Review

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Approach to the patient with acute severe autoimmune hepatitis

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Summary

Autoimmune hepatitis is associated with varied clinical presentations and natural history, as well as somewhat unpredictable treatment responses. Understanding how to stratify patients who require further escalation of therapy will help clinicians manage these patients. The presentation of acute severe autoimmune hepatitis (AS-AIH) is relatively uncommon, although its prevalence is potentially greater than currently perceived. Previous studies consist of small retrospective single-centre series and are not directly comparable due to the diversity of presentations, disease definitions and non-standardised treatment regimens. We define AS-AIH as those who present acutely with AIH and are icteric with an international normalised ratio ≥1.5 and no evidence of hepatic encephalopathy. Those with hepatic encephalopathy should be defined as having AS-AIH with acute liver failure. In this review, we provide a structured practical approach for diagnosing and managing this unique group of patients.

Keywords: Autoimmune hepatitis; Acute severe presentation; Acute liver failure; Corticosteroids; Liver transplantation

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Background

Autoimmune hepatitis (AIH) is a rare, immune-mediated, inflammatory condition of the liver that is characterised by circulating autoantibodies, hypergammaglobulinaemia and distinctive features on liver biopsy.[1] It typically responds to immunosuppression. However, if the disease is left untreated, cirrhosis, liver failure, transplantation and death can ensue.[2]

Several factors contribute to diagnostic uncertainty in AIH: its wide spectrum of presentations, absence of pathognomonic features and variability in treatment response. Recognising these issues and having an open mind when approaching a patient with acute hepatitis, cirrhosis or acute liver failure (ALF) will ensure this important treatable condition is not overlooked. As mentioned, the clinical presentation of AIH is heterogenous and can vary from asymptomatic disease to liver failure requiring liver transplantation (LT) (Fig. 1).

Definitions

The most widely accepted definition of ALF includes evidence of coagulopathy and any degree of hepatic encephalopathy (HE) within 26 weeks of the onset of illness in a patient without pre-existing cirrhosis.[3] Over time, several definitions of ALF have developed.[4–7] ALF can be further subcategorised into length of illness, *e.g.* "hyperacute" (<7 days), "acute" (7–21/28 days) and "subacute" (>21 days and <24/26 weeks).[3,8] Exact time frames vary between guidelines.

In those with an acute presentation (≤26 weeks) of AIH and no evidence of pre-existing liver disease, we have previously proposed the following categorisation[3,9]:

- ***Acute-icteric AIH:*** icteric with no evidence of coagulopathy or encephalopathy
- ***AS-AIH:*** icteric and coagulopathic (international normalised ratio [INR] ≥1.5), but no evidence of encephalopathy
- ***AS-AIH with ALF:*** icteric, coagulopathic (INR ≥1.5) and encephalopathic

In the context of AS-AIH without ALF, the time frame of <26 weeks indicates the time between the development of jaundice and coagulopathy. Studies with well-characterised cohorts of patients with AS-AIH ± ALF have previously excluded pre-existing liver disease based on the absence of histological lesions of severe fibrosis or cirrhosis.[10–13] Therefore, confirmation of AS-AIH may only be possible after biopsy or explant review.

Stratification of patients into the above categories may influence management and prognostication. We estimate that 50–60% of AS-AIH cases progress to ALF, although the true figure is unknown due to the lack of prospective data with well-characterised cohorts.[10,11]

According to guidelines, patients with acute presentations of AIH, Wilson's disease, HBV and Budd-Chiari syndrome can be included in the definition of ALF, despite the possibility of underlying chronic liver disease.[3,8] This is somewhat controversial and better understanding of pathological processes, clinical course, and outcomes are

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required if these conditions are to be included in the definition of AS-AIH.

Acute-on-chronic liver failure and AIH

Acute-on-chronic liver failure (ACLF) is a clinical syndrome of acute hepatic decompensation with superimposed acute injury observed in patients with pre-existing cirrhosis characterised by the presence of extrahepatic organ failure(s).[14,15] Precipitating factors include heavy alcohol intake, viral hepatitis, drugs, AIH, ischaemic hepatitis, infection/sepsis and haemorrhage.[14,15] Removal or treatment of the precipitating factor is an important aspect of management, alongside appropriate organ support. ACLF is associated with high mortality, costly intensive care admissions and the requirement for LT.[16,17]

Clinically, autoimmune-ALF can be difficult to distinguish from ACLF.[18] However, the histological features are distinct.[18,19] Lymphoid aggregates and perivenulitis are less common in AIH-ACLF, whilst advanced fibrosis (F3/F4), ductular reactions, and large areas of parenchymal collapse with lymphoplasmacytic inflammation are more common.[18,19] An Asian-Pacific study of 82 patients with AIH-ACLF demonstrated a survival benefit in those that received corticosteroids.[18] However, patients with model for end-stage liver disease (MELD) scores >27 and HE (≥F3) demonstrated poor corticosteroid response, potentially allowing for early stratification of patients.[18]

Epidemiology

The epidemiology of acute AIH is not well-described. Interestingly, Alaskans have a high prevalence of disease (43 per 100,000) with a significant proportion (35%) presenting acutely with jaundice.[20] Black patients with AIH are more likely to present with liver failure (70% in 1 study).[21] These findings were corroborated in a multicentre European study which showed that black patients with AIH are more likely to present at a younger age and have a greater risk of LT and liver-related mortality, despite similar corticosteroid response rates to the non-black group.[22]

Some studies have found no difference between the prevalence of human leukocyte antigen (HLA) DR3 and HLA DR4 in acute AIH and chronic AIH groups.[13,23] The absence of HLA B8 and the presence of HLA DR7 may be risk factors for AIH-induced ALF (*vs.* chronic hepatitis).[24] Furthermore, polymorphisms in HLA DRB1*03 may predict corticosteroid failure.[25]

Aetiology

The exact mechanisms behind the development of AIH are not fully understood. Simplistically, in a genetically predisposed individual who has been exposed to an environmental trigger, a complex immunological process based on T lymphocyte-mediated cell destruction, imbalance in the regulation of immune cells, loss of tolerance and a defective immune response can instigate damage to the liver.

Certain viruses (hepatitis A, B, C and measles) have been implicated in the pathogenesis of AIH and are believed to trigger ongoing immune-mediated hepatic inflammation, even after resolution of infection.[26–34] In a single-centre study (n = 52) investigating the potential triggers of AIH-ALF, a trigger was found in 50% of cases.[35] These were predominantly drug-related (58%), however, a viral cause was found in 31% of cases. These included Epstein-Barr virus (EBV), cytomegalovirus and HEV.[35]

Key points

- In the absence of pre-existing liver disease, AS-AIH is defined as an acute presentation of AIH characterised by jaundice and coagulopathy (INR ≥1.5) with no evidence of encephalopathy
- A proportion of these patients develop ALF with HE ± multi-organ failure
- Hypergammaglobulinaemia and autoantibody positivity are useful in the diagnosis of AS-AIH but may not be present early in the disease course
- The typical histological features of AIH are not always present in AS-AIH, however, more prominent features may include centri-lobular haemorrhagic necrosis, massive hepatic necrosis and central perivenulitis
- Based on these atypical findings, a more specific scoring system is required to aid the diagnosis of AS-AIH and autoimmune-ALF
- Corticosteroids in AS-AIH are the mainstay of treatment and are highly effective
- Carefully selected individuals with low grade HE may also benefit from corticosteroid therapy
- Better prognostic markers are required to allow stratification of patients based on corticosteroid response
- Assessment of corticosteroid response with change in bilirubin, INR and MELD-Na/UKELD scores should occur at 7 days, and potentially earlier if required
- Patients with features of advanced liver failure need to be considered for urgent liver transplantation, obviating the need for a trial of corticosteroids

Drug-induced liver injury

Drug-induced liver injury (DILI) can be associated with elevated liver enzymes, hypergammaglobulinaemia, autoantibody positivity and histological features of AIH. Drugs associated with autoimmune DILI are listed in Box 1.

Although not categorised in this manner in other guidelines,[36,37] the EASL guidelines on AIH describe 3 potential relationships between AIH and DILI[1,38,39]:

- ***AIH with superimposed DILI:*** pre-existent chronic AIH (±advanced fibrosis) with additional DILI insult.
- ***DILI-induced AIH:*** drug intake triggers an immune process which leads to the development of chronic AIH; patients may present with serological and/or histological markers of idiopathic AIH; long-term immunosuppression is usually required.
- ***Immune-mediated DILI:*** drug intake triggers AIH (limited time course); patients may present with serological and/or histological markers of idiopathic AIH; spontaneous remission after drug cessation and steroid withdrawal.

There is no international consensus on this categorisation. However, understanding these concepts is helpful, *e.g.* immunosuppression can be successfully withdrawn in patients with immune-mediated DILI. This may not be possible in cases of DILI-induced AIH, which can be difficult to distinguish clinically, serologically and histologically from idiopathic AIH. Despite the overlapping features between AIH and DILI, a liver biopsy can be useful. Portal inflammation, absence of fibrosis, portal neutrophils/plasma cells and intracellular cholestasis are more suggestive of DILI than idiopathic AIH.[40] In specific situations, genetic testing may also be diagnostically useful as the carriage

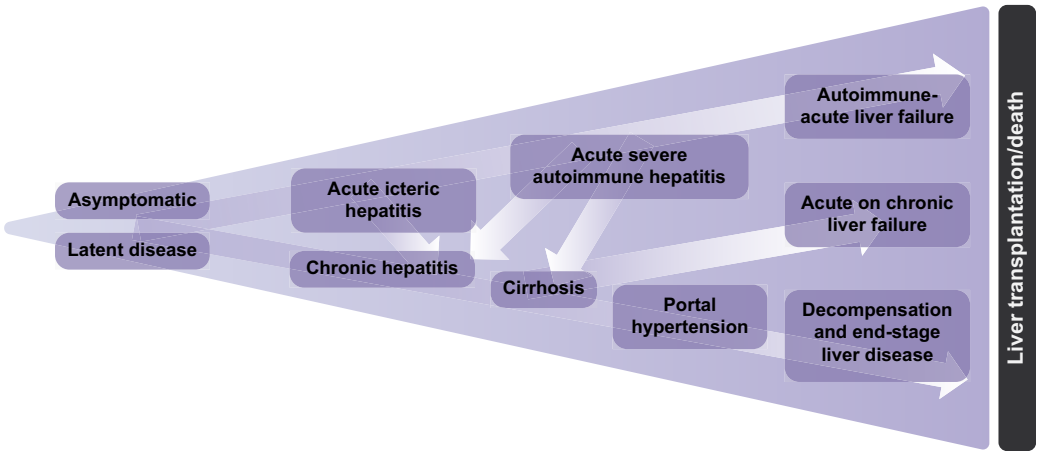

Fig. 1. The spectrum of presentations in AIH. AIH, autoimmune hepatitis.

Box 1. Potential drugs associated with autoimmune DILI.

Minocycline	Statins	Etanercept
Nitrofurantoin	Fenofibrate	Isoniazid
Isoniazid	Diclofenac	Phenytoin
Halothane	Interferons	Propylthiouracil
Hydralazine	Infliximab	Ipilimumab*
Methyldopa	Adalimumab	Nivolumab*

*Severity of damage with these drugs suggests a more severe pathological process and phenotype of disease. DILI, drug-induced liver injury.

of certain HLA alleles makes one diagnosis more likely than another.[37]

Immune checkpoint inhibitors

These agents restore/enhance T-cell responses and re-establish anti-tumour mechanisms. Unwanted side effects include immune-related hepatotoxicity (ranging from asymptomatic transaminitis to ALF) which can develop soon after treatment initiation, later in the treatment course or occasionally after drug cessation.[41,42] In particular, cytotoxic T lymphocyte associated protein-4 (CTLA-4) inhibitors (*e.g.* ipilimumab) are more hepatotoxic than programmed cell death ligand 1 (PD-L1) agents (*e.g.* nivolumab).[41]

Checkpoint inhibitor-induced hepatitis is typically seronegative. From a histological perspective, non-specific features of portal and peri-portal inflammation and hepatocellular necrosis with infiltrating lymphocytes, plasma cells and eosinophils can be observed, similar to acute viral hepatitis and AIH.[43,44] Anti-CTLA-4 drugs cause a granulomatous hepatitis with severe lobular necrosis and inflammatory activity, fibrin deposits and central vein endothelitis. Anti-PD-1/PD-L1 agents lead to a more heterogeneous phenotype characterised by active hepatitis with sporadic/confluent necrosis and mild/moderate peri-portal activity with no granulomatous inflammation.[45]

If discontinuation of the causative agent does not induce spontaneous resolution, corticosteroids are usually effective.[43–50] Some cases are poorly responsive to corticosteroids and require additional immunosuppression.

Making the diagnosis

The absence of pathognomonic features makes the diagnosis of AS-AIH challenging and one of exclusion. Furthermore, the potential complications of corticosteroid therapy necessitate thorough exclusion of alternative causes of acute severe hepatitis, including viral hepatitis, toxins, DILI, ischaemia and metabolic disorders. A full comprehensive history and blood work enables the exclusion of most of these conditions. Most studies on AS-AIH (±ALF) have not specified the exact method of excluding these aetiologies.[10,11,13,23,24,51,52] International guidelines suggest the following virological screening in cases of ALF[3,8]:

- Anti-HAV IgM
- Hepatitis B surface antigen and anti-HBV core IgM (HBV DNA/delta if positive)
- Anti-HCV, HCV RNA
- Anti-HEV IgM
- Anti-herpes simplex virus IgM, anti-varicella zoster virus IgM, EBV, cytomegalovirus and parvovirus

Additionally, EASL recommends a combination of serology and nucleic acid amplification techniques to diagnose HEV infection.[53] Cross-reactivity between HEV and liver autoantibodies raises the additional diagnostic dilemma of falsely positive HEV results.[53,54]

There is increasing recognition that AIH is an important cause of ALF of unknown origin (potentially up to 62% of cases).[7,55–60] Biopsy provides the opportunity to look for features of AIH, as well as to exclude other aetiologies (Fig. 4).

Another important aspect of diagnosis is clinical follow-up, which enables an assessment of developing chronicity. In previous studies on AS-AIH, the follow-up period and re-assessment of diagnosis of those not progressing to ALF is not always specified.

Clinical presentation

The lack of previous studies in well-defined cohorts of patients with AS-AIH makes direct comparison between studies difficult. Anorexia, jaundice, ascites and HE are more likely to be present in patients with acute severe forms of AIH (regardless of underlying cirrhosis/fibrosis status).[61,62] Bilirubin, alanine

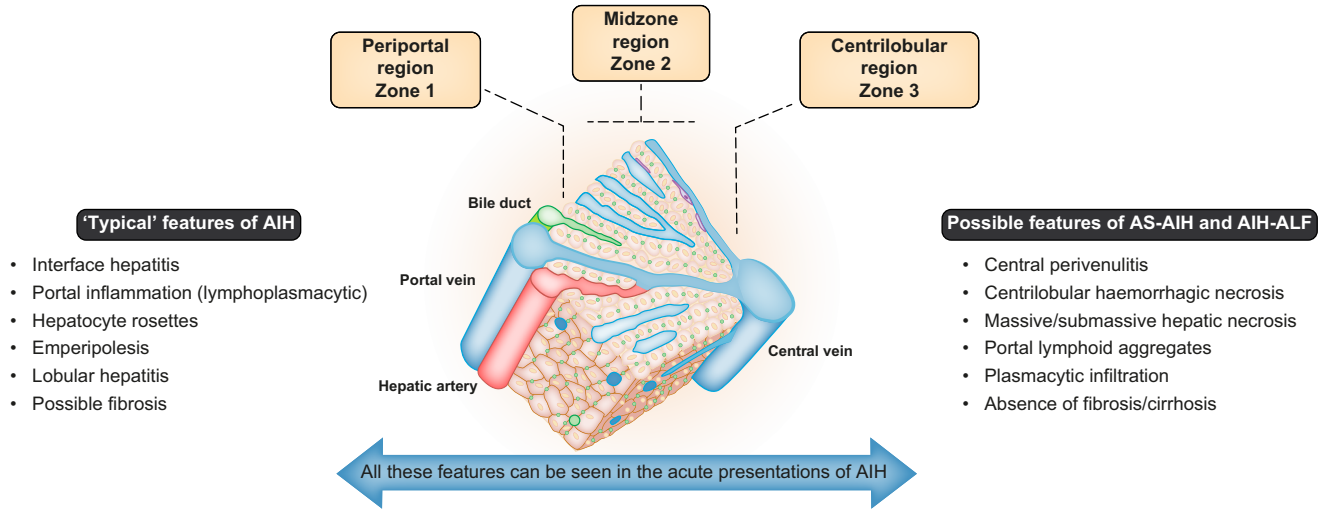

Fig. 2. Schematic diagram of a hepatic lobule and the potential histological changes in acute presentations of AIH. AIH, autoimmune hepatitis; AIH-ALF, autoimmune hepatitis-acute liver failure; AS-AIH, acute severe autoimmune hepatitis.

aminotransferase (ALT), aspartate aminotransferase (AST), gamma-globulins, INR and MELD scores have also been shown to be greater in acute and severe presentations of AIH, but not specifically AS-AIH (±ALF).[61,62]

Yeoman *et al.* studied a cohort of 32 patients with AS-AIH, defined as an acute presentation of AIH and an INR ≥1.5 at any time without histological evidence of cirrhosis. Compared to 15 patients with an acute exacerbation of chronic AIH, the median bilirubin was greater in the AS-AIH group compared to the acute exacerbation group (463 *vs.* 269 μmol/L respectively, $p = 0.015$). Additionally, globulin levels were significantly lower in the AS-AIH group compared to the acute exacerbation group (39 *vs.* 47 g/dl, respectively, $p = 0.02$). MELD and United Kingdom end-stage liver disease (UKELD, a modified version of the MELD-Na model) scores were higher in the AS-AIH group compared to the acute exacerbation group (29 *vs.* 23 [$p = 0.005$] and 62 *vs.* 58 [$p = 0.006$], respectively).[10]

Serology

Autoantibodies are diagnostically useful in the acute presentations of AIH:

- ***Type 1 AIH:*** Anti-nuclear antibody (ANA); anti-smooth muscle antibody (ASMA); anti-soluble liver antigen/liver pancreas antibodies (anti-SLA/LP)
- ***Type 2 AIH:*** Anti-liver kidney microsomal-1 and 3 antibodies (anti-LKM 1 and 3); anti-liver cytosol-1 antibody (anti-LC-1)

Autoantibodies are believed to develop during the course of disease and may potentially disappear during treatment, although they are not routinely used to assess treatment response.[63,64] Seronegativity in the early stages of an acute presentation of AIH is common (≈10–40%).[10,24,51,65] ANA is undetected or present in low titres in 30–40% of patients with severe or fulminant forms of AIH.[65,66] Additionally, gamma-globulins may be normal in 25–47% of cases.[10,65,66]

The absence of autoantibodies does not preclude a diagnosis of AS-AIH. This is relevant when using the International Autoimmune Hepatitis Group (IAIHG) diagnostic scoring systems. Yeoman *et al.* reported that 88% of their AS-AIH cohort tested positive for ANA, ASMA and/or LKM (including low titres). However, once the IAIHG recommendations of titre strengths were applied, only 66% had 'positive' autoantibodies.[10] If clinical suspicion is high, autoantibody results should not delay biopsy (or corticosteroid initiation). In cases of seronegativity, it is worth requesting an extended autoantibody screen (including anti-SLA/LP) as the conventional panel usually includes ANA, ASMA and anti-LKM. We also recommend repeating serology several months after disease onset.

Autoantibody testing can yield false positive results. For example, 20–30% of patients with non-alcoholic fatty liver disease or non-alcoholic steatohepatitis can have positive ANA antibodies.[67–69] ANA, ASMA and LKM antibodies can also be positive in patients with HCV infection.[70] Autoantibody results should therefore be interpreted with caution.

Imaging

Ultrasound is useful in the first instance, especially in ruling out vascular conditions. We also advocate the use of computed tomography (CT), although there is little evidence to support this recommendation. However, the identification of a 'collapsing' liver may indicate a subacute/acute pathology. CT can also reveal heterogenous hypo-attenuated regions within the liver in 65% of patients with autoimmune-ALF.[71] Liver volume is significantly reduced in non-acetaminophen-induced acute liver injury (ALI)/ALF, when compared to acetaminophen-induced ALI/ALF.[72] Not only is CT valuable for volumetric analysis, it also allows for the assessment of features of chronicity (*e.g.* portal hypertension), as well as potential radiological contraindications to LT such as inadequate vasculature and malignancy. Further studies are required to elucidate its true value.

Histology

The typical histological features of AIH (Fig. 2 and 3) may not be present early in the disease course or during an acute *de novo* presentation.[73,74] Despite this, a liver biopsy is crucial in making a diagnosis of AS-AIH (±ALF) and should be sought at the earliest opportunity.[40] Appropriate histological interpretation requires

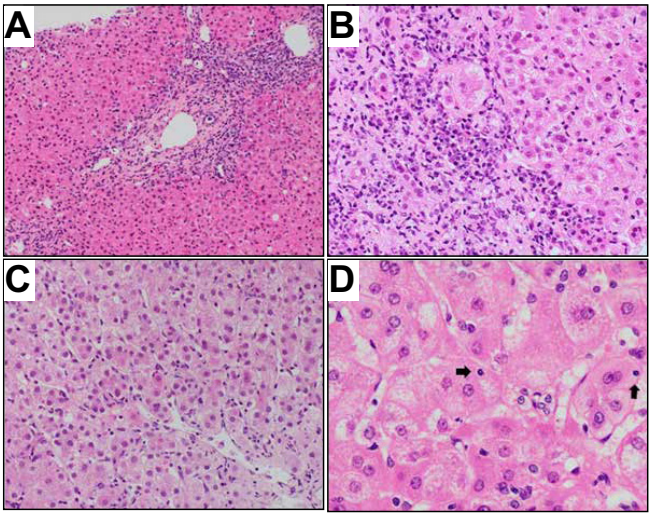

Fig. 3. Typical histological features of autoimmune hepatitis. (A) Portal inflammation with interface activity (H&E, 100×). (B) Detail of the interface between portal tract and hepatic parenchyma, with moderate activity associated with conspicuous plasma cell component (H&E, 200×). (C) Lobular hepatitis with disarray of the liver cell plates. Diffuse necro-inflammatory activity and regenerative hepatocellular resetting (H&E, 200×). (D) Occasional emperipolesis activity. Intracytoplasmic lymphocytes are spotted in some hepatocytes (arrows) (H&E, 400×).

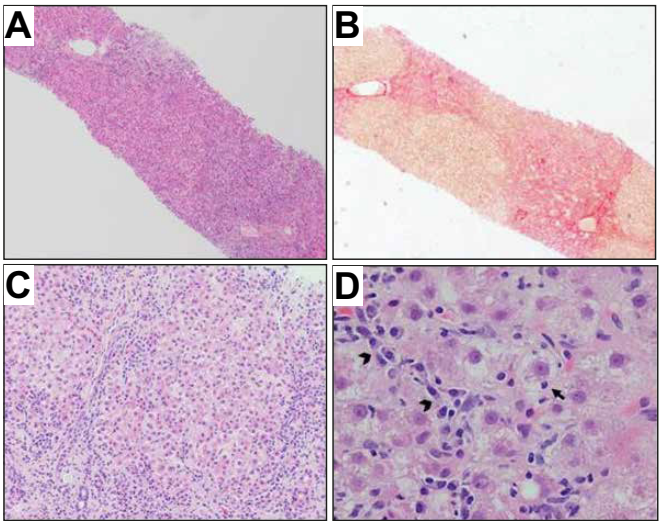

Fig. 4. Autoimmune-like acute hepatitis in a patient on nitrofurantoin. (A) Severe liver damage with areas of recent bridging necrosis and post-necrotic collapse (H&E, 40×). (B) The hepatic parenchyma shows nodular configuration secondary to post-necrosis collapse, with no obvious established fibrosis or very early collagen deposition (Picrosirius red, 40×). (C) Lobular disarray with multiple necro-inflammatory foci and reactive changes of the liver cell plates with regenerative rosettes (H&E, 200×). (D) Detail of an inflammatory area with clusters of plasma cells (arrowheads), hepatocyte reactive changes with cell ballooning and focal emperipolesis (arrow) (H&E, 400×).

useful background clinical information such as the time frame from onset of symptoms and potential viral/drug exposures.

Histologically, acute forms of AIH predominantly affect the centrilobular zones.[7] Centrilobular necrosis in the acute presentations of AIH may reflect the stage preceding portal involvement.[65,75–77] It is also a manifestation of disease severity.[62,78] However, it is not specific to an acute presentation and can be found in chronic AIH or acute-on-chronic disease.[62,78–80] Therefore, centrilobular necrosis may only be a useful feature in diagnosing new acute-onset disease if it is present in the absence of portal involvement.[81,82]

In a Japanese study looking at the histological features of patients with severe fulminant forms of AIH, 19/22 (86%) cases showed features of an acute hepatitis with centrizonal, submassive and massive necrosis.[66] Massive hepatic necrosis (MHN) is common (42–45%) in patients with AS-AIH and AIH-ALF, however, it can also be present in virally induced ALF and other aetiologies.[7,66] Another important feature in acute AIH is central perivenulitis, which is characterised by lymphoplasmacytic infiltration surrounding the central vein. This can be found in association with centrilobular necrosis, lymphoid aggregates and plasma cell-enriched infiltration.[7,66,78] As a result, the United States Acute Liver Failure (USALF) Study Group proposed the following criteria for autoimmune-ALF[7]:

- Central perivenulitis
- Lymphoid aggregates
- Plasma cell enrichment
- Type 4* or 5** MHN

(*Type 4 MHN = pan-lobular necrosis, prominent centrilobular necro-inflammation and haemorrhage; **Type 5 MHN = classical peri-portal AIH in conjunction with superimposed changes of massive necrosis ± centrilobular necro-inflammation)

Yeoman *et al.* assessed these criteria in their cohort of patients with AS-AIH and found that 15/22 (68%) cases had central venulitis, 16/22 (72%) had lymphoid aggregates and 17/22 (77%) had plasma cell enrichment. The criteria were less sensitive when assessing the MHN component; a type 4/5 pattern was only observed in 5/22 (23%) of cases.[10] However, type 5 MHN was more prevalent in a smaller study and potentially correlated with corticosteroid response.[11]

There are no pathognomonic histological features to aid the diagnosis of AS-AIH (±ALF). However, the presence of lobular hepatitis (consisting of diffuse necro-inflammation), scavenger macrophages and associated changes of cobblestone/regenerative hepatocytes, with central perivenulitis ± the classical features of AIH (portal inflammation, interface activity and emperipolesis) are highly indicative of the diagnosis.[80]

Assessment of fibrosis can differentiate between acute and chronic AIH. The challenges associated with this assessment are well recognised by histopathologists, particularly when distinguishing true fibrosis from post-necrotic collapse. Special stains to assess the liver architecture and connective tissue composition are of great importance to avoid overestimation of fibrosis. Recommendations from our institution include using a combination of reticulin (to assess liver structure), a stain for type 1 collagen (*e.g.* Masson's trichrome or Picrosirius red) and a stain for elastic fibres (*e.g.* orcein) in addition to assessment of copper-associated protein.[83–86] Identification of elastic fibres in areas with septal appearance is helpful in establishing old fibrosis, as this is not observed in recent post-necrosis collapse which mimics cirrhosis.[87,88]

Utility of scoring systems

The widely used IAIHG diagnostic criteria have not been validated for use in AS-AIH. Fujiwara *et al.* showed that the revised original IAIHG criteria may be superior to the simplified version in diagnosing patients with acute-onset AIH, as demonstrated in Fig. 6.[89] A subgroup analysis by Yeoman *et al.* of 70 patients with non-acetaminophen-induced ALF showed that only 24% of patients met the criteria for definite/probable AIH based on the simplified criteria, whilst 40% met the criteria based on the revised criteria.[90] These scoring systems may preclude the diagnosis of acute AIH and prevent the initiation of corticosteroids. One could argue that the IAIHG scoring systems should not be applied to any case of AS-AIH, which highlights the unmet need for new diagnostic criteria for AS-AIH.

Balitzer *et al.* proposed a modified histology-based scoring system including the assessment of inflammatory activity, plasma cell quantification and evaluation of copper and CK7 staining. With this scoring system, 17% of patients were upgraded into a diagnosis of probable/definite AIH, who would have otherwise been classified as non-AIH using the simplified criteria.[91]

Approach to treatment: Corticosteroids

Corticosteroid responsiveness is a defining/diagnostic feature of AIH. Although older series have reported response rates approaching 80–90% in patients with chronic AIH, newer data suggests that earlier studies overestimated biochemical remission rates, which are more likely to be in the region of 60–80% at 6 months.[92–99] In the acute severe presentation, corticosteroid response rates are more variable, *i.e.* 36–100%.[10,12,100] Potential reasons for this include diagnostic inaccuracy in the early stages of disease which may delay treatment to the point of irreversibility once hepatic failure and hepatocyte necrosis have occurred.

When reviewing the data on corticosteroid response in milder disease, corticosteroid therapy is clearly favourable. Yeoman *et al.* reported outcomes of 72 icteric patients with AIH, no HE and a median INR of 1.39. Half the patients had cirrhosis. There were 59 (82%) corticosteroid responders and 13 (18%) non-responders. The interval between presentation to corticosteroid initiation made no difference to response.[101]

Similarly, Zachou *et al.* reported on corticosteroid response in 34 patients with newly diagnosed acute hepatitis (onset <24 weeks), INR ≥1.5 and bilirubin ≥4 mg/dl without signs of HE or histological lesions of chronic liver disease.[23] All patients received intravenous corticosteroids. Induction regimens included prednisolone (1.5 mg/kg/day) or 3 days of Methylprednisolone (1 g/day) with a subsequent prednisolone dose of 63.2 ± 13.7 mg/day. Overall, 33/34 patients responded to treatment and no patient required LT. Response rates in this study were attributed to lower MELD scores at presentation, earlier initiation of corticosteroids and higher intravenous doses.

Yeoman *et al.* reported on corticosteroid responsiveness in patients with AS-AIH.[10] Twenty-three of 32 patients were treated with corticosteroids, whilst the decision to undergo LT without corticosteroid treatment was made in 9 patients. Of the 23 patients who received corticosteroids, 5 (22%) had grade I/II HE. By our definitions, the latter had AIH-ALF. In the corticosteroid cohort, 10/23 (43%) patients responded to corticosteroid therapy, 2/23 (9%) responded to additional immunosuppression (tacrolimus/mycophenolate mofetil) and 10/23 (43%) underwent LT. Of the 5 patients with low grade HE prior to corticosteroid initiation, HE was reversed in 2 patients with corticosteroids. In replies responding to this study, 2 groups described outcomes in 17 and 14 patients with AS-AIH and corroborated these findings, with corticosteroid response rates of 60–64%.[11,102]

The largest study to date (reported in abstract form) is a multicentre French study with a well-characterised cohort of 121 patients with AS-AIH. Inclusion criteria consisted of an acute presentation with an INR of ≥1.5 and/or bilirubin ≥200 μmol/L, histological features in keeping with AIH and an IAIHG score of definite/probable, and no previous history of hepatic disease. A total of 110 patients received corticosteroids, whilst 11 did not. HE was present in all 11 non-treated patients and in 8/110 corticosteroid-treated patients. Amongst the corticosteroid-treated patients, 67 (61%) responded, while 43 patients (39%) did not respond and either underwent LT or died. The strongest predictor of treatment failure was the presence of encephalopathy, with only 1/8 patients with HE responding to corticosteroids.[103]

A few small studies have reported no survival benefit when using corticosteroids in AS-AIH or autoimmune-ALF. However, as summarised in Table 1, these studies included more severe cohorts of AS-AIH with features of ALF, potentially at the point of irreversibility, thus making corticosteroid therapy futile. In patients with fulminant AIH, corticosteroid therapy may only be effective in 8–41% of patients.[12,51,104,105]

Part of the controversy surrounding corticosteroid use in AS-AIH is based on a French report of 16 patients who developed acute hepatitis with features of ALF/HE within 2 weeks (fulminant) or 2–12 weeks (sub-fulminant) of jaundice onset.[12] In this cohort, 10/16 patients experienced high grade HE. Notably, the median INR was 5.36 (1.7–12.2). Histologically, 6/16 patients had sub-massive hepatic necrosis and 10/16 patients had MHN on biopsy. Overall, 12/16 received corticosteroids. One patient had mild disease (bilirubin 400 μmol/L, INR 1.7) and responded to corticosteroids within 3 days. One patient had been on dual immunosuppression (corticosteroids/cyclosporin) prior to presentation and subsequently died of disseminated aspergillosis. The remaining 10 patients on corticosteroids underwent LT. In retrospect, corticosteroid failure was predictable based on the severity of disease in this cohort.

A retrospective analysis of patients with autoimmune, indeterminate and drug-induced ALF by the USALF Study Group included 66 patients with AIH, all of whom presented with coagulopathy and HE. Twenty-five patients received prednisone (median dose 60 mg/day) and were compared with 41 untreated patients. Corticosteroids did not improve overall or spontaneous survival in autoimmune-ALF, although this cohort was not well-characterised (*e.g.* unknown cirrhosis status and IAIHG scores). Corticosteroid use was associated with increased mortality in patients with higher MELD scores.[105]

Fujiwara *et al.* confirm the poor response of corticosteroid therapy in AIH-ALF.[52] In their study of 20 patients with AIH-ALF, 19 patients received corticosteroids and 8 (40%) recovered without LT, 4 (20%) underwent LT and 8 (40%) died without LT. In those with severe AIH (n = 5) with no HE, all responded to corticosteroid therapy. In those with fulminant AIH (n = 13), only 2 responded to corticosteroids, while 3 underwent LT and 8 died without LT. In 2 patients with late-onset hepatic failure, 1 patient responded to corticosteroids and 1 required LT.

Table 1. A summary of corticosteroid responses from previous studies on acute severe presentations of AIH – the 'sicker' cohorts had poorer response to corticosteroids.

Study	No. of patients	Definition of AS-AIH or AIH-ALF	Bilirubin of whole cohort	INR/PT of whole cohort	MELD of whole cohort	Corticosteroid therapy n (%)	Corticosteroid dose	HE prior to corticosteroid therapy n (%)	Outcome in corticosteroid cohort n (%)
Zachou *et al.* 2019	34	• Acute hepatitis (<24 weeks) • No HE • Transaminases >10 × ULN • Bilirubin >4 mg/dl • INR ≥1.5 • No histological lesions of chronic disease	Median **173** μmol/L (54–619)	Median INR **1.52** (1.5-2.27)	Median **18** (12–24)	34/34 (100%)	Induction regimens: Prednisolone 1.5 mg/kg/day (intravenous) **or** 3 days of Methylprednisolone 1 g/day with subsequent Prednisolone dose of 63.2 ±13.7 mg/day (intravenous)	0	• 33 **(97%)** responded to corticosteroids • 1 died on waiting list for LT
Anastasiou *et al.* 2018	32	• Acute presentation (<4 weeks from symptom onset) of HE (any degree) • INR ≥1.5 • No apparent pre-existing liver disease at admission • Advanced fibrosis/cirrhosis not excluded	Median **275** μmol/L (188)	Median INR **1.7** (0.6)	Median **22** (5)	32/32 (100%)	Average Prednisolone dose 153.9 mg/day (60–500 mg) (oral or intravenous)	?All (100%)	• ?29 **(91%)** responders to corticosteroids • 1 LT • 2 died
de Martin *et al.* 2017	121	• Acute presentation • Histological features of AIH • INR ≥1.5 ± total bilirubin >200 μmol/L • Advanced fibrosis/ cirrhosis not excluded (52% with F0-F1)	Median **252** μmol/L (188-376)	Median INR **1.9** (1.5-2.8)	Median **25** (21-28)	110/121 (91%)	Corticosteroid dose of 1 mg/kg/day (unspecified route)	8/110 (7%)	• 77 **(70%)** responded to corticosteroids • 32 LT • 1 died
Moenne-Loccoz *et al.* 2016	17	• Acute presentation (<26 weeks) • INR ≥1.5 • No histological lesions of chronic disease	Median **429** μmol/L (106–797)	Median INR **2.3** (1.5-5.5)	Median **26** (20–51)	15/17 (88%)	Majority Prednisolone, 3 treated with Methylprednisolone Initial median dose of 60 mg/day (40-100 mg) (unspecified route)	?1 or 2/15 (7 or 13%)	• 9 **(60%)** responded to corticosteroids • 6 LT
Fujiwara *et al.* 2016	20	• Acute presentation: Severe hepatitis (no HE); Fulminant hepatitis (>grade 2 HE within 8 weeks of symptoms onset); Late-onset hepatic failure (HE development between 8 and 24 weeks after symptom onset) • PT <40%	Mean **304** μmol/L (SD ± 160)	Mean PT **29%** (SD ± 13)	Mean **27 ± 7**	19/20 (25%)	Prednisolone 40-60 mg/day (unspecified route) **or** Methylprednisolone 500-1000 mg/day (unspecified route)	14/19 (74%)	Severe hepatitis: • 5/5 **(100%)** responded to corticosteroids Fulminant hepatitis: • 2/13 **(15%)** responded to corticosteroids • 3 LT • 8 died without LT Late-onset hepatic failure: • 1/2 **(50%)** responded to corticosteroids • 1 LT

(*continued on next page*)

Table 1 (*continued*)

Study	No. of patients	Definition of AS-AIH or AIH-ALF	Bilirubin of whole cohort	INR/PT of whole cohort	MELD of whole cohort	Corticosteroid therapy n (%)	Corticosteroid dose	HE prior to corticosteroid therapy n (%)	Outcome in corticosteroid cohort n (%)
Yeoman *et al.* 2014	32	• Acute presentation (<26 weeks) • INR ≥1.5 • No histological lesions of chronic disease	Median **463** μmol/L (55-1,208)	Median INR **2.2** (1.5-3.5)	Median **29** (22-40)	23/32 (72%)	Prednisolone 20-40 mg/day (oral) **or** Hydrocortisone 100 mg TDS (intravenous)	5/23 (21%) grade 1-2	• 10 **(43%)** responded to corticosteroids • 2 responded to additional immunosuppression • 10 LT
Mendizibal *et al.* 2015	40	• Acute presentation (<26 weeks) of HE (any degree) since onset of first symptoms • INR ≥1.5 or PT <50% • No known underlying liver disease, but only 11 patients with no fibrosis on biopsy	Median **361** μmol/L ±133	Median INR **2.92** ± 1.45	Median **29** ± 5	17/40 (43%)	Meprednisone 40-60 mg/day (unspecified route)	4 /17 (24%) ≥ grade 3	• 7 **(41%)** responded to corticosteroids • 8 LT • 2 died from pneumonia
Karkhanis *et al.* 2014	66	• Acute presentation • HE (any degree) • INR ≥1.5 • Each centre determined diagnosis of AIH, some reclassified after histology review • Fibrosis/cirrhosis stage not discussed	Mean **397** μmol/L (SD ± 156)	Mean INR **3.33** (SD 3.17)	Mean **30.9** (SD 9.5)	25/66 (38%)	Mean prednisone dose 42.5 mg/day (unspecified route)	25/25 (100%)	• 8 **(32%)** spontaneous survival • ?7 (28%) LT • ?10 (40%) died
Ichai *et al.* 2007	16	• Acute hepatitis with ALF/HE <2 weeks (fulminant) or 2-12 weeks (sub-fulminant) after onset of jaundice • No histological lesions of chronic disease	Median **425** μmol/L (278-850)	Median INR **5.36** (1.7-12.2)	Median **37** (24-47)	12/16 (75%)	Mean prednisone dose 1.3 mg/kg/day (intravenous)	8/12 (67%) grade 1: 1 grade 2: 2 grade 3: 3 grade 4: 2	• 1 **(8%)** responded to corticosteroids • 10 LT • 1 died of sepsis

? not clear in study report.
AIH, autoimmune hepatitis; ALF, acute liver failure; ALI, acute liver injury; AS-AIH, acute severe autoimmune hepatitis; HE, hepatic encephalopathy; IAIHG, International Autoimmune Hepatitis Group; INR, international normalised ratio; LT, liver transplantation; MELD, model for end-stage liver disease; PT, prothrombin time; ULN, upper limit of normal.

In summary, careful patient selection is important in ensuring corticosteroid success. If a patient has acute-icteric hepatitis or AS-AIH, there is a reasonable probability that they will respond to a trial of corticosteroids. However, assessment of response is required after the initiation of therapy, to evaluate the need for LT. The development of HE and other features of ALF, make response to corticosteroids less likely. However, some studies have reported reversibility of HE with corticosteroid therapy.[10,24,52,103]

Predictors of corticosteroid failure at presentation

For patients with AS-AIH and HE, it is crucial to identify those that may respond to corticosteroids and those that would benefit from immediate LT. At present, there is no guidance on risk stratification.

Previous studies have shown that bilirubin and INR levels at presentation may predict corticosteroid response.[101,103,106] In a cohort of acute-icteric AIH, Yeoman *et al.* showed that their corticosteroid failure group had higher median bilirubin (451 *vs.* 262 μmol/L, $p = 0.02$) and INR (1.62 *vs.* 1.33, $p = 0.005$) values at diagnosis.[101] Moenne-Loccoz *et al.* demonstrated in their cohort of AS-AIH that an INR >2.46 (analysis of area under the receiver operator characteristic curve [AUROC] 0.81; 95% CI 0.55–1.00; $p = 0.01$) before starting corticosteroid therapy was predictive of failure.[11] The interval time from symptom onset to treatment initiation was similar between responders and non-responders. Ichai *et al.* demonstrated poor corticosteroid response in patients with severe fulminant forms of AIH (median INR 5.36).[12]

Additionally, the presence of low grade HE and absence of MHN on histology may be associated with corticosteroid response.[51,103,106,107] If MHN is present on histology, the presence of type 5 MHN may predict corticosteroid response as this is more indicative of autoimmune aetiology.[11,100] Saying that, Yeoman *et al.* demonstrated that the MHN patterns proposed by the USALF group lacked sensitivity in their cohort.[10]

Other studies have reported that MELD scores ≤27 or UKELD scores ≤57 may correlate with treatment response.[11,51,101] This was corroborated by Moenne-Loccoz *et al.* who found that an MELD score >28.5 (AUROC 0.85; 95% CI 0.65–1.00; $p < 0.01$) before starting corticosteroid therapy was predictive of failure.[11] Conversely, Yeoman *et al.* demonstrated no significant difference in MELD scores at admission between corticosteroid responders and non-responders.[10] An older study from the Mayo Clinic of 214 patients with type 1 AIH (including patients with cirrhosis), demonstrated that the MELD score may be useful for identifying patients likely to fail corticosteroid therapy. They also demonstrated that hyperbilirubinemia and presence of HLA DRB1*03 may predict corticosteroid failure.[108]

Assessing response once corticosteroids have started

Transaminase activity

Serum transaminases are not useful markers of response once corticosteroids have been initiated.[10,11,51,101,107] One study observed a decrease in serum ALT levels in both responder and non-responder groups. In the latter group, they postulated that the lower production of hepatic enzymes was secondary to disease severity and poor hepatocyte regeneration.[11]

Bilirubin and INR

Serum bilirubin and INR levels are perhaps better markers of response. In a historical, but important, study on early prognostic predictors in patients with severe chronic active AIH, failure to improve pre-treatment hyperbilirubinaemia after 2 weeks of corticosteroid therapy was invariably associated with early mortality.[109]

In a subgroup analysis (n = 14) looking at the impact of ethnicity on the natural history of AIH in those that presented with liver failure (INR ≥2 ± HE, including patients with cirrhosis), deteriorating bilirubin and INR levels after 3.7 ± 0.6 days of corticosteroid therapy were associated with poor outcome.[21,100]

In those with acute (±chronic) liver failure, bilirubin and INR may also be useful markers to assess corticosteroid response. In a small series of AIH-ALF patients, Miyake *et al.* indicate that the key time to assess the most significant difference in bilirubin levels between survivors and non-survivors was between 8–15 days after corticosteroid initiation.[107]

Although this is a useful parameter in assessing response, in clinical practice, a quicker time frame for assessment would be more valuable in patients who deteriorate rapidly. Yeoman *et al.* reported that in their acute-icteric patients with AIH, failure to respond at day 7 after the initiation of corticosteroids should be a cut-off point for withdrawal.[101] Similarly, yet to be published data from a multicentre French study report that an improvement in bilirubin at day 7 is associated with a higher likelihood of corticosteroid response.[103]

In a series (published in abstract form) of 31 patients with fulminant AIH, 25 received corticosteroid therapy. A 20% increase in the prothrombin time (PT) on day 3 after the initiation of corticosteroids was deemed to be a poor prognostic marker.[106] Fujiwara *et al.* have also suggested that PT activity is the best marker of improvement during the first fortnight of treatment, whilst other markers (*e.g.* bilirubin) can be slower to recover.[52]

Change in prognostic indices

Specific to acute-icteric AIH, Yeoman *et al.* showed that failure to improve MELD-Na or UKELD scores within 7 days of corticosteroid therapy indicates a high risk of progressing to ALF. In this study, AUROC values at day 7 identified that changes in bilirubin (AUROC 0.68), creatinine (0.69), MELD (0.79), MELD-Na (0.83) and UKELD (0.83) were the best predictors of treatment failure. Specifically, a fall in UKELD of <2 points predicted treatment failure with a sensitivity of 85% and specificity of 68%.[101]

In the multicentre French study already described, amongst the corticosteroid-treated patients with AS-AIH, 67/110 (61%) responded with a median decline in MELD of 4 points between days 0 and 7 of therapy. A detectable improvement was also demonstrated at day 3.[103] This concept of early treatment response is appealing as it would allow for early stratification of patients into responders and non-responders.

To conclude, there is a need for reliable prognostic predictors to facilitate patient selection for LT. If the point of corticosteroid rescue has passed and there is no improvement in bilirubin, INR/PT or MELD-Na after 7 days of corticosteroid therapy, continuing them may be futile and patients should be assessed for LT immediately. For the sickest cohort (*e.g.* those with HE), assessment at day 3 of corticosteroid therapy requires further evaluation.

Additional therapies

There is no specific data supporting the use of N-acetylcysteine (NAC) in autoimmune-ALF. However, prompt NAC administration

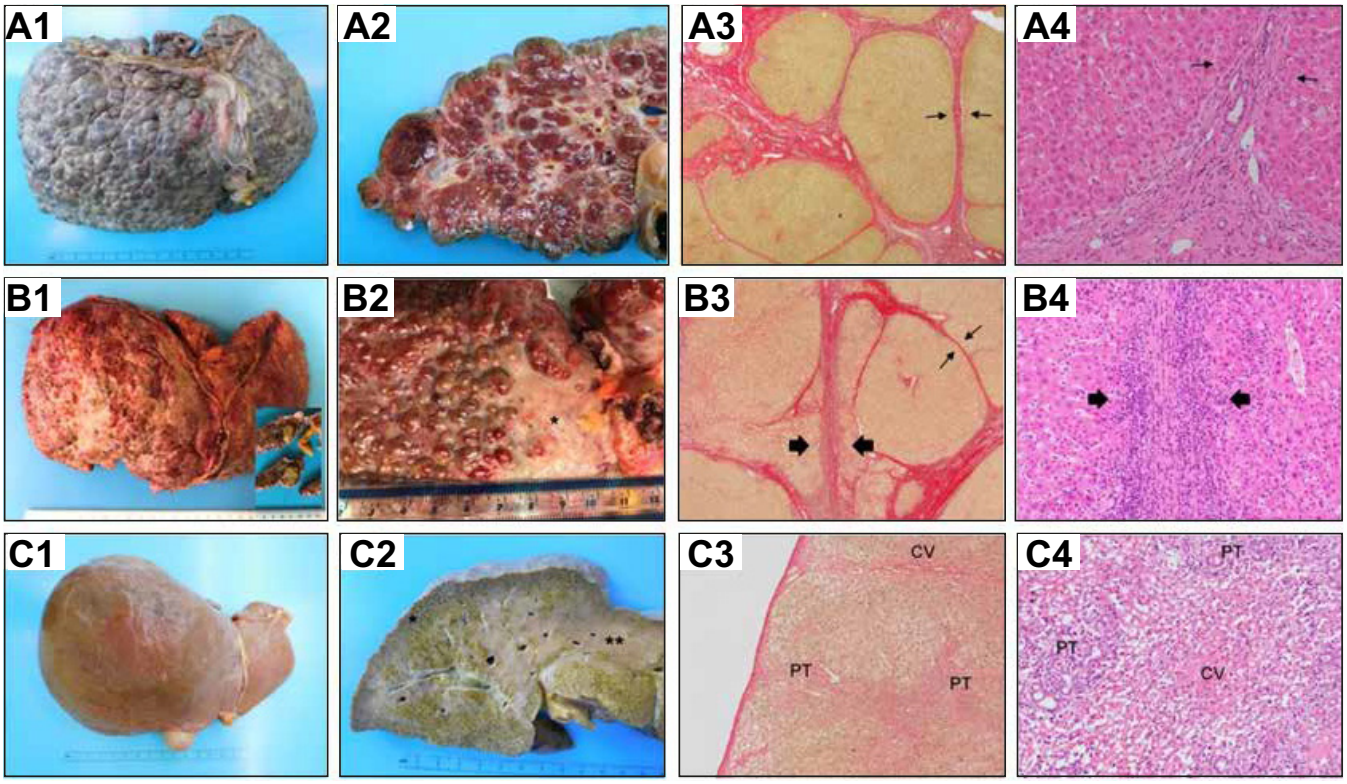

Fig. 5. Histopathological spectrum of liver damage at the time of transplantation. (A) Chronic autoimmune hepatitis in stage of established cirrhosis, with no inflammatory activity, in a 22-year-old female, diagnosed with autoimmune hepatitis aged 12. (A1) Macroscopy of the explanted liver, with macronodular cirrhosis predominantly. (A2) Macroscopy of a liver section with macro-regenerative nodules up to 15 mm in greatest dimension. (A3) On microscopy, regenerative nodules show well-demarcated outlines, with predominantly thin fibrous septa (arrows) (Picrosirius red, 20×). (A4) No residual significant inflammation is of note at the porto-septal areas. No interface activity is present (arrows), (H&E, 200×). (B) Chronic autoimmune hepatitis in stage of cirrhosis, with persistent inflammatory activity, in a male patient aged 53, diagnosed with AIH 13 years ago. He developed portal hypertension and suffered episodes of variceal bleeding, ascites and encephalopathy. (B1) Macroscopy of the explanted liver (1,299 grams). Of note is the heterogeneous capsular surface, with whitish areas of capsular depression. An incidental hepatocellular carcinoma (inset) was found at the explant, 18 mm, moderately differentiated. (B2) Detail of the liver capsule surface, with micro-macronodular cirrhosis and a large area of fibrous scarring (*) secondary to previous multiacinar necrosis. B3, Fibrous septa and regenerative nodules show variable appearance. Some of the regenerative nodules show well-defined outline (thin arrows) while blurred interface is observed in many areas (thick arrows) (Picrosirius red, 20×). (B4) Detail of the blurred interface area in image B3, corresponding with marked interface activity (H&E, 200×). (C) Small explanted liver (857 grams) in the clinical context of subacute liver failure secondary to AIH in a 21-year-old male with no underlying chronic liver disease. (B1) Notice the smooth capsular surface in comparison with the liver explants in figure A1 and B1. (C2) Macroscopic appearance of liver sections, showing map-like areas of residual cholestatic (green) parenchyma*, alternating with areas of parenchymal extinction where massive hepatocellular loss has occurred**. (C3) Microscopy of the Glisson's capsule (thin and smooth) and subcapsular parenchyma (area * of figure C2). The hepatic parenchyma shows vague nodularity secondary to bridging necrosis but no evidence of fibrosis, indicating the acute/subacute damage (Picrosirius red, 20×). (C4) Microscopy of the area of collapse (area ** of figure C2), with complete hepatocellular loss in areas of multiacinar necrosis and secondary micro-haemorrhage in the centrilobular area, centred by a terminal hepatic venule (CV). Portal tracts (PT) at the periphery of this area show mild inflammatory component and some degree of ductular reaction (H&E, 200×).

has proven to be an effective therapy for non-acetaminophen-induced ALF, improving transplant-free and post-transplant survival, particularly if used in patients with low grade HE.[110–114] It has also been reported to reduce HE, multi-organ failure and need for intensive care.

Plasma exchange has reportedly been used for acute presentations of AIH. The presence of confounding factors makes it difficult to prove its independent benefit and true role in influencing transplant-free survival.[26,71,115–119]

In the event of corticosteroid failure, the role of alternative immunosuppressive agents, *e.g.* tacrolimus, has not been established. Their use has been reported in some studies, but the numbers are small, and the results are inconclusive.[10]

Infections secondary to corticosteroids in autoimmune-ALF

ALF itself is associated with increased rates of infectious complications.[10,12] In addition, corticosteroid exposure may propagate bacterial septicaemia or fungaemia which subsequently complicates the LT process. Fujiwara *et al.* reported that in 19 patients with AIH-ALF treated with corticosteroids, the cumulative incidence of infections was 6% at 7 days, 17% at 10 days, 35% at 14 days and 54% at 21 days from the induction of corticosteroids. Furthermore, these rates were increased after the onset of grade 2 HE in patients with fulminant hepatitis and late-onset hepatic failure.[120] Whilst on corticosteroids, close monitoring (with

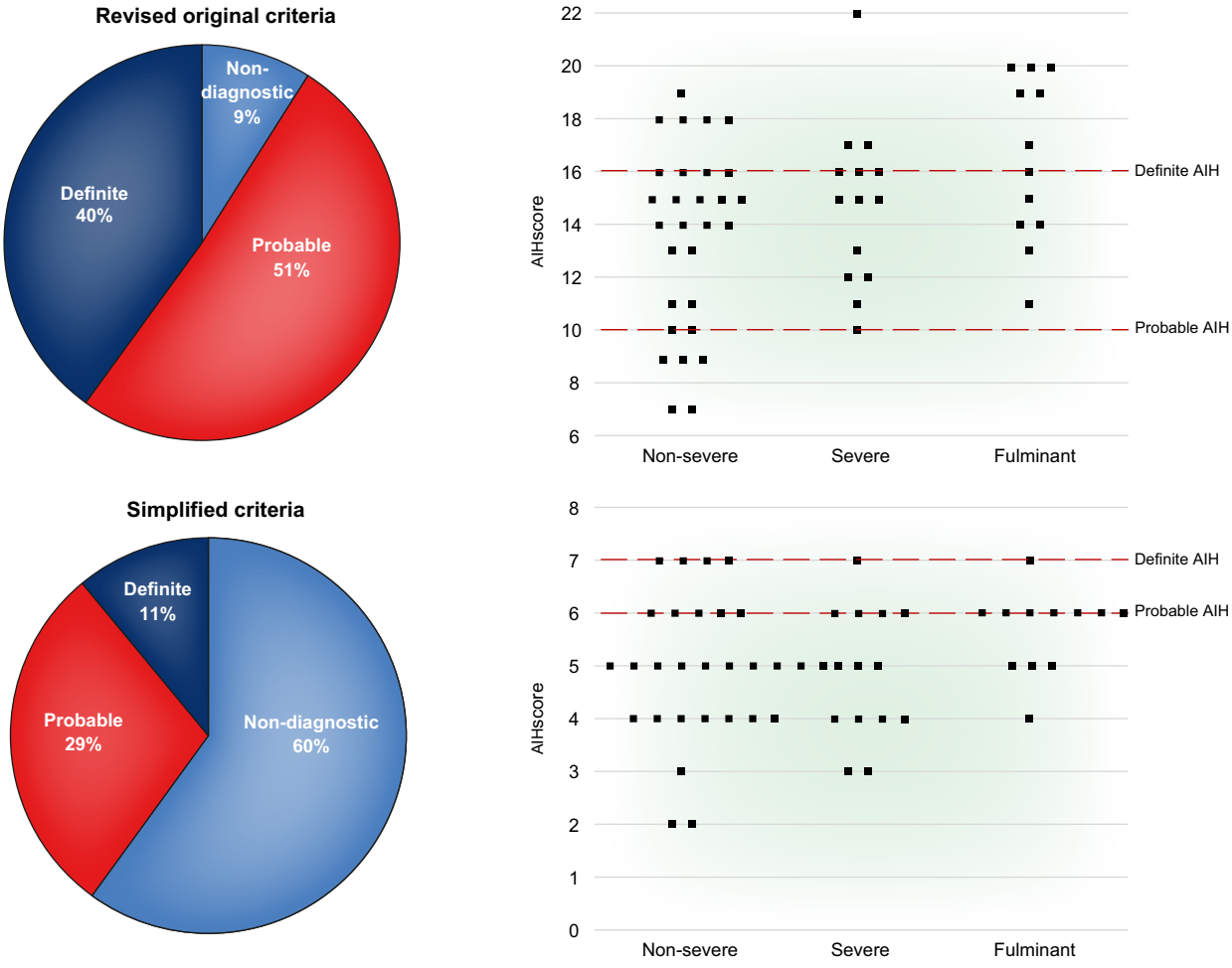

Fig. 6. Comparing the diagnostic sensitivity of the IAIHG criteria in acute-onset AIH. AIH, autoimmune hepatitis; IAIHG, International Autoimmune Hepatitis Group. Reproduced from Fujiwara et al.[89]

bacterial/fungal biomarkers) for sepsis is imperative, with the early instigation of antimicrobials if required. Empirical treatment can be considered, but there is no strong evidence supporting this, in addition to concerns regarding antimicrobial stewardship.

Liver transplantation

With rates of spontaneous recovery as low as 7–15%, LT may be the only effective rescue therapy for some patients with AS-AIH and AIH-ALF.[7,121] LT should not be delayed by protracted courses of corticosteroids. In practice, simultaneous transplant assessment should run parallel to a trial of corticosteroids. Assessment of corticosteroid response early in the disease course is crucial in deciding the right time to pursue LT, ideally before septic complications and irreversible brain injury occur. The decision to proceed to urgent listing should be made within a multidisciplinary setting with intensivists, transplant physicians and surgeons.

Outcomes for LT in AS-AIH and AIH-ALF are similar to those of other aetiologies of ALF (1-year survival 80–94%).[122,123] Although the frequency of post-transplant rejection (acute/late) is increased in patients with AIH compared to those with non-AIH disease, the frequency of rejection is similar between patients with acute or chronic AIH.[124–127] Indeed, some reports have potentially shown survival benefit in those who present with autoimmune-ALF as opposed to chronic AIH with cirrhosis.[127]

Recurrent AIH is common post-LT and can occur in 8–12% of transplanted patients at 1 year and 36–68% at 5 years.[124,125,128–130] Histological examination of the explanted liver (Fig. 5) and correlation with pre-transplant serology provides useful information to the transplant team. Elevated liver enzymes and immunoglobulins before LT, as well as lymphoplasmacytic infiltration with moderate to severe inflammatory activity in explants, may be associated with a greater probability of recurrent AIH post-transplantation.[124–126] One study showed no significant difference in post-transplant AIH recurrence between acute and chronic liver failure secondary to AIH.[124] Ayata *et al.* showed that the presence of severe necro-inflammatory activity in the native liver at the time of LT correlated with a higher AIH recurrence rate.[126] Conversely, Reich *et al.* reported that AIH was less likely to recur in patients who initially presented with ALF compared to those who had chronic disease.[129]

True rates of post-transplant AIH recurrence in autoimmune-ALF are unknown.[124,131–133]

Many advocate the use of long-term corticosteroids post-transplantation to prevent rejection and recurrent disease, however, we know that complete corticosteroid withdrawal is possible after transplantation in chronic AIH.[2,130,134] Successful corticosteroid withdrawal in AS-AIH (not requiring LT) has also been reported.[23]

Paediatric disease

There are no studies evaluating AS-AIH as a specific entity in children/adolescents. However, fulminant AIH has been extensively described.[135–141] During childhood, the mode of AIH presentation can be variable. The differentials of an acute severe hepatitis most commonly include HAV, HBV and Wilson's disease. However, AIH should be suspected and excluded in all children with this presentation.

Type 2 AIH (anti-LKM positivity) is not only more common in children, it is also associated with acute-onset liver failure. Up to 25% of children with a severe acute presentation of AIH have normal IgG at presentation, however, low-titre autoantibodies may still indicate AIH as the aetiology.[142,143] Autoantibody positivity should be interpreted with caution, as autoantibodies can be found in other conditions that lead to ALF in children. One study showed that autoantibodies were detected in most children with HAV (63%), as well as AIH (79%). In the same study, gamma-globulins were significantly higher in the HAV group (1.93 ± 0.57 g/dl), but overall lower when compared to the AIH group (2.93 ± 1.2 g/dl).[144] Smolka *et al.* observed significantly lower levels of albumin, higher levels of bilirubin, INR, IgG and more severe histological findings in their acute AIH group compared to their chronic AIH group, although there was no difference in autoantibody positivity between the groups.[145] Histological features can be similar to adult AS-AIH and AIH-ALF.[135,145]

Corticosteroid therapy can be effective in children with ALF secondary to AIH, although LT is still sometimes required.[146] Paediatric end-stage liver disease scores on admission may be useful in predicting outcome.[147] In a UK-based study, children with fulminant hepatic failure due to AIH were more likely to survive without LT, compared to those with other aetiologies of hepatic failure.[138]

Conclusions

AS-AIH is a rare disorder, and its true incidence and prevalence are unknown. We have attempted to define this condition, but it requires better characterisation and understanding as an entity. It can pose a diagnostic challenge due to its non-specific symptoms, limitations in serology and confounding drug/viral triggers. It has been demonstrated that an autoimmune process may account for a proportion of patients with indeterminant or seronegative ALF. The typical scoring systems for AIH are obsolete in AS-AIH and autoimmune-ALF. If there is diagnostic uncertainty, an early liver biopsy can be informative, ideally before severe coagulopathy and high grade HE develop. Assessment of liver volume with CT is also valuable and requires better understanding as a prognostic tool.

Based on these results, a trial of corticosteroids is justified with early evaluation of response. The optimal corticosteroid dose and route of administration has yet to be determined, although we suspect in the appropriately selected individual, oral corticosteroids should suffice. However, standardisation of therapy is required universally. To assess response, we recommend evaluating the change in bilirubin and MELD-Na score at 7 days. Earlier assessment may be required if the patient deteriorates in the interim. The presence or development of high grade HE is an indication to proceed to urgent LT. We also need to understand the value of alternative therapies and whether they have a role in the treatment algorithm of AS-AIH.

Due to the rarity of the disease, international collaboration through registries and merging of existing data will be required to answer these important questions.

Abbreviations

ACLF, acute-on-chronic liver failure; AIH, autoimmune hepatitis; ALF, acute liver failure; ALI, acute liver injury; ALT, alanine aminotransferase; ANA, anti-nuclear antibody; anti-LC-1, anti-liver cytosol-1; anti-LKM, anti-liver kidney microsomal; AS-AIH, acute severe autoimmune hepatitis; anti-SLA/LP, anti-soluble liver antigen/liver pancreas; ASMA, anti-smooth muscle antibody; AST, aspartate aminotransferase; AUROC, analysis of area under the receiver operator characteristic curve; CT, computed tomography; DILI, drug-induced liver injury; EBV, Epstein-Barr virus; HE, hepatic encephalopathy; HLA, human leukocyte antigen; IAIHG, International Autoimmune Hepatitis Group; INR, international normalised ratio; LT, liver transplantation; MELD, model for end-stage liver disease; MELD-Na, model for end-stage liver disease-sodium; MHN, massive hepatic necrosis; NAC, N-acetylcysteine; PT, prothrombin time; UKELD, United Kingdom end-stage liver disease; USALF, United States Acute Liver Failure.

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Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

MNR: Conceptualization; Visualization; Writing original draft; Writing review & editing. RM: Writing original draft; Writing review & editing; Reviewing histology. MAH: Conceptualization; Supervision; Writing review & editing.

Supplementary data

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Author names in bold designate shared co-first authorship

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