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Autoimmune hepatitis: Brighton Collaboration case definition and guidelines for data collection, analysis, and presentation of immunisation safety data

Sonali Kochhar[a,b,*], **David N. Assis**[c], **Cara Mack**[d], **Hector S. Izurieta**[e], **Luigi Muratori**[f], **Alma Munoz**[g], **Dale Nordenberg**[h], **Jane F. Gidudu**[i], **Erin F. Blau**[i], **John M. Vierling**[j]

[a]Department of Global Health, University of Washington, Seattle, WA, USA

[b]Global Healthcare Consulting, New Delhi, India

[c]Section of Digestive Diseases, Yale School of Medicine, New Haven, CT, USA

[d]Medical College of Wisconsin, Children's Wisconsin, Division of Pediatric Gastroenterology, Hepatology & Nutrition, Department of Pediatrics, Milwaukee, WI, USA

[e]OVRR/CBER/Food and Drug Administration, Silver Spring, MD, USA

[f]DIMEC Università di Bologna and IRCCS Policlinico di Sant'Orsola, Bologna, Italy

[g]Instituto de Salud Pública, Santiago, Chile

[h]Thriive, 250 – 25th Street, West Vancouver, BC V7V 4J1, USA

[i]Global Immunization Division, Centers for Disease Control and Prevention, Atlanta, GA, USA

[j]Departments of Medicine and Surgery, Baylor College of Medicine, USA

Abstract

This report introduces a Brighton Collaboration (BC) case definition for autoimmune hepatitis (AIH), which has been classified as a priority adverse event of special interest (AESI), as there were possible cases seen following COVID-19 vaccination. The case definition was developed by a group of subject matter and BC process experts to facilitate safety data comparability across pre- and post-licensure clinical trials, as well as pharmacovigilance activities in multiple settings with diverse resources and healthcare access. The usual BC case definition development process was followed in an expedited manner, and took two months to complete, including finalising the

[*]Corresponding author at: Department of Global Health, University of Washington, Seattle, WA, USA. sonalikochhar@yahoo.co.in (S. Kochhar).

Disclaimer

The findings, opinions and assertions contained in this consensus document are those of the individual scientific professional members of the working group. They do not necessarily represent the official positions of each participant's organisation (e.g., government, university, or corporation).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2024.01.021.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: CM declares participation in advisory boards for Mirum. SK, DNA, HSI, LM, AM, DN, JG, EB and JV declare no conflicts of interest.

manuscript for publication, instead of the usual 1 year development time. It includes a systematic review of the literature and an expert consensus to define levels of diagnostic certainty for AIH, and provides specific guidelines for data collection and analysis. Histology, serological and biochemical tests and exclusion of alternate diagnosis were considered necessary to define the levels of certainty (definitive, probable and possible). AEFI reports of suspected AIH were independently classified by the WG members to test its useability and these classifications were used to finalise the case definition. The document underwent peer review by external AIH experts and a Reference Group of vaccine safety stakeholders in high-, low- and middle-income countries to ensure case definition useability, applicability, and scientific integrity. The expedited process can be replicated for development of other standardised case definitions for priority AESIs for endemics and epidemics. While applicable to cases reported following immunisation, the case definition is independent of lapsed time following vaccination and, as such, can also be used to determine background incidence for vaccinated and unvaccinated control groups in studies of causal association. While use of this case definition is also appropriate for the study of safety of other products including drugs, it is not meant to guide clinical case management.

Keywords

Autoimmune hepatitis; COVID-19; Vaccine; Adverse event; Case definition; Brighton Collaboration; Liver; Rare disease

1. Introduction

The purpose of this paper is to provide a standard Brighton Collaboration case definition of autoimmune hepatitis (AIH), which is an inflammatory liver disease of unknown aetiology. AIH has recently been identified as a priority adverse event of special interest (AESI) following COVID-19 vaccination. Genetic, environmental and immunological factors appear to interact to trigger the disease. Autoimmunity to hepatocytes resulting in hepatitis with parenchymal destruction and potentially fibrosis of the liver.

Table 1 summarises the key objectives, features, intended applications and limitations that apply to the AIH Brighton Collaboration case definition, which follows previously published processes [1,2].

2. Rationale for developing a new Brighton Collaboration case definition for autoimmune hepatitis as an adverse event

Interest in autoimmune hepatitis (AIH) increased during the SARS-CoV-2 pandemic since it emerged as a possible adverse event following coronavirus disease 2019 (COVID-19) and a possible rare adverse event following COVID-19 vaccination, as per case reports. [3–6]. As there is no universally accepted definition of AIH and the need for a case definition is a priority, the Brighton Collaboration AIH Working Group has developed a case definition for AIH using an expedited process. A common case definition is essential to ensure data comparability across trials and surveillance systems to facilitate accurate data interpretation and promote the scientific understanding of the event.

3. Methods for development of the autoimmune hepatitis case definition

The Brighton Collaboration AIH Working Group (WG) was formed in August 2023 by invitation from the Global Immunization Safety Team, U.S. Centers for Disease Control and Prevention. The final WG consisting of clinicians (adult and paediatric hepatologists with expertise in auto-immune hepatitis), and academic, vaccine safety, pharmacovigilance, public health and regulatory experts from high-, and low- and middle-income-countries. A literature search was performed using established search engines and databases. Because the case definition was considered a priority to support ongoing suspect case validation, it was developed in an expedited manner (with a 83 percent shorter time period), using all the standard processes for developing Brighton Collaboration case definitions The AIH WG met weekly to develop the case definition and guidelines based on expert consensus and review of the evidence from the literature search. The WG members independently classified AEFI reports of suspected AIH using the preliminary case definition to test its useability. These classifications contributed to finalising the case definition, which then underwent external review by the Brighton Collaboration reviewers and external AIH expert peer reviewers in high-, low-and middle-income countries. The AIH WG reviewed and incorporated the feedback into the final case definition. This expedited process allowed development of the case definition and finalisation of the manuscript for publication within two months, rather than the usual 1-year development time. Thus, this expedited process can be used to develop other standardised case definitions for priority AESIs for endemics and epidemics.

4. Definitions and general description of autoimmune hepatitis

4.1. Autoimmune hepatitis

AIH is an inflammatory liver disease of unknown aetiology, in which loss of immune tolerance to hepatocytes results in inflammatory parenchymal destruction. It may be triggered by genetic, immunological, and environmental factors, including infections, toxins and drugs [7]. Diagnosis is based on a combination of histopathology, serological and laboratory testing and exclusion of other diagnosis that exhibit similar features, as there is no pathognomonic diagnostic biomarker for AIH. Characteristic histological features on a liver biopsy (a simple bedside procedure, often done under local anaestheisa on an outpatient basis with post procedure observation, where a heathcare provider uses a hollow needle to draw a small tissue sample from the liver, which is studied under a microscope by a pathologist) include portal tract infiltrates containing lymphocytes and plasma cells, prominent interface hepatitis (i.e., extension of inflammation into the parenchyma causing destruction of hepatocytes at the interface of the portal tracts and hepatic parenchyma), and expansion of portal zone connective tissue. Biochemically, this is accompanied by elevated aminotransferase levels and hypergammaglobulinemia, and serologically by tissue-directed autoantibodies [8–12]. Timely diagnosis and initiation of appropriate therapy are important; however, diagnosis can be challenging because of the variability of clinical, biochemical, serological and histological features and absence of a specific diagnostic test and liver biopsies not beng done commonly in many low income settings. If left untreated, AIH can result in cirrhosis, complications of portal hypertension, and either liver transplantation

or death. Hepatocellular carcinoma has also been reported in 0.2–12.3 % of patients with cirrhosis caused by AIH [13].

Clinical and biochemical remissions are feasible in up to 85 % of patients, reducing the need for transplantation [11]. Reports from large datasets indicate 60–68 % biochemical remission to standard of care immunosuppression for AIH [14].

Clinical features are non-specific and vary among patients, ranging from asymptomatic hepatitis to acute liver failure. Signs and symptoms may include anorexia, fatigue, malaise, arthralgia involving small joints, nausea, vomiting, abdominal pain, weight loss, transient erythematous rash, hepatomegaly, splenomegaly, jaundice, and amenorrhea in women [15]. Other extrahepatic autoimmune diseases are common, including autoimmune thyroiditis, rheumatoid arthritis, vitiligo, Sjogren's syndrome, systemic lupus erythematosus (SLE), ulcerative colitis, celiac disease, Crohn's disease, psoriasis and type 1 diabetes [16,17].

4.2. Autoimmune hepatitis and SARS-CoV-2 infections

In the complex pathophysiology of autoimmune diseases, infections are the most important environmental trigger, especially in individuals with genetic susceptibility [18]. Potential mechanisms to explain how infections might provoke autoimmune reactions include cross-reaction or molecular mimicry, bystander activation, epitope spreading, and presentation of cryptic antigens [19]. AIH has been reported in patients with Epstein-Barr virus (EBV) and hepatitis C infections [20,21].

Associations between SARS-CoV-2 infection and the development of autoimmunity have been reported [18,22–24]. Autoinflammatory dysregulation appears to have contributed to tissue damage in several cases of SARS-CoV-2 infection [22]. It is thought that SARS-CoV-2 could act as a triggering factor for autoinflammatory dysregulation in genetically predisposed individuals [25]. AIH has been reported in patients following SARS-CoV-2 infection, including in unvaccinated patients, but has rarely occurred after COVID-19 vaccination [3,26–29]. Molecular mimicry between viral and human proteins, immunological intolerance, cytokine release syndrome or cytokine storm, epitope spreading, bystander activation, and purported hepatotropism of SARS-CoV-2 are some of the postulated mechanisms for these occurrences [22,30,31]. However, the concurrent use of drugs, such as antibiotics and statins that can trigger autoimmunity, are confounding factors, raising questions on the possible causality, thus, no consensus has been reached [32,33].

5. Autoimmune hepatitis background information relevant to the case definition and guidelines on data collection, analysis and presentation

The following sections focus on evidence considered key to constructing the case definition and developing the associated guidelines.

5.1. Epidemiology

AIH, a rare liver disease with a global distribution, affects both sexes and all ages [34]. This disease mainly affects females, irrespective of age, race or ethnicity, and the female-to-male ratio may be as high as 10:1 in adults [35,36].

The reported annual incidence of AIH ranges from 0.67 cases per 100,000 persons in Israel to 2.0 cases per 100,000 persons in New Zealand [37,38]. The reported prevalence of AIH ranges from 4.0 cases per 100,000 persons in Singapore to 42.9 cases per 100,000 persons in Alaska [35,39].

Pooled annual incidences are 1.31, 1.37, and 1.00 per 100 000 persons for Asian, European, and American populations, respectively. Pooled prevalences are 12.99, 19.44 and 22.80 per 100 000 persons, respectively [40]. With limited diagnostic capacity and a shortage of medical specialists, there is a lack data from low- and middle-income countries (LMICs) and the global incidence and prevalence of AIH is likely underestimated [41].

Results from population-based studies in Denmark and in England suggest that the incidence of AIH is increasing [42,43]. In Denmark, the incidence increased from 1.37 per 100,000 population in 1994 to 2.33 per 100,000 population in 2014 and in England the incidence doubled from 1.27 per 100,000 population to 2.56 per 100,000 population from 1997 to 2015.

Although AIH can develop at any age, a bimodal peak of onset has been observed during the second and sixth decade of life [34].

5.2. Risk factors and aetiology

AIH is a complex, multifactorial disorder thought to develop in genetically predisposed individuals who encounter one or more triggering factors [44]. A genetic predisposition involving alleles of the HLA-DRB1 gene is frequently observed in patients with AIH, particularly DRB1*03:01 and DRB1*04:01 in white North Americans and northern Europeans. However, this genetic association is not disease-specific or always present, and therefore, it has been suggested that additional HLA and non-HLA associations may be present. Environmental factors, such as viral infections, dietary deficiencies, toxins, drugs, alcohol, smoking, ionising radiation, and air pollution are likely to play a role in the aetiology of AIH, possibly inducing critical epigenetic modifications [44]. In addition, molecular mimicry between linear or conformational epitopes of environmental pathogens, vaccines, and gut-derived microbial products may lead to epigenetic modifications which are potential causative mechanisms of AIH [45].

5.3. Pathophysiology and pathogenesis

AIH is regarded as a model autoimmune disease, but its immunopathogenesis is poorly understood [46]. AIH arises in persons with immunogenetic susceptibility to autoimmunity. Hepatocyte autoantigens presented in the antigen-binding grooves of HLA class I and class II molecules on professional antigen-presenting cells (APCs) activate autoreactive T cell receptors (TCRs) of CD4 T helper (Th) subsets and CD8 cytotoxic T lymphocytes (CTLs). Concurrently, different autoantigens bind to B cell immunoglobulin receptors and activate

B cells to secrete autoantibodies. A proinflammatory milieu of cytokines and chemokines produced by environmental triggers, such as viral infections, xenobiotic exposures, and dysbiosis of the gut, appear essential for such breaks in self-tolerance to autoantigens. AIH has been reported after vaccination for influenza [47,48], hepatitis A virus (HAV) [49–51], hepatitis B virus (HBV) [51], human papilloma virus (HPV) [52], yellow fever [50], and diphtheria, pertussis, and tetanus (DPT) [50,51]. There have been case reports of AIH following COVID-19 vaccination sugesting a theoretical possibility of an association with the vaccines [26].

Progressive AIH has been attributed to failure of induced CD4 regulatory T cells (iTregs) to control and terminate the autoreactive immune response [53]. Of note, the inhibitory function of autoantigen specific CD4 iTregs in AIH can also be subverted by cytokine-mediated transformation of CD4 iTregs into pathogenic CD4 Th17 cells.

Susceptibility to AIH and other autoimmune diseases map to HLA alleles indicating their importance in presentation of hepatic autoantigens to T cells [54]. However, AIH is complex genetic disease associated with both HLA and non-HLA gene polymorphisms as well as epigenetic changes [55].

Following autoantigen activation and costimulation of CD 4 Th0 cells and CD8 CTLs, the T cells proliferate and differentiate into fully functional, autoantigen-specific effector cells. The local cytokine microenvironment dictates whether proliferating CD4 Th cells differentiate into CD4 Th1, Th2, Th9, Th17, iTregs, or T follicular helper (Tfh) cell subsets. The dynamic balance among CD4 Th subsets determines the type, intensity, and duration of local immune responses. CD4 Th1 cytokines stimulate proliferation of CD4 Th subsets, CD8 CTLs, activate cytotoxic macrophages and inhibit CD4 Th2 cells. Conversely, CD4 Th2 cytokines increase immunoglobulin secretion by B cells and inhibit CD4 Th1 cells. CD4 iTregs downregulate antigen-specific inflammatory responses. Conversely, Th9 cells increase and sustain inflammation and tissue injury. CD4 Th17 cells disproportionately intensify inflammation and cytotoxicity. CD4 Tfh convert activated B cells into plasma cells. Finally, B cells also secrete cytokines and act as APCs to amplify immune responses.

Non-autoantigen-specific effector cells also may contribute to the pathogenesis of AIH. Mucosal-associated invariant T (MAIT) cells have invariant TCRα chains that react with vitamin B antigens processed by gut bacteria presented by major histocompatibility (MHC) class I-related (MR-1) molecules on APCs. MAIT cells can transdifferentiate to express dual characteristics of CD4 Th1 and CD4 Th17 cells after exposure to proinflammatory cytokines. MAIT cell expression of cytotoxic granzyme B granules and the ability to induce cholangiocyte secretion of cytokines that transform CD4 iTregs into pathogenic CD4 Th17 cells also suggest pathogenic roles. Finally, cytokine-activated macrophages function as antigen-nonspecific cytotoxic cells.

Immunopathogenic mechanisms in AIH culminate in necro-inflammatory destruction of hepatocytes from the combined effects of cell-mediated, antibody-mediated and cytokine-mediated cytotoxicity [46]. The pathogenic role of antibody-mediated cytotoxicity in AIH is debated since there is no evidence that autoantibodies are directly cytotoxic for hepatocytes.

However, non-cytotoxic autoantibodies could cause antibody-dependent cellular cytotoxicity mediated by NK cells.

The pathophysiological consequences of immunopathogenesis in AIH can manifest in diverse presentations, including acute liver failure (ALF), severe acute AIH or chronic hepatitis [56]. Insidious progression may also result in cirrhosis prior to diagnosis. ALF due to AIH is characterised by extensive hepatocellular necrosis. Severe acute AIH typically has dense portal lymphoplasmacytic inflammatory infiltrates, signficant interface hepatitis, lobular hepatitis and perivenulitis of the central veins (Fig. 1). Chronic AIH hepatitis typically has lymphoplasmacytic portal inflammation, moderate to severe interface hepatitis, variable amounts of lobular hepatitis and, infrequently, central perivenulitis (Fig. 1). Portal inflammatory infiltrates are composed of CD4 Th1 cells, CD8 CTLs, B cells, plasma cells, MAIT cells, and innate immune cells (e.g., activated macrophages, NK and NKT cells).

The infiltrates extending into the parenchyma in interface hepatitis are composed of CD8 CTLs, CD4 Th subtypes and plasma cells.

AIH is a progressive disease in the absence of effective immunosuppressive treatment. ALF or severe acute hepatitis may be rapidly lethal (5), and liver transplantation is the only life-saving option [56]. In chronic AIH, necro-inflammatory destruction of hepatocytes activates periportal stellate cell differentiation into fibrogenic myofibroblasts. Extension of periportal fibrosis results in fibroinflammatory bridging between portal tracts and between portal tracts and central veins. Ultimately, fibrosis transitions to cirrhosis, defined as nodules of regenerating hepatocytes contained by circumferential fibrosis. Cirrhosis confers new risks for complications of portal hypertension, hepatocellular carcinoma, and liver failure [57]. Decompensated cirrhosis, defined by the onset of complications of portal hypertension (i.e., ascites, gastroesophageal bleeding, hepatic encephalopathy, or jaundice), markedly increases risks of liver-related death and need for liver transplantation.

5.4. Clinical presentation and variations in presentation/forms

The clinical presentation of AIH is heterogeneous, ranging from asymptomatic patients with chronic, mild elevation of serum liver enzymes to patients presenting with acute liver failure (ALF) [15]. The majority present with a gradual onset of nonspecific symptoms such as fatigue and arthralgias. Typically, at presentation, there are no signs of AIH on physical examination other than those indicative of cirrhosis, when advanced liver disease has already developed. Up to a third of newly-diagnosed AIH patients report no symptoms at all, though this subgroup of patients may develop symptoms within 1–3 years. Those with asymptomatic presentation may have indistinguishable histologic findings compared to patients who present symptomatically [58]. When AIH is undetected for a prolonged period there is a greater likelihood of cirrhosis at diagnosis and subsequently a reduced survival over time [59,60].

A subset of patients with AIH present with acute hepatocellular jaundice. This new-onset jaundice, if accompanied by INR elevation ≥ 1.5 and in the absence hepatic encephalopathy, is termed acute severe AIH [61]. It is important to be aware that several typical features of AIH, including hypergammaglobulinemia, and ANA positivity, are often absent early in the

course of severe acute AIH [61]. Furthermore, histological features may show prominent central perivenulitis and centrilobular necrosis with a less prominent or even absent plasma cell-rich interface hepatitis in the acute phase [62]. A minority of patients with AIH (3–6 %) present with ALF, defined as hepatocellular jaundice with INR ≥ 2 and the presence of hepatic encephalopathy that develops within 26 weeks of the onset of disease in a patient with no previously recognized liver abnormalities [63]. Patients with acute severe AIH and ALF require immediate treatment with corticosteroids and close assessment of treatment response to determine the need for urgent liver transplant evaluation [63,64].

The clinical course of AIH is characterized by a high risk of relapse following withdrawal of immunosuppression, even after years of successful treatment, a risk that exceeds 80 % [PMID: 22989569]. Therefore, patients with AIH who do not have a clear drug-induced aetiology often require indefinite immunosuppression, and for some patients a biopsy prior to attempted withdrawal can be performed [15]. Lastly, withdrawal of immunosuppression is contraindicated in patients who initially presented with hepatocellular jaundice and acute liver failure, given that relapses in these patients can be as severe and life-threatening as the initial presentation.

5.5. Diagnosis of autoimmune hepatitis and existing case definitions

The diagnosis of AIH requires both a constellation of supportive clinical, biochemical, serological and histological findings and the exclusion of alternate causes of hepatic inflammation. There is currently no single pathognomonic diagnostic marker for AIH, however key features are observed in most cases. These include characteristic histopathological findings on liver biopsy such as interface hepatitis with lymphocytes and plasma cells (Fig. 1), elevation of serum AST and ALT, elevation of serum immunoglobulin G (IgG), and the presence of one or more autoantibodies with a titer greater than 1:40 including antinuclear antibody (ANA), smooth muscle antibody (SMA) or anti-f-actin antibody, anti-liver kidney microsome (LKM-1), or anti-soluble liver antigen (SLA). Although not a part of formal diagnostic criteria, more than 40 % of AIH patients have a concurrent autoimmune disease or family history of the same, particularly autoimmune thyroid disease, celiac disease, type 1 diabetes, rheumatoid arthritis, and vitiligo [17]. AIH has been traditionally classified on the basis of autoantibodies into AIH Type 1, characterized by ANA or SMA positive autoantibody, and Type 2, characterized by LKM-1 antibody. However, the clinical importance of these serological subgroups is unclear except in paediatric populations.

In the United States, up to 80 % of adults with AIH have detectable ANA [65]. However, ANA is also commonly detected in patients with several other autoimmune disorders including systemic lupus erythematosus, in families of patients with autoimmune disease, and in the general population, and, therefore, it is not diagnostic of AIH in isolation. The presence of more than one autoantibody (e.g., ANA and SMA) increases the likelihood of AIH, although histological confirmation is still required for diagnosis. It is relevant to note that 20–30 % of patients with metabolic dysfunction-associated steatotic liver disease (MASLD) may exhibit non-specific elevation of autoantibodies including ANA and SMA as an epiphenomenon and not a manifestation of AIH [66]. The performance of the traditional

immunofluorescence testing (IFT) on rodent tissue has recently been compared with newer methods such as IFT on human epithelioma-2 (HEp-2) cells and ELISA-based testing [67].

Despite the typical occurrence of elevated ANA, SMA, or anti-LKM1, the absence of these antibodies has been described in up to 30 % of cases, including cases initially classified as cryptogenic [68]. In such patients, testing for anti-SLA may be particularly useful because it may be the sole autoantibody detected in up to 20 % of patients and therefore is highly specific for AIH [69]. Even with testing for SLA, however, a significant minority of patients with AIH are autoantibody negative. The diagnosis of AIH in these seronegative patients can still be made based on other supporting evidence, particularly histopathologic findings.

Between 10 and 20 % of patients with AIH have a normal serum IgG level. Thus, the absence of IgG elevation does not preclude the diagnosis of AIH. In such instances, the clinical features are often comparable to those with AIH and IgG elevation. However, a recent study suggested that IgG-negative patients have a higher likelihood of successful withdrawal of immunosuppression over time [70]. IgG elevation is not only helpful in the diagnostic process in most patients, but can be used as a biomarker of treatment response, with normalization of both ALT and IgG defining a complete biochemical response [71].

Although persistent elevations serum of AST and ALT are usually found in patients with newly diagnosed AIH, the degree of elevation is not a valid indicator of the severity of hepatic injury or fibrosis, particularly in those with non-acute presentations. Furthermore, a subset of patients may have significant histological inflammation due to AIH despite normal ALT, particularly in the setting of cirrhosis [72].

The International Autoimmune Hepatitis Group (IAIHG) has developed the most well-known scoring systems for the diagnosis of AIH. Three iterations have been published to date including the original (1993) [73], revised (1999) [74], and simplified (2008) [75] diagnostic systems. The revised original scoring system is more extensive and may be particularly helpful for patients with less typical presentations. The revised scoring system also includes response to immunosuppression therapy and relapse after immunosuppression withdrawal, as confirmations of the diagnosis. The simplified scoring system focuses on the core features of typical AIH patients: autoantibody titers, IgG, histology, and negative tests for viral hepatitis. It should be noted that neither scoring systems has been prospectively validated. In addition, these systems were also not designed to differentiate AIH from MASLD, which is currently relevant globally as both a comorbid liver disease and as a differential diagnosis of AIH.Table 2

5.6. Differential diagnosis of autoimmune hepatitis

All other causes of chronic hepatitis must be excluded before diagnosing AIH since its aetiology is still unknown [76]. Without a pathognomonic test for AIH, an accurate diagnosis requires exclusion of other causes, as well as indicative clinical, serological, biochemical, and histological findings [77]. Several factors, such as, viral hepatitis, drug induced liver injury, alcohol associated hepatitis, metabolic and other autoimmune liver disease, should be considered in the differential diagnosis.

Some studies indicate that hepatitis viruses (hepatitis A, B, C, E), cytomegalovirus, and Epstein–Barr virus can be initiators of AIH [20,60,78]. Postulated pathogenic mechanisms include molecular mimicry, whereby immune responses to pathogens are pathogenically redirected towards structurally similar self-antigens and immune presentation of autoantigens or virally-induced neoantigens from dying hepatocytes [79].

Several drugs have been associated with the development of a condition resembling AIH. Nitrofurantoin and minocycline have been associated with induction of AIH. Other drugs and herbal remedies have also been occasionally reported to induce AIH, including oxyphenisatin, ornidazole, methyldopa, diclofenac, interferon, atorvastatin, highly active antiretroviral treatment, and biologic agents such as infliximab, natalizumab, and adalimumab [80]. At least three clinical scenarios have been proposed that refers to drug induced autoimmune liver disease (DIAILD) [81]:

- AIH with drug-induced liver injury (DILI);
- Drug induced-AIH (DIAIH); and
- Immune mediated DILI (IM-DILI)

The clinical features of drug-induced liver injury are indistinguishable from idiopathic AIH as both can have positive AIH-related autoantibodies, elevated IgG, as well as similar histopathological findings. In patients who show no clinical improvement, or have progressive liver injury stopping the suspected drug, a liver biopsy should be considered [82].

Products of alcohol metabolism, acetaldehyde, alcohol dehydrogenase, and malondialdehyde (MMA), can induce autoantibodies in humans and experimental models [83]. AIH should be considered in patients with alcohol use, as these patients seem to have worse prognosis than those with AIH alone. Reliable autoantibody testing and cautious interpretation of liver histology are essential for AIH diagnosis in these difficult to diagnose patients [84].

Wilson’s disease (WD) should be considered when investigating chronic liver disease with negative viral serologies and if the patient only partially responds to initial therapy with prednisone [85]. Alpha-1-antitrypsin (A1AT) deficiency may cause a chronic pattern of hepatic injury. It is not uncommon to have co-existing heterozygous A1AT deficiency in patients with other liver diseases, such as viral hepatitis, AIH, or alcohol abuse [86]. Hemochromatosis, a genetic disease of iron metabolism, can cause asymptomatic elevation of liver transaminase levels due to iron deposition in the liver. Initial testing should include serum iron and ferritin levels, and total iron-binding capacity [87].

Autoimmune liver diseases may coexist or develop in patients with other chronic liver disease. A very small proportion of patients with AIH may show prominent cholestatic features, suggesting coexistent overlapping primary biliary cholangitis (PBC) or primary sclerosing cholangitis (PSC) [80].

It is not uncommon for AIH patients to have other extrahepatic autoimmune conditions [88]. The association of AIH with celiac disease (CD) is well established, and individuals with AIH have a higher prevalence of CD compared with the general population [88,89].

Thyroid dysfunction is also more prevalent in patients with AIH than in healthy individuals [90]. However, it is unclear if AIH is caused by thyroid dysfunction or vice versa. Patients diagnosed with AIH should be screened for thyroid dysfunction.

6. Rationale for Working Group decisions about the case definition of autoimmune hepatitis

6.1. Formulating a case definition that reflects diagnostic certainty

The case definition, which is applicable for adult, adolescent and paediatric populations, has been developed so that the Level 1 definition is highly specific for AIH. Since high specificity usually results in sensitivity loss, two additional diagnostic levels have been included in the definition. To capture all cases of AIH, an acceptable level of specificity at all levels was maintained, despite stepwise increases of sensitivity from Level 1 down to Level 3. This is shown in Table 3 and the pictorial algorithm in Fig. 2.

6.2. Rationale for selected decisions about the case definition for autoimmune hepatitis as an adverse event of special interest following immunisation

The Level 1 classification can be reached by presence of characteristic liver histology, serum biochemical tests (including ALT or AST, and IgG above their upper limits of normal (ULN), presence of one or more autoimmune antibodies and assessment by a medical specialist (e.g., hepatologist, gastroenterologist) treating the patient to exclude alternative diagnoses with similar features. The Working Group determined that expertise in conducting a proper evaluation and excluding alternative diagnosis for the illness are necessary to establish a Level 1 diagnosis.

The difference between Level 1 and Level 2 classifications is that the IgG can be within normal limits. It should be noted that in some settings, including acute presentations in paediatric patients and in a subset of adult patients with AIH, serum IgG can be persistently normal.

An important distinction between Level 2 and Level 3 is either negative autoantibody test results or absence of results due to the inability to perform autoantibody testing [91]. Therefore, Level 3 of diagnostic certainty requires the presence of characteristic or atypical liver histology and elevated serum ALT or AST (above the ULN), while IgG may be within normal limits or above the ULN, negative results or inability to perform testing for autoimmune antibodies and assessment by a non-specialist medical professional to rule out alternative diagnoses.

Level 4 is met when the AIH Levels 1–3 have not been met. Level 4 signifies a reported AIH case with insufficient evidence to meet the case definition. This may include reports which document AIH without a description of any relevant tests or exclusion of alternative diagnosis for illness. Level 5 is met when the AEFI is definitely ‘not a case of AIH’. This is to be applied when sufficient information has been provided for review and an alternate diagnosis is clearly present. The case definition is not specific to vaccination and needs

to be applicable prior to initiation of treatment, hence criterias specific to vaccination and treatment have not been included in the levels of certainity.

Alternative diagnoses for AIH can include viral hepatitis (which is the most common, including hepatitis A, B, C, E, Epstein Barr or cytomegalovirus), drug-induced liver injury, alcohol-associated hepatitis, metabolic liver diseases, including Wilson's disease, Alpha-1-antitrypsin deficiency, hereditary hemochromatosis and iron overload, and auto-immune liver diseases like celiac disease, primary biliary cholangitis (PBC), and primary sclerosing cholangitis (PSC).

7. Rationale for individual criteria or decisions made related to the case definition

7.1. Diagnostic testing

A medical professional treating the patient (i.e. a medical specialist e.g., hepatologist, gastroenterologist for level of certainty 1 and 2 and a non-specialist medical professional for level of certainty 3) must assess test results to exclude possible alternative diagnoses. It is important to use standardised diagnostic tests. The specific tests possible for viral hepatitis are described in the case definition (Table 3).

7.1.1. Pathology, radiology, and laboratory findings—The Working Group established that both histopathology and laboratory testing are necessary to establish a diagnosis of AIH, as described in the case definition. No radiographic or imaging tests are required.

7.1.2. Influence of treatment on fulfilment of case definition—The Working Group decided against including response to immunosuppression as a diagnostic criterion for the AIH case definition because a substantial response to immunosuppression is not always observed in AIH.

7.1.3. Timing post immunisation—For case definitions to be a suitable tool for assessing causality, the ascertainment of the outcome (i.e., AIH) needs to be independent of the exposure (e.g., immunisation). In addition, AIH often occurs outside the controlled setting of a clinical trial, where it might be difficult to obtain a clear course for the event. To avoid selection bias, a restrictive time interval from immunisation to onset of AIH should not be an integral part of the case definition. Where feasible, details of this interval should be assessed and reported as described in the data collection guidelines. (Appendix A).

7.1.4. Considerations for limited resource settings—Lack of access to and availability of diagnostic procedures, including liver biopsies, and testing, and medical specialists, significantly diminishes the ability to meet the AIH case definition criteria in certain clinical or surveillance settings. Because the diagnostic criteria required to meet the AIH case definition includes liver histology and serum biochemical testing at all levels of certainty, implementation is more feasible in clinical and surveillance settings in major metropolitan areas or in well-funded private institutions. Despite these limitations, the AIH

Working Group strongly endorsed the need for liver histology and serum biochemical testing for Levels 1–3 because of the need to exclude other possible diagnoses that can mimic AIH. The AIH Working Group also considered the global variability in clinical practice and availability of autoimmune serological testing required to meet Levels 1 and 2 of certainty and included inability to perform autoimmune serological testing to meet Level 3 of certainty. Identification of a pathognomonic biomarker for AIH will be required for new case definitions that are applicable for surveillance implementation in low- and middle-income countries.

7.2. Considerations for special populations

7.2.1. Paediatric populations—AIH in children has many unique aspects compared to adults. The prevalence of AIH in children is much lower than in adults, with a frequency of ~3 cases per 100,000 people [92]. The proportion of children with seronegative AIH is also high, ranging from 15 % to 30 % of all paediatric cases [92]. Absence of autoantibody positivity makes the diagnosis of AIH more challenging. In contrast, the frequency of type 2 AIH (anti-LKM or anti-liver cytosol positivity) is much higher in children, especially those who present at a younger age with ALF or severe acute hepatitis [79].

7.2.2. Pregnant women—The onset of AIH presenting during pregnancy or postpartum is very rare but can be life-threatening, since it may present as ALF. Most pregnant women with pre-existing AIH have a more indolent course. However, some women experience a flare of AIH while pregnant, and those with cirrhosis have an increased risk of complications of portal hypertension due to increased blood volumes and cardiac output in pregnancy [93]. It is important to confirm that AIH is the correct diagnosis, and to consider other liver diseases occurring in pregnancy, such as acute viral hepatitis, thrombotic liver disease, intrahepatic cholestasis of pregnancy, acute fatty liver of pregnancy and HELLP syndrome (hemolysis, elevated liver tests, low platelets) [94].

7.2.3. Immunodeficiency populations—The majority of immunodeficiencies associated with the development of AIH are due to genetic defects [92]. Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome results from mutations in the AIRE gene and up to 20 % of these patients will develop AIH. Immunodysregulation polyendocrinopathy enteropathy X-linked syndrome, caused by FOXP3 mutations, results in deficient functioning of Tregs with multi-system autoimmunity, including AIH. Common variable immunodeficiency can cause an autoimmune phenotype. It is essential to have a high index of suspicion for an underlying immunodeficiency in the setting of AIH with other concurrent autoimmune diseases or recurrent infections.

8. Definition of selected criterion terms

8.1. Brighton Collaboration case definition of autoimmune hepatitis

The case definition is summarised in Table 3 and Fig. 2.

AIH is a clinical syndrome characterised by inflammatory liver disease. There is no single or unique diagnostic biomarker for AIH. The AIH Working Group considered that a

characteristic liver histology is required to meet Levels 1 and 2 of certainty and that a characteristic or atypical liver histology is required to meet Levels 3.

8.2. Guidelines for data collection, analysis and presentation specific to autoimmune hepatitis

Brighton Collaboration guidelines for data collection, analysis and presentation of vaccine safety data accompany the case definition. These are structured according to the steps of conducting a clinical trial, i.e., data collection, analysis and presentation. The case definition and the guidelines were developed to improve case ascertainment and data comparability in epidemiological, observational or interventional research. They are not intended to establish criteria or guide the clinical management of infants, children, or adults with AIH.

8.3. Data collection

A case report form specific to the criteria needed to fulfil the AIH case definition can be found in Supplementary material.

To ensure that data on key case definition are collected in comparable fashion the working group recommends the following

Guidelines numbers 1–43 below have been developed to address data elements for the collection of adverse event information as specified in general drug safety guidelines by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use,[i] and the form for reporting of drug adverse events by the Council for International Organizations of Medical Sciences. [ii] These data elements include an identifiable reporter and patient, one or more prior immunisations, and a detailed description of the adverse event of AIH following immunisation. The additional guidelines have been developed as guidance for the collection of additional information to allow for a more comprehensive understanding of AIH following immunisation.

8.4. Source of information/reporter

For all cases and/or all study participants, as appropriate, the following information should be recorded:

1. Date of report.
2. Name and contact information of person reporting and/or diagnosing the AIH as specified by country-specific data protection law.
3. Name and contact information of the investigator responsible for the subject, as applicable.
4. Relation to the patient (e.g., immunizer [clinician, nurse], family member [indicate relationship], other).

[1] [i]ICH. Post-approval safety data management: definitions and standards for expedited reporting E2D 2003 Accesed on 23 Oct 2023 at https://www.ema.europa.eu/en/ich-e2d-post-approval-safety-data-management-scientific-guideline
[ii]CIOMS. Accessed on 23 Oct 2023 at: https://cioms.ch/wp-content/uploads/2019/11/Fillable-Form_CIOMS-to-E2B.pdf.

Vaccinee or control

Demographics: For all cases or study participants, as appropriate, the following information should be recorded:

5. Case/study participant identifiers (e.g., first name initial followed by last name initial) or code (or in accordance with country-specific data protection laws).
6. Date of birth, age, and sex.
7. For infants: gestational age and birth weight.

Clinical and immunisation history: For all cases or study participants, as appropriate, the following information should be recorded:

8. Past medical history, including hospitalizations, underlying diseases/disorders, pre- immunisation signs and symptoms including identification of indicators for, or the absence of, a history of allergy to vaccines, vaccine components or medications; food allergy; allergic rhinitis; eczema; asthma.
9. Any medication history (other than treatment for the event described) prior to, during, and after immunisation including prescription and non-prescription medication as well as medication or treatment with long half-life or long-term effect. (e.g., immunoglobulins, blood transfusion and immunosuppressants).
10. immunisation history (i.e., previous immunisations and any adverse event following immunisation (AEFI)), in particular occurrence of AIH after a previous immunisation.

Details of the immunisation: For all cases or study participants, as appropriate, the following information should be recorded:

11. Date and time of immunisation(s).
12. Description of vaccine(s) (name of vaccine, manufacturer, lot number, dose (e.g., 0.25 mL, 0.5 mL) and number of dose if part of a series of immunisations against the same disease).
13. The anatomical sites (including left or right side) of all immunisations (e.g., vaccine A in proximal left lateral thigh, vaccine B in left deltoid).
14. Route and method of administration (e.g., intramuscular, intra-dermal, subcutaneous, and needle-free (including type and size), other injection devices).
15. Needle length and gauge.

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16. For all cases at any level of diagnostic certainty and for reported events with insufficient evidence, the criteria fulfilled to meet the case definition should be recorded.

The following should be specifically documented:

17. Clinical description of signs and symptoms of AIH, and if there was medical confirmation of the event (i.e., patient seen by specialist or other physician or qualified healthcare provider).

18. Date/time of onset[iii] of the first symtom, first observation[iv] and diagnosis[v], end of episode[vi] and final outcome[vii].

19. Concurrent signs, symptoms, and diseases.

20. Measurement/testing:

    - values and units of routinely measured parameters (e.g., temperature, blood pressure) – in particular those indicating the severity of the event;
    - method of measurement (e.g., type of thermometer, oral or other route, duration of measurement);
    - results of laboratory examinations, histological findings characteristic or atypical for AIH reported by the pathologist reviewing the liver biopsy sample and diagnoses, if present.

21. Treatment given for AIH, in particular, specify what treatment, dose and duration.

22. Outcome[vi] at last observation.

23. Objective clinical evidence supporting classification of the event as 'serious'[iv].

24. Exposures other than the immunisation within 14 days before or after immunisation (e.g., food, drug, environmental xenobiotic) considered potentially relevant to the reported event (based on expert opinion)[15].

8.5. Recommended duration of surveillance for Autoimmune hepatitis

25. The duration of surveillance for AIH should be predefined based on:

    - biologic characteristics of the vaccine e.g., live attenuated versus inactivated component vaccines;
    - biologic characteristics of the vaccine-targeted disease;

[iii] e.g., recovery to pre-immunization health status, spontaneous resolution, therapeutic intervention, persistence of the event, sequelae, death.

[iv] An AEFI is defined as serious by international standards if it meets one or more of the following criteria: 1) results in death, 2) is life-threatening, 3) requires inpatient hospitalization or results in prolongation of existing hospitalization, 4) results in persistent or significant disability or incapacity, 5) is a congenital anomaly/birth defect, 6) is a medically important event or reaction.

[v] To determine the appropriate category, the user should first establish, whether a reported event meets the criteria for the lowest applicable level of diagnostic certainty, e.g., Level three. If the lowest applicable level of diagnostic certainty of the definition is met, and there is evidence that the criteria of the next higher level of diagnostic certainty are met, the event should be classified in the next category. This approach should be continued until the highest level of diagnostic certainty for a given event could be determined. Major criteria can be used to satisfy the requirement of minor criteria. If the lowest level of the case definition is not met, it should be ruled out that any of the higher levels of diagnostic certainty are met and the event should be classified in additional categories four or five.

[vi] If the evidence available for an event is insufficient because information is missing, such an event should be categorized as 'Reported case of AIH with insufficient evidence to meet the case definition' (Level 4).

[vii] Accessed on 23 Oct 2023 at https://www.equator-network.org/

- biologic characteristics of AIH, including patterns identified in previous trials (e.g., early-phase trials); and
- biologic characteristics of the vaccinee (e.g., underlying disease, presence of risk factors).

26. The duration of follow-up reported during the surveillance period should also be predefined. It should aim to continue until resolution of the event.

27. Methods of data collection should be consistent within and between study groups, if applicable.

28. Follow-up of cases should attempt to verify and complete the information collected as outlined in data collection guidelines 1 to 24.

29. Investigators of patients with AIH should provide guidance to reporters to optimize the quality and completeness of information provided.

30. Reports of AIH should be collected throughout the study period regardless of the time elapsed between immunisation and the adverse event. If this is not feasible due to the study design, the study periods during which safety data are being collected should be clearly defined.

8.6. Data analysis

The following guidelines represent a desirable standard for analysis of data on AIH to allow for comparability of data, and are recommended as an addition to data analyzed for the specific study question and setting.

8.6.1. Case classification−As shown in Section 5 each case can and should be classified as falling into one of ‘n’ categories:

31. Reported events should be classified in one of the following five categories including the three levels of diagnostic certainty as specified in the case definition. Events that do not meet the case definition should be classified in the additional categories for analysis.

Event classification in five categories[1]

Event meets case definition: Level 1: Criteria as specified in the AIH case definition

Level 2: Criteria as specified in the AIH case definition

Level 3: Criteria as specified in the AIH case definition

Event does not meet case definition: Additional categories for analysis

Level 4: Reported case of AIH with insufficient evidence to meet the case definition[j]

Level 5: Not a case of AIH

ii. Interval from immunisation to autoimmune hepatitis

32. The interval between immunisation and reported AIH could be defined as the date and time of immunisation to the date and time of onset[ii] of the first symptoms or signs consistent with the definition. If few cases are reported, the concrete time course could be analyzed for each. If a large number of cases, data can be analyzed using the following intervals:

Patients with AIH by interval to presentation

Interval	Number (%)
<2 weeks after immunisation	
2 − <6 weeks after immunisation	
6 − <12 weeks after immunisation	
>12 week after immunisation	
TOTAL	

33. The duration of a possible AIH could be analyzed as the interval between the date/time of onset[i] of the first symptoms and/or signs consistent with the definition and the end of episode[v] and/or final outcome[vi]. Whatever start and ending dates/times are used, they should be used consistently within and across study groups.

34. If more than one measurement of a particular criterion is taken and recorded, the value corresponding to the greatest magnitude of the adverse experience could be used as the basis for analysis. Analysis may also include other characteristics like qualitative patterns of criteria defining the event.

35. The distribution of data (such as numerator and denominator data) could be analyzed in predefined increments (e.g., measured values, times), where applicable. Increments specified above should be used. When only a small number of cases is presented, the respective values or time course can be presented individually.

36. Data on AIH obtained from subjects receiving a vaccine should be compared with those obtained from an appropriately selected and documented control group(s) to assess background rates of hypersensitivity in non-exposed populations, and should be analyzed by study arm and dose where possible, e.g., in prospective clinical trials.

8.7. Data presentation

These guidelines represent a desirable standard for the presentation and publication of data on AIH following immunisation to allow for comparability of data, and are recommended as an addition to data presented for the specific study question and setting. Additionally, it is recommended to refer to existing general guidelines for the presentation and publication of randomized controlled trials, systematic reviews, and *meta*-analyses of observational studies in epidemiology (e.g., statements of Consolidated Standards of Reporting Trials

(CONSORT), of Improving the quality of reports of *meta*-analyses of randomized controlled trials (QUORUM), and of Meta-analysis Of Observational Studies in Epidemiology (MOOSE), respectively) [vii].

37. All reported events of AIH should be presented according to the categories listed in guideline 31.

38. Data on possible AIH events should be presented in accordance with data collection guidelines 1–24 and data analysis guidelines 31–36.

39. Terms to describe AIH such as ‘low-grade’, ‘mild’, ‘moderate’, ‘high’, ‘severe’ or ‘significant’ are highly subjective, prone to wide interpretation, and should be avoided, unless clearly defined.

40. Data should be presented with numerator and denominator (n/N) (and not only in percentages), if available.

Although denominator data are usually not readily available in immunisation safety surveillance systems, attempts should be made to identify approximate denominators. The source of the denominator data should be reported and calculations of estimates should be described (e. g., manufacturer data on total doses distributed, reporting by ministry of health, coverage/population-based data).

41. The incidence of cases in the study population should be presented and clearly identified as such in the text.

42. If the distribution of data is skewed, medians and ranges are usually more appropriate statistical descriptors than means. However, the means and standard deviations should also be provided.

43. Any publication of data on AIH should include a detailed description of the methods used for data collection and analysis as possible. It is essential to specify:

- the study design;
- the method, frequency and duration of monitoring for AIH;
- the trial profile, indicating participant flow during a study including drop-outs and withdrawals to indicate the size and nature of the respective groups under investigation;
- the type of surveillance (e.g., passive or active surveillance);
- the characteristics of the surveillance system (e.g., population covered, mode of report solicitation);
- the search strategy in surveillance databases;
- comparison group(s), if used for analysis;
- the instrument of data collection (e.g., standardized questionnaire, diary card, report form);

- clear indication if the day of immunisation was considered ‘day one’ or ‘day zero’ in the analysis;
- if the date of onsetii or the date of first observationiii or the date of diagnosisivwere used for analysis; and
- use of this case definition for AIH, in the abstract or methods section of a publication[viii].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability

No data was used for the research described in the article.

References

[1]. Kohl KS, Bonhoeffer J, Chen R, Duclos P, Heijbel H, Heininger U, et al. The Brighton Collaboration: enhancing comparability of vaccine safety data. Pharmacoepidemiol Drug Saf 2003;12:335–40. 10.1002/pds.851. [PubMed: 12812014]

[2]. Kohl KS, Bonhoeffer J, Braun MM, Chen RT, Duclos P, Heijbel H, et al. The Brighton Collaboration: Creating a global standard for case definitions (and guidelines) for adverse events following immunization. In: Henriksen K, Battles JB, Marks ES, Lewin DI, editors. Advances in Patient Safety: From Research to Implementation (Volume 2: Concepts and Methodology). Rockville (MD): Agency for Healthcare Research and Quality (US); 2005.

[3]. Durazo FA, Kristbaum K, Miller J, Saeian K, Selim M, Hong JC. De Novo autoimmune hepatitis after COVID-19 infection in an unvaccinated patient. Case Reports Hepatol 2022;2022:8409269. 10.1155/2022/8409269.

[4]. Izagirre A, Arzallus T, Garmendia M, Torrente S, Castiella A, Zapata EM. Autoimmune hepatitis following COVID-19 vaccination. J Autoimmun 2022;132: 102874. 10.1016/j.jaut.2022.102874.

[5]. Sergi CM. COVID-19 vaccination-related autoimmune hepatitis-a perspective. Front Pharmacol 2023;14:1190367. 10.3389/fphar.2023.1190367.

[6]. Wang M, Qi J, Liu Y. Autoimmune hepatitis following COVID-19 vaccination: Clinical characteristics of 35 reported cases. Drug Discov Ther 2023;17:177–82. 10.5582/ddt.2023.01022. [PubMed: 37331808]

[7]. Garrido I, Lopes S, Simões MS, Liberal R, Lopes J, Carneiro F, et al. Autoimmune hepatitis after COVID-19 vaccine −more than a coincidence. J Autoimmun 2021; 125:102741. 10.1016/j.jaut.2021.102741.

[viii]Use of this document should preferably be referenced by referring to the link on the Brighton Collaboration website Accessed on 23 Oct 2023 at https://brightoncollaboration.us/.

[8]. Sebode M, Weiler-Normann C, Liwinski T, Schramm C. Autoantibodies in autoimmune liver disease-clinical and diagnostic relevance. Front Immunol 2018; 9:609. 10.3389/fimmu.2018.00609. [PubMed: 29636752]

[9]. Zachou K, Rigopoulou E, Dalekos GN. Autoantibodies and autoantigens in autoimmune hepatitis: important tools in clinical practice and to study pathogenesis of the disease. J Autoimmune Dis 2004;1:2. 10.1186/1740-2557-1-2. [PubMed: 15679907]

[10]. Domerecka W, Kowalska-Kępczyńska A, Michalak A, Homa-Mlak I, Mlak R, Cichoż-Lach H, et al. Etiopathogenesis and diagnostic strategies in autoimmune hepatitis. Diagnostics (Basel) 2021;11. 10.3390/diagnostics11081418.

[11]. Geller SA. Autoimmune hepatitis: Histopathology. Clin Liver Dis (Hoboken) 2014; 3:19–23. 10.1002/cld.301. [PubMed: 31236264]

[12]. Komori A. Recent updates on the management of autoimmune hepatitis. Clin Mol Hepatol 2021;27:58–69. 10.3350/cmh.2020.0189. [PubMed: 33291862]

[13]. Valean S, Acalovschi M, Dumitrascu DL, Ciobanu L, Nagy G, Chira R. Hepatocellular carcinoma in patients with autoimmune hepatitis −a systematic review of the literature published between 1989–2016. Med Pharm Rep 2019;92:99–105. 10.15386/mpr-1228. [PubMed: 31086834]

[14]. Slooter S, van den Brand FF, Lleo A, Colapietro F, Lenzi M, Muratori P, et al. Lack of complete biochemical response in autoimmune hepatitis leads to adverse outcome: first report of the IAIHG retrospective registry. Hepatology 2023. 10.1097/hep.0000000000000589.

[15]. Mack CL, Adams D, Assis DN, Kerkar N, Manns MP, Mayo MJ, et al. Diagnosis and management of autoimmune hepatitis in adults and children: 2019 Practice guidance and guidelines from the American Association for the Study of Liver Diseases. Hepatology 2020;72:671–722. 10.1002/hep.31065. [PubMed: 31863477]

[16]. Linzay CD, Sharma B, Pandit S. Autoimmune hepatitis. StatPearls. Treasure Island (FL): StatPearls Publishing Copyright © 2023, StatPearls Publishing LLC.; 2023.

[17]. Teufel A, Weinmann A, Kahaly GJ, Centner C, Piendl A, Wörns M, et al. Concurrent autoimmune diseases in patients with autoimmune hepatitis. J Clin Gastroenterol 2010;44:208–13. 10.1097/MCG.0b013e3181c74e0d. [PubMed: 20087196]

[18]. Yazdanpanah N, Rezaei N. Autoimmune complications of COVID-19. J Med Virol 2022;94:54–62. 10.1002/jmv.27292. [PubMed: 34427929]

[19]. Ercolini AM, Miller SD. The role of infections in autoimmune disease. Clin Exp Immunol 2009;155:1–15. 10.1111/j.1365-2249.2008.03834.x. [PubMed: 19076824]

[20]. Cabibi D. Autoimmune hepatitis following Epstein-Barr virus infection. bcr0620080071 BMJ Case Rep 2008;2008. 10.1136/bcr.06.2008.0071.

[21]. Tampaki M, Koskinas J. Extrahepatic immune related manifestations in chronic hepatitis C virus infection. World J Gastroenterol 2014;20:12372–80. 10.3748/wjg.v20.i35.12372. [PubMed: 25253938]

[22]. Ehrenfeld M, Tincani A, Andreoli L, Cattalini M, Greenbaum A, Kanduc D, et al. Covid-19 and autoimmunity. Autoimmun Rev 2020;19:102597. 10.1016/j.autrev.2020.102597.

[23]. Sharma C, Bayry J. High risk of autoimmune diseases after COVID-19. Nat Rev Rheumatol 2023;19:399–400. 10.1038/s41584-023-00964-y. [PubMed: 37046064]

[24]. Toscano G, Palmerini F, Ravaglia S, Ruiz L, Invernizzi P, Cuzzoni MG, et al. Guillain-Barré Syndrome associated with SARS-CoV-2. N Engl J Med 2020;382:2574–6. 10.1056/NEJMc2009191. [PubMed: 32302082]

[25]. Caso F, Costa L, Ruscitti P, Navarini L, Del Puente A, Giacomelli R, et al. Could SARS-coronavirus-2 trigger autoimmune and/or autoinflammatory mechanisms in genetically predisposed subjects? Autoimmun Rev 2020;19:102524. 10.1016/j.autrev.2020.102524.

[26]. Ghielmetti M, Schaufelberger HD, Mieli-Vergani G, Cerny A, Dayer E, Vergani D, et al. Acute autoimmune-like hepatitis with atypical anti-mitochondrial antibody after mRNA COVID-19 vaccination: A novel clinical entity? J Autoimmun 2021; 123:102706. 10.1016/j.jaut.2021.102706.

[27]. Rajendiran G, Cowman B, Erickson K, Oliver T, Manatsathit W. Autoimmune hepatitis associated with COVID-19 infection −a diagnostic and therapeutic dilemma. S D Med 2020;73:528–32. [PubMed: 33684272]

[28]. Rela M, Jothimani D, Vij M, Rajakumar A, Rammohan A. Auto-immune hepatitis following COVID vaccination. J Autoimmun 2021;123:102688. 10.1016/j.jaut.2021.102688.

[29]. Vuille-Lessard É, Montani M, Bosch J, Semmo N. Autoimmune hepatitis triggered by SARS-CoV-2 vaccination. J Autoimmun 2021;123:102710. 10.1016/j.jaut.2021.102710.

[30]. Liu Y, Sawalha AH, Lu Q. COVID-19 and autoimmune diseases. Curr Opin Rheumatol 2021;33:155–62. 10.1097/bor.0000000000000776. [PubMed: 33332890]

[31]. Cañas CA. The triggering of post-COVID-19 autoimmunity phenomena could be associated with both transient immunosuppression and an inappropriate form of immune reconstitution in susceptible individuals. Med Hypotheses 2020;145: 110345. 10.1016/j.mehy.2020.110345.

[32]. Roy A, Verma N, Singh S, Pradhan P, Taneja S, Singh M. Immune-mediated liver injury following COVID-19 vaccination: A systematic review. Hepatol Commun 2022;6:2513–22. 10.1002/hep4.1979. [PubMed: 35507736]

[33]. Zheng H, Zhang T, Xu Y, Lu X, Sang X. Autoimmune hepatitis after COVID-19 vaccination. Front Immunol 2022;13:1035073. 10.3389/fimmu.2022.1035073.

[34]. Trivedi PJ, Hirschfield GM. Recent advances in clinical practice: epidemiology of autoimmune liver diseases. Gut 2021;70:1989–2003. 10.1136/gutjnl-2020-322362. [PubMed: 34266966]

[35]. Lee YM, Teo EK, Ng TM, Khor C, Fock KM. Autoimmune hepatitis in Singapore: a rare syndrome affecting middle-aged women. J Gastroenterol Hepatol 2001;16: 1384–9. 10.1046/j.1440-1746.2001.02646.x. [PubMed: 11851837]

[36]. Czaja AJ. Autoimmune hepatitis in diverse ethnic populations and geographical regions. Expert Rev Gastroenterol Hepatol 2013;7:365–85. 10.1586/egh.13.21. [PubMed: 23639095]

[37]. Delgado JS, Vodonos A, Malnick S, Kriger O, Wilkof-Segev R, Delgado B, et al. Autoimmune hepatitis in southern Israel: a 15-year multicenter study. J Dig Dis 2013;14:611–8. 10.1111/1751-2980.12085. [PubMed: 23815477]

[38]. Ngu JH, Bechly K, Chapman BA, Burt MJ, Barclay ML, Gearry RB, et al. Population-based epidemiology study of autoimmune hepatitis: a disease of older women? J Gastroenterol Hepatol 2010;25:1681–6. 10.1111/j.1440-1746.2010.06384.x. [PubMed: 20880179]

[39]. Hurlburt KJ, McMahon BJ, Deubner H, Hsu-Trawinski B, Williams JL, Kowdley KV. Prevalence of autoimmune liver disease in Alaska Natives. Am J Gastroenterol 2002;97:2402–7. 10.1111/j.1572-0241.2002.06019.x. [PubMed: 12358264]

[40]. Lv T, Li M, Zeng N, Zhang J, Li S, Chen S, et al. Systematic review and meta-analysis on the incidence and prevalence of autoimmune hepatitis in Asian, European, and American population. J Gastroenterol Hepatol 2019;34:1676–84. 10.1111/jgh.14746. [PubMed: 31146297]

[41]. Afaa TJ, Amegan-Aho KH, Dono MT, Odei E, Awuku YA. Clinical characteristics of paediatric autoimmune hepatitis at a referral hospital in Sub Saharan Africa. PLoS One 2020;15:e0239964.

[42]. Grønbæk L, Vilstrup H, Jepsen P. Autoimmune hepatitis in Denmark: incidence, prevalence, prognosis, and causes of death. A nationwide registry-based cohort study. J Hepatol 2014;60:612–7. 10.1016/j.jhep.2013.10.020. [PubMed: 24326217]

[43]. Grønbaek L, Otete H, Ban L, Crooks C, Card T, Jepsen P, et al. Incidence, prevalence and mortality of autoimmune hepatitis in England 1997–2015. A population-based cohort study. Liver Int 2020;40:1634–44. 10.1111/liv.14480. [PubMed: 32304617]

[44]. Czaja AJ. Missing causality and heritability of autoimmune hepatitis. Dig Dis Sci 2023;68:1585–604. 10.1007/s10620-022-07728-w. [PubMed: 36261672]

[45]. Czaja AJ. Incorporating the molecular mimicry of environmental antigens into the causality of autoimmune hepatitis. Dig Dis Sci 2023;68:2824–42. 10.1007/s10620-023-07967-5. [PubMed: 37160542]

[46]. Sirbe C, Simu G, Szabo I, Grama A, Pop TL. Pathogenesis of autoimmune hepatitis-cellular and molecular mechanisms. Int J Mol Sci 2021;22. 10.3390/ijms222413578.

[47]. Muratori P, Serio I, Lalanne C, Lenzi M. Development of autoimmune hepatitis after influenza vaccination; trigger or killer? Clin Res Hepatol Gastroenterol 2019; 43:e95–6. 10.1016/j.clinre.2019.02.007. [PubMed: 30926201]

[48]. Sasaki T, Suzuki Y, Ishida K, Kakisaka K, Abe H, Sugai T, et al. Autoimmune hepatitis following influenza virus vaccination: Two case reports. Medicine (Baltimore) 2018;97:e11621.

[49]. Berry PA, Smith-Laing G. Hepatitis A vaccine associated with autoimmune hepatitis. World J Gastroenterol 2007;13:2238–9. 10.3748/wjg.v13.i15.2238. [PubMed: 17465509]

[50]. Perumalswami P, Peng L, Odin JA. Vaccination as a triggering event for autoimmune hepatitis. Semin Liver Dis 2009;29:331–4. 10.1055/s-0029-1233537. [PubMed: 19676005]

[51]. van Gemeren MA, van Wijngaarden P, Doukas M, de Man RA. Vaccine-related autoimmune hepatitis: the same disease as idiopathic autoimmune hepatitis? Two clinical reports and review. Scand J Gastroenterol 2017;52:18–22. 10.1080/00365521.2016.1224379. [PubMed: 27565372]

[52]. Della Corte C, Carlucci A, Francalanci P, Alisi A, Nobili V. Autoimmune hepatitis type 2 following anti-papillomavirus vaccination in a 11-year-old girl. Vaccine 2011;29:4654–6. 10.1016/j.vaccine.2011.05.002. [PubMed: 21596082]

[53]. Vuerich M, Wang N, Kalbasi A, Graham JJ, Longhi MS. Dysfunctional immune regulation in autoimmune hepatitis: from pathogenesis to novel therapies. Front Immunol 2021;12:746436. 10.3389/fimmu.2021.746436.

[54]. Higuchi T, Oka S, Furukawa H, Tohma S, Yatsuhashi H, Migita K. Genetic risk factors for autoimmune hepatitis: implications for phenotypic heterogeneity and biomarkers for drug response. Hum Genomics 2021;15:6. 10.1186/s40246-020-00301-4. [PubMed: 33509297]

[55]. Czaja AJ. Epigenetic aspects and prospects in autoimmune hepatitis. Front Immunol 2022;13:921765. 10.3389/fimmu.2022.921765.

[56]. Enke T, Livingston S, Rule J, Stravitz T, Rakela J, Bass N, et al. Autoimmune hepatitis presenting as acute liver failure: A 20-year retrospective review of North America. Liver Transpl 2023;29:570–80. 10.1097/lvt.0000000000000105. [PubMed: 36825579]

[57]. Wang Z, Sheng L, Yang Y, Yang F, Xiao X, Hua J, et al. The management of autoimmune hepatitis patients with decompensated cirrhosis: real-world experience and a comprehensive review. Clin Rev Allergy Immunol 2017;52:424–35. 10.1007/s12016-016-8583-2. [PubMed: 27515672]

[58]. Kogan J, Safadi R, Ashur Y, Shouval D, Ilan Y. Prognosis of symptomatic versus asymptomatic autoimmune hepatitis: a study of 68 patients. J Clin Gastroenterol 2002;35:75–81. 10.1097/00004836-200207000-00016. [PubMed: 12080231]

[59]. Czaja AJ. Features and consequences of untreated type 1 autoimmune hepatitis. Liver Int 2009;29:816–23. 10.1111/j.1478-3231.2008.01904.x. [PubMed: 19018980]

[60]. Krawitt EL. Autoimmune hepatitis. N Engl J Med 2006;354:54–66. 10.1056/NEJMra050408. [PubMed: 16394302]

[61]. Rahim MN, Miquel R, Heneghan MA. Approach to the patient with acute severe autoimmune hepatitis. JHEP Rep 2020;2:100149. 10.1016/j.jhepr.2020.100149.

[62]. Czaja AJ. Acute and acute severe (fulminant) autoimmune hepatitis. Dig Dis Sci 2013;58:897–914. 10.1007/s10620-012-2445-4. [PubMed: 23090425]

[63]. Stravitz RT, Lefkowitch JH, Fontana RJ, Gershwin ME, Leung PS, Sterling RK, et al. Autoimmune acute liver failure: proposed clinical and histological criteria. Hepatology 2011;53:517–26. 10.1002/hep.24080. [PubMed: 21274872]

[64]. Yeoman AD, Westbrook RH, Zen Y, Bernal W, Al-Chalabi T, Wendon JA, et al. Prognosis of acute severe autoimmune hepatitis (AS-AIH): the role of corticosteroids in modifying outcome. J Hepatol 2014;61:876–82. 10.1016/j.jhep.2014.05.021. [PubMed: 24842305]

[65]. Czaja AJ. Performance parameters of the conventional serological markers for autoimmune hepatitis. Dig Dis Sci 2011;56:545–54. 10.1007/s10620-010-1501-1. [PubMed: 21127976]

[66]. Loria P, Lonardo A, Leonardi F, Fontana C, Carulli L, Verrone AM, et al. Non-organ-specific autoantibodies in nonalcoholic fatty liver disease: prevalence and correlates. Dig Dis Sci 2003;48:2173–81. 10.1023/b:ddas.0000004522.36120.08. [PubMed: 14705824]

[67]. Galaski J, Weiler-Normann C, Schakat M, Zachou K, Muratori P, Lampalzer S, et al. Update of the simplified criteria for autoimmune hepatitis: Evaluation of the methodology for immunoserological testing. J Hepatol 2021;74:312–20. 10.1016/j.jhep.2020.07.032. [PubMed: 32730794]

[68]. Heringlake S, Schütte A, Flemming P, Schmiegel W, Manns MP, Tillmann HL. Presumed cryptogenic liver disease in Germany: High prevalence of autoantibody-negative autoimmune hepatitis, low prevalence of NASH, no evidence for occult viral etiology. Z Gastroenterol 2009;47:417–23. 10.1055/s-0028-1109146. [PubMed: 19418409]

[69]. Ballot E, Homberg JC, Johanet C. Antibodies to soluble liver antigen: an additional marker in type 1 auto-immune hepatitis. J Hepatol 2000;33:208–15. 10.1016/s0168-8278(00)80361-x. [PubMed: 10952238]

[70]. Hartl J, Miquel R, Zachou K, Wong GW, Asghar A, Pape S, et al. Features and outcome of AIH patients without elevation of IgG. JHEP Rep 2020;2:100094. 10.1016/j.jhepr.2020.100094.

[71]. Pape S, Snijders R, Gevers TJG, Chazouilleres O, Dalekos GN, Hirschfield GM, et al. Systematic review of response criteria and endpoints in autoimmune hepatitis by the International Autoimmune Hepatitis Group. J Hepatol 2022;76:841–9. 10.1016/j.jhep.2021.12.041. [PubMed: 35066089]

[72]. Laschtowitz A, Zachou K, Lygoura V, Pape S, Derben F, Jaeckel E, et al. Histological activity despite normal ALT and IgG serum levels in patients with autoimmune hepatitis and cirrhosis. JHEP Rep 2021;3:100321. 10.1016/j.jhepr.2021.100321.

[73]. Johnson PJ, McFarlane IG. Meeting report: International Autoimmune Hepatitis Group. Hepatology 1993;18:998–1005. 10.1002/hep.1840180435. [PubMed: 8406375]

[74]. Alvarez F, Berg PA, Bianchi FB, Bianchi L, Burroughs AK, Cancado EL, et al. International Autoimmune Hepatitis Group Report: review of criteria for diagnosis of autoimmune hepatitis. J Hepatol 1999;31:929–38. 10.1016/s0168-8278(99)80297-9. [PubMed: 10580593]

[75]. Hennes EM, Zeniya M, Czaja AJ, Parés A, Dalekos GN, Krawitt EL, et al. Simplified criteria for the diagnosis of autoimmune hepatitis. Hepatology 2008;48:169–76. 10.1002/hep.22322. [PubMed: 18537184]

[76]. Gatselis NK, Zachou K, Koukoulis GK, Dalekos GN. Autoimmune hepatitis, one disease with many faces: etiopathogenetic, clinico-laboratory and histological characteristics. World J Gastroenterol 2015;21:60–83. 10.3748/wjg.v21.i1.60. [PubMed: 25574080]

[77]. Janmohamed A, Hirschfield GM. Autoimmune hepatitis and complexities in management. Frontline Gastroenterol 2019;10:77–87. 10.1136/flgastro-2018-101015. [PubMed: 30651962]

[78]. Vento S, Guella L, Mirandola F, Cainelli F, Di Perri G, Solbiati M, et al. Epstein-Barr virus as a trigger for autoimmune hepatitis in susceptible individuals. Lancet 1995; 346:608–9. 10.1016/s0140-6736(95)91438-2. [PubMed: 7651006]

[79]. Terziroli Beretta-Piccoli B, Mieli-Vergani G, Vergani D. Autoimmmune hepatitis. Cell Mol Immunol 2022;19:158–76. 10.1038/s41423-021-00768-8. [PubMed: 34580437]

[80]. Muratori L, Lohse AW, Lenzi M. Diagnosis and management of autoimmune hepatitis. BMJ 2023;380:e070201.

[81]. Castiella A, Zapata E, Lucena MI, Andrade RJ. Drug-induced autoimmune liver disease: A diagnostic dilemma of an increasingly reported disease. World J Hepatol 2014;6:160–8. 10.4254/wjh.v6.i4.160. [PubMed: 24799984]

[82]. Tan CK, Ho D, Wang LM, Kumar R. Drug-induced autoimmune hepatitis: A minireview. World J Gastroenterol 2022;28:2654–66. 10.3748/wjg.v28.i24.2654. [PubMed: 35979160]

[83]. Floreani A, Restrepo-Jiménez P, Secchi MF, De Martin S, Leung PSC, Krawitt E, et al. Etiopathogenesis of autoimmune hepatitis. J Autoimmun 2018;95:133–43. 10.1016/j.jaut.2018.10.020. [PubMed: 30385083]

[84]. Rigopoulou EI, Gatselis N, Arvaniti P, Koukoulis GK, Dalekos GN. Alcoholic liver disease and autoimmune hepatitis: Sometimes a closer look under the surface is needed. Eur J Intern Med 2021;85:86–91. 10.1016/j.ejim.2020.12.024. [PubMed: 33451888]

[85]. Santos BC, Guedes LR, Faria LC, Couto CA. Wilson's disease presentation resembling autoimmune hepatitis. BMJ Case Rep 2019:12. 10.1136/bcr-2019-230721.

[86]. Choi W-T, Gill RM. Pathologic features and differential diagnosis of chronic hepatitis. Diagn Histopathol 2023;29:12–22. 10.1016/j.mpdhp.2022.10.003.

[87]. Oh RC, Hustead TR. Causes and evaluation of mildly elevated liver transaminase levels. Am Fam Physician 2011;84:1003–8. [PubMed: 22046940]

[88]. Iqbal U, Chaudhary A, Karim MA, Siddiqui MA, Anwar H, Merrell N. Association of autoimmune hepatitis and celiac disease: role of gluten-free diet in reversing liver dysfunction. 2324709617705679 J Investig Med High Impact Case Rep 2017;5. 10.1177/2324709617705679.

[89]. Lauret E, Rodrigo L. Celiac disease and autoimmune-associated conditions. Biomed Res Int 2013;2013:127589. 10.1155/2013/127589.

[90]. Khoury T, Kadah A, Mari A, Sbeit W, Drori A, Mahamid M. Thyroid dysfunction is prevalent in autoimmune hepatitis: a case control study. Isr Med Assoc J 2020;22:100–3. [PubMed: 32043327]

[91]. Terziroli Beretta-Piccoli B, Mieli-Vergani G, Vergani D. Autoimmune hepatitis: serum autoantibodies in clinical practice. Clin Rev Allergy Immunol 2022;63:124–37. 10.1007/s12016-021-08888-9. [PubMed: 34491531]

[92]. Kemme S, Mack CL. Pediatric autoimmune liver diseases: autoimmune hepatitis and primary sclerosing cholangitis. Pediatr Clin North Am 2021;68:1293–307. 10.1016/j.pcl.2021.07.006. [PubMed: 34736590]

[93]. Braga A, Vasconcelos C, Braga J. Autoimmune hepatitis and pregnancy. Best Pract Res Clin Obstet Gynaecol 2020;68:23–31. 10.1016/j.bpobgyn.2020.03.007. [PubMed: 32376296]

[94]. Chung YY, Heneghan MA. Autoimmune hepatitis in pregnancy: Pearls and pitfalls. Hepatology 2022;76:502–17. 10.1002/hep.32410. [PubMed: 35182079]

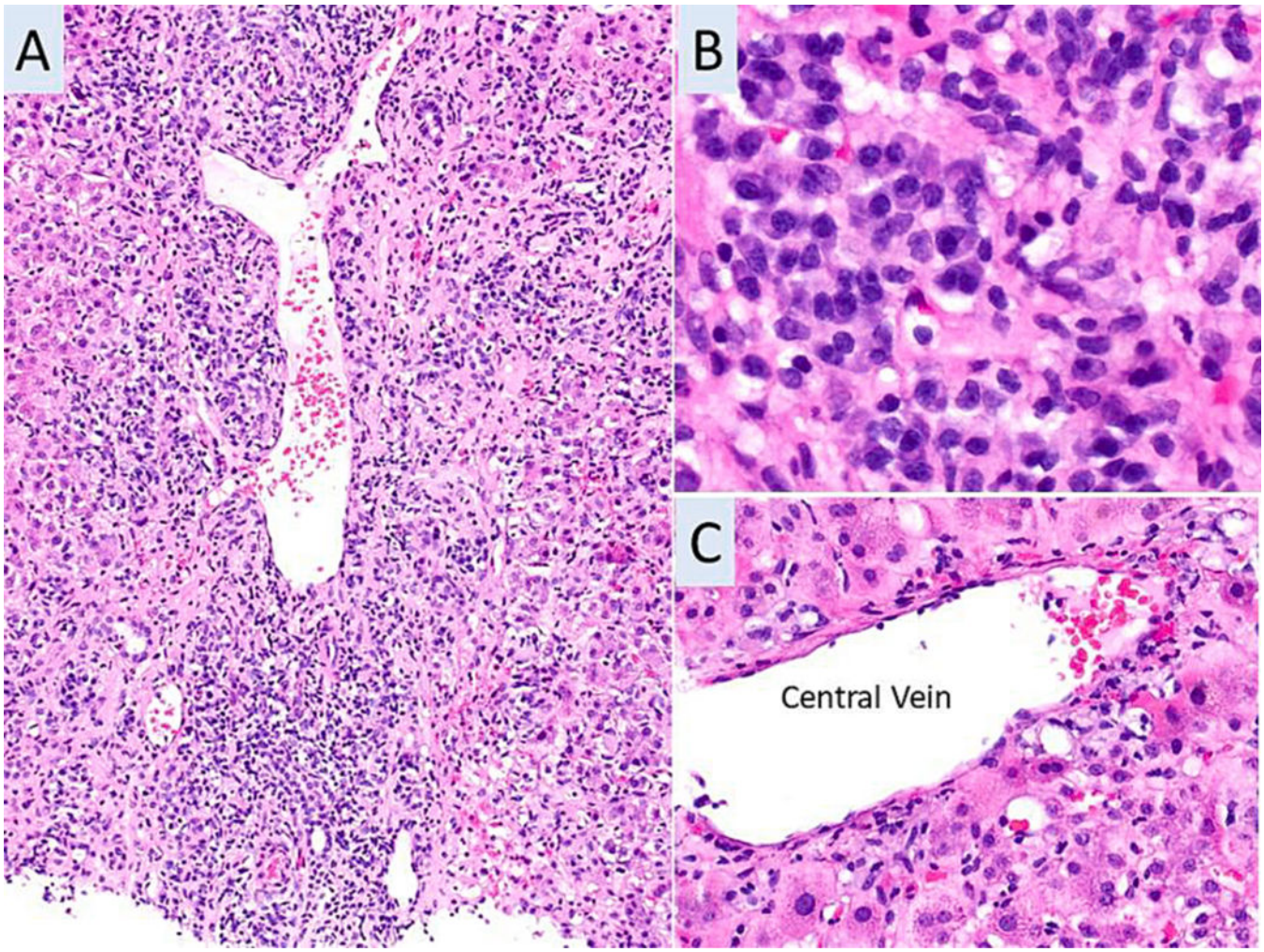

Fig. 1.

Characteristic histopathological features of autoimmune hepatitis. A. Severe interface hepatitis with lymphoplasmacytic inflammatory infiltrates of the portal tracts extending into the periportal hepatocytes of the hepatic lobule (hematoxylin and eosin, 100X). B. Clusters of plasma cells (identified by abundant cytoplasmic Golgi) in the lymphoplasmacytic inflammatory infiltrates of a portal tract (hematoxylin and eosin, 400X). C. Destructive lesion of perivenulitis of a portion of a central vein (hematoxylin and eosin, 200X). Since none of these histological features are pathognomonic for autoimmune hepatitis, they must be interpreted in the context of clinical, biochemical and serological test results. *Photomicrographs courtesy of Shilpa Jain, M.D., Department of Pathology, Baylor College of Medicine, Houston, TX, USA.*

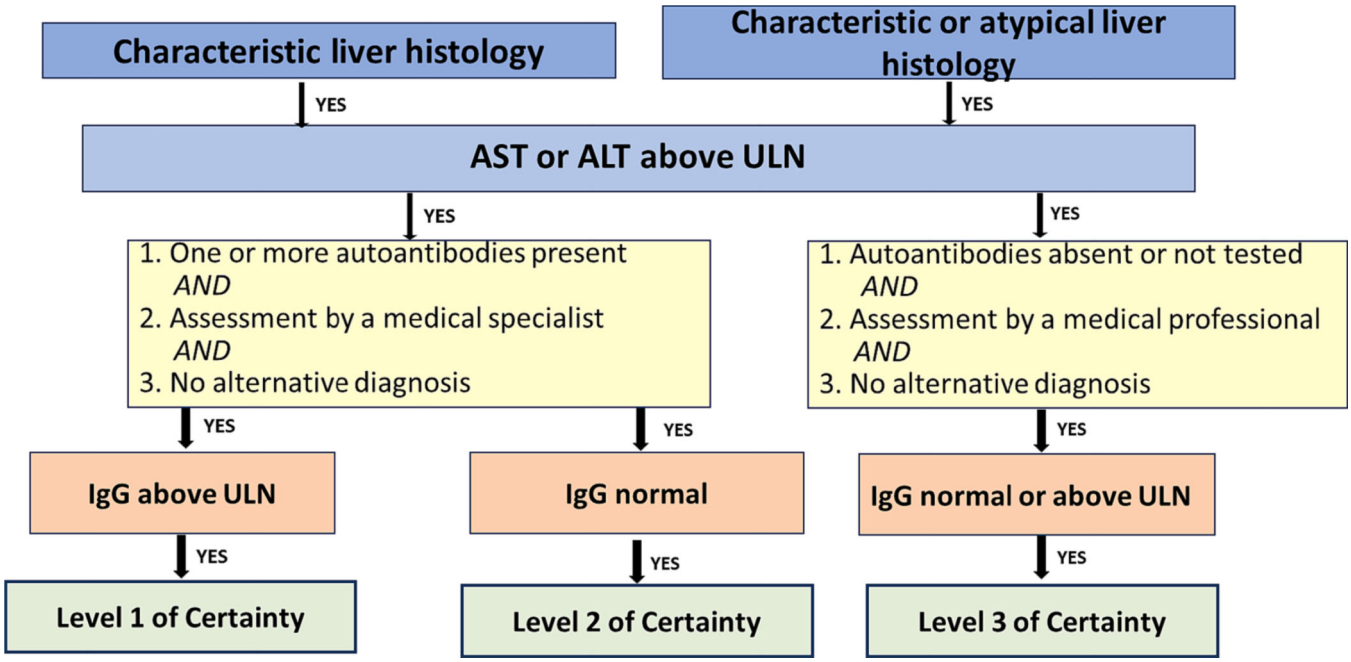

Fig. 2.

Pictorial algorithm for autoimmune hepatitis in adults and children levels of certainty AST: aspartate aminotransferase ALT: alanine transaminaseULN: Upper Limit of Normal IgG: Immunoglobulin G.

Table 1

Brighton Collaboration autoimmune hepatitis case definition and associated guidelines for data collection and analysis.

Objective	Case definition format to meet objective
1. To enable comparability of vaccine safety data for clinical trials and surveillance conducted in high, middle and low resource settings. While focused on vaccine safety context, the case definitions may also be used for other product safety research.	• Classified in up to three levels of diagnostic certainty from most specific/least sensitive (Level 1) to least specific/most sensitive (Level 3). The levels do not reflect clinical severity or seriousness. • Based on scientific evidence and consensus from a balanced group of subject matter and Brighton Collaboration process experts. • Includes specific guidelines on adverse event data collection and analysis. • Enable all cases to be classified, even if case definition not met: ○ Meets case definition at level 1, 2 or 3 of diagnostic certainty; ○ Fails to meet any level of certainty because of missing data; ○ Not a case because exclusion criterion met or necessary criterion known to be missing.
2. To enhance background incidence data quality and reduce causality study bias by providing a definition that can be applied equally to exposed and non-exposed groups.	• Interval from exposure (immunisation) to adverse event onset is not a criterion for the case definition, unless it is specific to a known vaccine-event causal association (e.g., generalized vaccinia following exposure to vaccinia virus).
3. To avoid use in unintended settings, namely clinical case management.	• In general, response to treatment is not included as a case definition criterion.

Table 2

A comparison between the revised original (1999) and the simplified (2008) diagnostic scoring systems for autoimmune hepatitis [74,75].

Revised original scoring system		Simplified scoring system		
Feature	**Score**	**Feature**	**Value**	**Score**
*Female sex	2	*ANA or SMA	≥1:40 titer	1
*ALP:AST (or ALT) ratio				
<1.5	2	*ANA or SMA	≥1:80 titer	
1.5–3.0	0	or *LKM-1	≥1:40 titer	2
>3.0	−2	or *SLA	Positive	
* Serum globulins or IgG > ULN				
>2.0	3	*IgG	>ULN	1
1.5–2.0	2		>1.1 × ULN	2
1.0–1.5	1			
<1.0	0	*Liver histology	Compatible	1
*ANA, SMA or LKM-1			Typical	2
>1:80	3			
1:80	2	*Negative viral markers	Yes	2
01:40	1			
<1:40	0	Diagnostic score:		
*Antimitochondrial antibody positive	−4	Probable AIH		≥6
*Viral Hepatitis		Definite AIH		≥7
Positive	−3			
Negative	3			
*Drug history (DILI)				
Positive	−4			
Negative	1			
*Average alcohol intake				
<25 g/day	2			
>60 g/day	−2			
*Liver histology				
Interface hepatitis	3			

Revised original scoring system		Simplified scoring system	
Feature	**Score**	**Feature**	**Value**	**Score**
Predominantly lymphoplasmacytic infiltrate	1			
Rosetting of liver cells	1			
None of the above	−5			
Biliary changes	−3			
Other changes	−3			
*Other autoimmune diseases	2			
*Optional additional parameters				
Other defined autoantibodies	2			
HLA DRB1*03 or DRB1*04	1			
*Response to therapy				
Complete	2			
Relapse	3			
Pre-treatment score:				
Definite AIH	>15			
Probable AIH	10–15			
Post-treatment score:				
Definite AIH	>17			
Probable AIH	12–17			

Table 3

Autoimmune hepatitis in adults and children case definition and levels of diagnostic certainty AIH is an inflammatory liver disease. There is no single/unique diagnostic biomarker for AIH. Therefore, diagnosis is based on a combination of histopathology, biochemical and serological testing, and exclusion of other diagnosis that exhibit similar features.

Level of certainty 1 (Definitive case)
1. Presence of characteristic liver histology[a]
AND
2. Serum biochemical tests
Presence of both of the following
• Serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) above the upper limit of normal (ULN)[b]
• Immunoglobulin G (IgG) above the ULN[b]
AND
3. Autoimmune serological tests
Presence of 1 or more of the following[c]
• ANA (antinuclear antibodies)
• Anti-SMA (smooth muscle antibodies)
• Anti-LKM1 (antibodies to liver-kidney microsome type 1)
• Anti-SLA (antibodies to soluble liver antigen)
AND
4. Assessment by a medical specialist (e.g., hepatologist, gastroenterologist) to exclude alternative diagnosis for illness [d]
Level of certainty 2 (Probable case)
1. Presence of characteristic liver histology[a]
AND
2. Serum biochemical tests
Presence of both of the following
• Serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) above the ULN[b]
• Immunoglobulin G (IgG) within normal limits[b]
AND
3. Autoimmune serological tests

Level of certainty 1 (Definitive case)

Presence of 1 or more of the following[c]

• ANA (antinuclear antibodies)

• Anti-SMA (smooth muscle antibodies)

• Anti-LKM1 (antibodies to liver-kidney microsome type 1)

• Anti-SLA (antibodies to soluble liver antigen)

AND

4. Assessment by a medical specialist (e.g. hepatologist, gastroenterologist) to exclude alternative diagnosis for illness [d]

Level of certainty 3 (Possible case)

1. Presence of characteristic or atypical liver histology[a]

AND

2. Serum biochemical tests

Presence of both of the following

• Serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) above the ULN[b]

• Immunoglobulin G (IgG) within normal limits, or above the ULN[b]

AND

2. Autoimmune serological tests

Negative results or inability to perform the following testing[c]

• ANA (antinuclear antibodies)

• Anti-SMA (smooth muscle antibodies)

• Anti-LKM1 (antibodies to liver-kidney microsome type 1)

AND

3. Assessment by a medical professional to exclude alternative diagnosis for illness [d]

Level of certainty 4

Insufficient information available to meet any level of certainty of autoimmune hepatitis

Level of certainty 5

Sufficient information provided for review and classified as not a case of autoimmune hepatitis

Upper Limit of Normal (ULN) Values [*]

ALT (alanine transaminase)/ SGPT (serum glutamate pyruvate transaminase)

Normal levels (units per litre)

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Level of certainty 1 (Definitive case)	
Adults: 7–56 U/L	
Women: 7–35 U/L	
Men: 7–40 U/L	
Children: 5–45 U/L	
AST (aspartate aminotransferase)/ SGOT (serum glutamic oxaloacetic transaminase)	
Adults: 5–40 U/L	
Males: 10–40 U/L	
Females: 9–32 U/L	
Children: 10–40 IU/L	
Immunoglobulin G (IgG)	
Age	Normal levels (g/L/mg/dL)
Up to 2 weeks	5.0 – 17.0/ 500–1700
2 – 4 weeks	3.9 – 13.0/ 390–1300 mg/dl
1 – 3 months	2.1 – 7.7/ 210–770
3 – 6 months	2.4 – 8.8/240–880
6 – 9 months	3.0 – 9.0/ 300–900
9 – 12 months	3.0 – 10.9/300–1090
1 – 2 years	3.1 – 13.8/310–1380
2 – 3 years	3.7 – 15.8/370–1580
3 – 6 years	4.9 – 16.1/490–1610
6 –15 years	5.4 – 16.1/540–1610
16 years and older	6.0 – 16.0/600–1600
Glossary	
Interface hepatitis	Death of hepatocytes at the interface of the hepatic parenchyma and the portal zone connective tissue, accompanied by a variable degree of inflammation and fibrosis
Perivenulitis	Inflammatory lesions involving the perivenular regions of the liver parenchyma

Notes

[a]Characteristic liver histology, reported by the pathologist reviewing the patient's liver biopsy tissue, shows interface hepatitis and lymphocytes and plasma cell infiltration of the liver. Perivenulitis of the central vein may be a prominent lesion in acute severe AIH cases.

Atypical histology shows interface hepatitis and lymphocytes infiltration in the absence of plasma cells.

[b] The upper limit of normal ranges is detailed in the table below:

[*] Normal value ranges may vary slightly among different laboratories

[c] ANA (antinuclear antibodies) is seen in approx. 60–70% of AIH, Anti-SMA (smooth muscle antibodies) in up to 85% of AIH and Anti-LKM1 (antibodies to liver-kidney microsome type 1) in approx. 70% of AIH-2. Rarely other antibodies are seen including Anti-LC-1 (anti-liver cytosol −1 antibody) in 30% AIH-2, anti-SLA/LP (anti-soluble liver antigen/liver pancreas antibodies) in 20–30% AIH-1 and AIH-2, anti-LKM3 (anti-liver-kidney microsomal antibody type 3) in 20–30% of paediatric case sand up to 10% of adult AIH cases [91].

[d] Negative results for appropriate testing for alternative diagnosis as determined by the medical professional, such as

- Viral hepatitis (***common***)
  - Hepatitis A (IgM anti-HAV)
  - Hepatitis B (HBsAg, total anti-HBc, anti-HBs)
  - Hepatitis C (anti-HCV ab, HCV RNA PCR)
  - Hepatitis E (IgM/IgG anti-HEV RNA PCR)
  - Epstein Barr
  - Cytomegalovirus (CMV)
  - Drug-induced liver injury *(common)*
- Alcohol-associated hepatitis *(common)*
- Metabolic liver diseases: Wilson's disease, Alpha-1-antitrypsin deficiency, hereditary hemochromatosis, iron overload *(less common)*

Other autoimmune liver diseases: primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), Celiac syndrome*) (less common)*

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