg/kg/day) prednisolone therapy for most cases of ICI-related hepatitis. However, 40–50% of cases resolve without steroids,[427 428] and improvement seems unrelated to prednisolone dose (≤1 vs >1 mg/kg/day).[418 429] An evidence-based graded management strategy has been developed.[430]

No data exist in children with regard to DI-AIH.

RECOMMENDATIONS SECTION O

1. We recommend routine consideration of the possibility of drug-induced autoimmune-like hepatitis (DI-ALH) and prompt cessation of any suspected precipitant. *Grade of evidence: low. Strength of recommendation: strong.*

2. We recommend performing a liver biopsy if there is not prompt resolution of liver injury on withdrawal of the suspected precipitant. *Grade of evidence: low. Strength of recommendation: strong.*

3. For DI-AILH, we recommend starting prednisolone (0.5 mg/kg/day or up to 40 mg/day, as for idiopathic AIH), if there is either (a) jaundice, (b) advanced fibrosis on liver biopsy or (c) failure of serum transaminases to fall substantially within a week of stopping the suspected precipitant. Patients with liver failure should be discussed with a transplant centre. *Grade of evidence: low. Strength of recommendation: strong.*

4. We recommend that (a) prednisolone be tapered as for standard AIH, until serum transaminases (and IgG, if elevated) have fallen to normal, and then be phased out gradually, (b) patients then be monitored by serial serum transaminases. In the event of hepatitis relapse, subsequent management is that of standard AIH, with prednisolone and a steroid-sparing agent. *Grade of evidence: low. strength of recommendation: weak.*

5. Features of chronicity (such as advanced fibrosis on biopsy) also make it less likely that the drug is the sole cause. We recommend treating such patients as if they have standard AIH. Always consider seeking an expert clinical opinion. *Grade of evidence: low. Strength of recommendation: weak.*

SECTION P. COVID-19 AND AIH[431]

COVID-19 might involve the liver,[431] and cause abnormal liver tests.[432] In patients with AIH, COVID-19 might cause a 'flare' in serum transaminase,[433] which is usually mild, but in cirrhotic patients might result in acute on chronic liver failure.[431]

COVID-19 might be more severe in patients taking immunosuppressive drugs, including rituximab,[434] high-dose steroids, thiopurines, and (possibly) mycophenolate and tacrolimus.[435] However, other surveys[436] do not support this Thus some, although not all, guidelines suggest modest reduction of immunosuppression dose.[437 438] NICE guidance recommends[439 440] specific antiviral treatment within 5–7 days of symptoms in patients with cirrhosis, and in those taking immunosuppressive drugs.

Several cases have been reported of AIH developing shortly after COVID-19.[19 20] However many are probably coincidental.

Patients with AIH should receive COVID vaccination. About half, especially those taking steroids or mycophenolate, had impaired cellular and humoral responses to two doses of COVID vaccine; however, a third dose then achieved an adequate humoral (though not cellular) response.[441] Despite this, COVID-19 infection in AIH is less severe in vaccinated patients.[442]

Several cases of an acute AIH-like illness have been reported within 4 weeks of COVID-19 vaccination, including both the viral vector (Oxford and Janssen) and mRNA (Pfizer and Moderna) variants.[443–445] AIH is usually, mild and responds to corticosteroids, but a few cases have been fatal or have required liver transplantation. Incidence of post-vaccine liver injury[446] is low: 4 per 10 000, and some cases are probably coincidental. However, AIH following COVID vaccination rarely causes advanced fibrosis, and rarely relapses after steroids are stopped. In some reports,[444 447] liver injury developed twice after repeated exposure to the same vaccine, although not after re-exposure to a different vaccine. These features suggest a causative role for the vaccine in some cases.

Box 3 Proposed standards for diagnosis and management of autoimmune hepatitis.

(A) Patients within 10 years of diagnosis

1. Documented exclusion of viral cause: at diagnosis.
   For acute icteric presentation: (HAV, HBV, HCV, HEV, EBV, CMV, HIV)
   For indolent presentations (HBV, HCV, HIV)
   2. Diagnostic liver biopsy: performance, or documented reason for not performing.
   3. Documentation of biopsy discussion at clinical-pathological meeting.
   4. Time between initial raised serum ALT and starting steroid treatment <18 weeks, and <4 weeks, if jaundiced (peak bilirubin >60 mmol/L).
   5. Initial prednisolone dose ≤40 mg or 0.5 mg/kg/day 6. Steroid-sparing agent introduced within 4 weeks of starting steroid in patients with compensated liver disease and serum bilirubin <100 mmol/L.

Tests performed to assess achieved:

   8. Documented fracture risk assessment (FRAX score or DEXA) within 3 months of starting steroids.
   9. Documented encouragement of annual eye examination if age >60 and on steroids for >12 months.
   10. Steroids stopped within 12 months of starting or documented reason for continuing.

(B) All patients

11. Patients on thiopurines or mycophenolate: full blood count documented ≥3 times over past 365 days.
   12. Patients on azathioprine of mycophenolate for >3 years: documented discussion about pros and cons of stopping.
   13. Non-invasive fibrosis imaging assessment performed at least once over past 3 years

RECOMMENDATIONS SECTION P

1. We recommend that patients with AIH with cirrhosis/or those receiving immunosuppressive treatment who develop COVID-19 infection, be considered for appropriate antiviral therapy. *Grade of evidence: high. Strength of recommendation: strong.*

2. We recommend that steroid therapy usually be continued during COVID-19 infection. The decision to withhold steroid-sparing agents should be individualised, based on infection severity. *Grade of evidence: low. Strength of recommendation: weak.*

CONCLUSION

In these guidelines, we have described what we think are the best strategies for managing patients with AIH, based on current knowledge. In box 3 we propose diagnostic and management standards, against which services could be audited. Organisation of services for AIH in the UK and elsewhere could potentially be improved, and in box 4, we make proposals for this. Finally, our understanding of AIH and its management remains incomplete, and so, in box 5, we propose some priorities for clinical research.

Box 4 Proposals for organisation of services

1. Most patients with AIH can be managed in their local hospital if their consultant has appropriate knowledge and experience.
2. In each centre, no more than three consultants (hepatologists, or gastroenterologists with a maintained interest in liver disease) should provide continuing care for patients with AIH.
3. The roles of specialist nurses and of associated care practitioners in caring for patients with AIH should be developed.
4. Liver biopsies from patients with suspected AIH should be reported by a histopathologist with liver expertise and discussed at a clinical-pathological meeting.
5. Departments should maintain a database of patients attending with AIH, to facilitate audit and collaborative research.
6. Regional AIH networks should be developed, analogous to those in England for hepatitis C and primary biliary cholangitis. These should: (i) involve consultants, specialist nurses and histopathologists with an interest in the liver, (ii) hold regular virtual clinical meetings, (iii) encourage development of collaborative audit and research, (iv) include a formal arrangement with a transplant centre.

Box 5 Proposed clinical research priorities.

1. Validation of an updated AIH diagnostic score incorporating the recent consensus histological criteria.
2. Evaluation (using large datasets) of environmental factors (including viral infections and medication use) associated with recent-onset AIH.
3. Further validation of complete biochemical remission (CBR) as the best early predictor of longer-term outcome.
4. Validation of serial non-invasive tests as predictors of longer-term outcome and their incorporation into clinical trials.
5. Further evaluation of patient-reported outcome measures (including development of an AIH-specific measure) and their incorporation into trials of AIH treatment.
6. Clarification of the role of mycophenolate mofetil as a first-line steroid-sparing agent.
7. Evaluation of initial therapy with existing agents (eg, rituximab) and novel biological agents in prospective trials against steroid-based therapy.
8. Evaluation of these novel agents, compared with tacrolimus or mycophenolate, as second-/third-line drugs in patients.
9. Evaluation of budesonide as a longer-term maintenance treatment.
10. Evaluation of second-/third-line treatments (eg, tacrolimus) in avoiding need for transplant in patients with acute severe AIH without early response to prednisolone.

PATIENT summary

This guideline has been written, on behalf of the British Society of Gastroenterology, by a group of experts in the diagnosis and management of AIH plus two patients with AIH. It is intended for healthcare professionals involved in the management of patients with AIH and also for patients themselves to understand their condition and the care they receive. It incorporates the advances in the understanding of AIH since the previous guideline was published in 2011. However, it is not intended simply as a set of instructions—every patient is unique and treatment of AIH needs to be personalised.

AIH is one of many autoimmune diseases that result from damage caused by the immune system, which helps to protect us from infections and some cancers, but normally tolerates the body's own organs. Autoimmune diseases result from a breakdown in this tolerance. With AIH, the immune damage is directed at the liver. AIH affects 15 000–20 000 people in the UK, of all ages and from all ethnic groups. It is not infectious. Three out of four patients are female and AIH is becoming more common. We do not fully understand what causes AIH. Some people might be at increased risk, based on the genes they inherit. We do not think AIH is related to any particular lifestyle, but occasionally it can be caused by certain medicines.

AIH affects patients in many ways. Some patients have no symptoms, but many have fatigue, and some have other symptoms. Occasionally the first indication of AIH can be when patients are seen with liver failure. In children, growth failure and poor nutrition might be early signs . There is no single test for AIH. Rather it is diagnosed by ruling out other conditions (such as viral hepatitis and bile duct obstruction), by suggestive blood test results (high immunoglobulin levels and so-called 'auto' antibodies). Usually, a firm diagnosis of AIH requires a liver biopsy, interpreted by a pathologist with relevant expertise. The biopsy usually distinguishes AIH from other liver conditions, which require different treatment. It is also the only reliable way of assessing scarring in an inflamed liver (severe scarring is labelled cirrhosis).

AIH can be an aggressive disease; about a quarter of patients already have cirrhosis (scarring of the liver) at diagnosis. Without effective treatment, AIH continues to damage the liver and some patients will need a liver transplant. However, steroid treatment effectively damps down the liver inflammation and has been shown to improve survival. Nearly all patients with AIH (unless it is very mild) benefit from steroid treatment. Two main steroids are used—prednisolone and budesonide. Budesonide might have fewer cosmetic side effects then prednisolone but is not more (and is possibly less) effective in achieving AIH remission; also, its longer-term effectiveness is unknown. It can be used instead, if prednisolone causes side effects (or is expected to). In adults, initial dose of prednisolone should be about 0.5 mg/kg/day and not usually exceed 40 mg/day (up to 2 mg/kg in children to a maximum of 40 mg/day)

Addition of a second drug (usually azathioprine) allows reduction of the steroid dose and might further improve survival. Mycophenolate is a promising alternative to azathioprine but cannot be used in pregnancy. Patients taking AIH treatment need regular blood tests. They might also need interventions to maintain bone health.

Around the time of starting treatment patients need to be up to date with their vaccinations against infections such as influenza, pneumococcus and chickenpox/shingles.

Improvement in symptoms and in liver blood tests usually indicate a good response to treatment. A follow-up liver biopsy to confirm that AIH has gone into remission is no longer recommended routinely but might sometimes be helpful in guiding management.

Options for patients who do not improve on treatment include, reconsidering the diagnosis, and assessing adherence to treatment. This should be done in a respectful, non-confrontational and non-stigmatising manner. Other options include changing the steroid, checking that the azathioprine

dose is adequate (by checking its blood levels) and changing to another drug, such as mycophenolate, tacrolimus or rituximab. Experience with these treatments is very limited, so expert advice is often helpful here.

When normal blood test—so called 'complete biochemical response'—has been achieved (and confirmed 2–4 weeks later), we recommend that steroid dose should be reduced gradually to zero.

If remission is maintained over 2–3 years, the second drug (usually azathioprine) can sometimes be stopped (under medical guidance and with regular continued monitoring). There is a risk of disease relapse but (if promptly treated and if the patient does not have cirrhosis) relapses are usually without symptoms and are rarely dangerous. Relapses can be retreated with steroids and then, a longer-term treatment to prevent further relapse (usually azathioprine) can be considered. However, patients with AIH have a slightly increased risk of cancer, which might be related to these drugs damping down the immune system. Thus, in all patients without cirrhosis, we recommend at least one attempt to stop medication.

Most studies indicate that quality of life (QoL) in patients with AIH is lower than in the general population. We need to understand more about this—and in particular, which treatments for AIH improve QoL—and which make it worse.

In a minority of patients, liver damage progresses despite treatment and such patients need monitoring for complications of cirrhosis and consideration of liver transplantation. Overall results are good, although AIH might recur in the transplanted liver.

Pregnancy in women with AIH is nearly always successful, although there are modest increases in risk to both mother and baby. With the important exception of mycophenolate (which might damage the baby), we recommend continuing drugs for AIH throughout pregnancy to prevent disease flares.

Patients with AIH can usually be managed well in smaller as well as large hospitals, although children should maintain contact with a specialist. We recommend that they be under the care of only two–three designated consultants and have input from a specialist nurse. A patient database should be maintained for audit purposes. We recommend formation of regional AIH networks, with online meetings at which challenging problems can be discussed and biopsy slides reviewed. Advice from a transplant centre must be easily and rapidly available, especially for patients with severe disease, most of whom should be transferred.

We emphasise the need for further research. We need to better understand the effect of treatments on patients' quality of life and assess newer drugs which damp down the immune system in clinical trials. Some existing treatments need further evaluation (for example mycophenolate and budesonide to prevent relapse).

DISCLAIMER

These BSG guidelines represent a consensus of best practice based on the available evidence at the time of preparation. They might not apply in all situations and should be interpreted in the light of specific clinical situations and resource availability. Further controlled clinical studies might be needed to clarify aspects of these statements, and revision might be necessary as new data appear. Clinical consideration might justify a course of action at variance to these recommendations, but we suggest that reasons for this are documented in the medical record. BSG guidelines are intended to be an educational device to provide information that might assist in providing care to patients. They are not rules and should not be construed as establishing a legal standard of care or as encouraging, advocating, requiring, or discouraging any particular treatment.

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