Overlap syndromes: The International Autoimmune Hepatitis Group (IAIHG) position statement on a controversial issue

Kirsten Muri Boberg 1,*, Roger W. Chapman 2, Gideon M. Hirschfield 3, Ansgar W. Lohse 4, Michael P. Manns 5, Erik Schrumpf 1, on behalf of the International Autoimmune Hepatitis Group

1 Clinic for Specialized Medicine and Surgery, Oslo University Hospital, Oslo, Norway; 2 Gastroenterology Unit, John Radcliffe Hospital, Headington, Oxford, United Kingdom; 3 Liver Centre, Toronto Western Hospital, Department of Medicine, University of Toronto, Toronto, Canada; 4 Department of Medicine, University Medical Centre Hamburg-Eppendorf, Hamburg, Germany; 5 Department of Gastroenterology, Hepatology and Endocrinology, Medical School of Hannover, Hannover, Germany

Some patients present with overlapping features between disorders within the spectrum of autoimmune liver diseases (i.e. autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC), and primary sclerosing cholangitis (PSC)) and are commonly classified as having an “overlap syndrome”. Standardized definitions of “overlap syndromes” are lacking.

The aim of this report by the International Autoimmune Hepatitis Group (IAIHG) is to evaluate if there are important reasons to classify conditions with overlapping features between autoimmune liver diseases as separate diagnostic entities.

Definition of diagnostic criteria for overlap conditions can only be arbitrary. The IAIHG scoring system for diagnosis of AIH has been widely used to diagnose “overlap syndromes”, but was not intended for such use and has not proven to be an efficient tool for this purpose. Some patients with overlapping features between a cholestatic and hepatitic disorder appear to benefit from treatment with a combination of ursodeoxycholic acid and immunosuppressants, but this strategy is not evidence-based, and it seems unjustified to define new diagnostic groups in this regard.

The IAIHG suggests that patients with autoimmune liver disease should be categorized according to the predominating feature(s) as AIH, PBC, and PSC/small duct PSC, respectively, and that those with overlapping features are not considered as being distinct diagnostic entities. The IAIHG scoring system should not be used to establish subgroups of patients.

Patients with PBC and PSC with features of AIH should be considered for immunosuppressive treatment. Due to the low prevalence of such “overlap syndromes”, prospective interventional therapeutic trials cannot be expected in the foreseeable future.

© 2010 European Association for the Study of the Liver. Published by Elsevier B.V. All rights reserved.

Introduction

Some patients within the spectrum of autoimmune liver diseases present with characteristics of both a cholestatic liver disease (i.e. primary biliary cirrhosis (PBC) or primary sclerosing cholangitis (PSC)) and autoimmune hepatitis (AIH). These conditions may be difficult to classify and are commonly designated as “overlap syndromes” [1–5]. As internationally agreed criteria defining “overlaps” are lacking, a variety of definitions have been applied.

The terms “AIH–PBC overlap”, “autoimmune cholangitis”, and “AIH–PSC overlap” are to a large extent used as diagnostic entities, to be distinguished from “classical” AIH, PBC, and PSC. Due to the lack of standardization and variations in the populations under study, the characteristics of these entities vary between studies.

The International Autoimmune Hepatitis Group (IAIHG) has published three reports on criteria for the diagnosis of AIH [6–8]. The initial report provided a set of descriptive criteria and also a scoring system to be used in conjunction with the descriptive criteria for difficult cases or when a more objective assessment is required [6]. The criteria were later revised to increase the diagnostic specificity for AIH [7]. “Overlap” of AIH with PBC, PSC, or Wilson’s disease was recognized as an interesting, albeit difficult diagnostic problem that should be addressed by an international collaboration [6,7]. Simplified diagnostic criteria for AIH
were recently published, but need to be validated [8]. In the meanwhile, the IAIHG scoring system has been widely applied to define “overlaps”, although it was not actually intended for such use.

The aim of the current report by the IAIHG is to evaluate if, indeed, there are important reasons to classify conditions with overlapping features between autoimmune liver diseases as separate diagnostic syndromes, or alternatively that they should be considered variants of the “classical” diseases.

**Diagnosis and heterogeneity of AIH, PBC, and PSC**

AIH, PBC, and PSC all possess features that describe the archetype of patients within each disorder. On the other hand, the classical disorders are not homogeneous, and patients within each diagnosis may present with a range of clinical, biochemical, serological, and histological findings (Table 1). These variations within each disorder can make the differential diagnosis between them a challenge and lead the clinician to resort to a diagnosis of “overlap syndrome”. It must be taken into account that there are limitations to the strengths, validity, and reproducibility of diagnostic tests and that disease features in the single patient can change over time and appear modified by treatment [9]. Moreover, the possibility of drug induced liver injury that can be associated with a variety of presentations, should be considered in the differential diagnosis.

**AIH: diagnosis and features that may overlap with those of PBC or PSC**

AIH occurs in all age groups. The patients commonly are young or middle-aged, but approximately 20% of adults with AIH present after the age of 60 years [10–12]. The majority (60–75%) of patients are female. The typical AIH patient presents with elevated serum aminotransferase levels (often 3- to 10-fold increase), marked hypergammaglobulinemia (typically IgG), positive titers of auto-antibodies, and histological findings of interface hepatitis and a portal plasma cell infiltrate [10,11]. Symptoms may be non-specific with varying severity, including fatigue, malaise, anorexia, nausea, and abdominal pain. Some patients experience jaundice and even pruritus [11,13]. Clinical findings may be normal or comprise jaundice, hepatomegaly, splenomegaly, and signs of liver cirrhosis.

An elevated serum aminotransferase activity is the predominant biochemical finding, but a variable increase in bilirubin levels and moderately elevated alkaline phosphatase (ALP) activity may also be seen [14,15]. Circulating auto-antibodies represent a hallmark of AIH and include antinuclear antibodies (ANA), smooth muscles antibodies (SMA), anti-actin antibody, antibodies against liver kidney microsome 1 (anti-LKM-1), antibodies to liver cytosol antigen type 1 (anti-LC1), antibodies to soluble liver antigen/liver pancreas (anti-SLA/LP), and perinuclear antineutrophil cytoplasmic antibodies (pANCA) (often atypical: perinuclear anti-neutrophil cytoplasmatic antibodies (pANNA)) [11,16]. The difference in antibody patterns has led to the discrimination between two subtypes of AIH [7,10,11,15,17,18]. Significant titers (≥1:40) of ANA and/or SMA are present in 70–80% of the patients (AIH type 1). Anti-LKM-1 is detected in 3–4% of AIH cases (AIH type 2) along with anti-LC1, but typically in the absence of ANA and SMA. Anti-SLA/LP is detected in 10–30% of cases. Anti-SLA/LP is most often found in cases of AIH-1 or AIH-2, but may also be seen among the 20–30% of AIH patients who are negative for the conventional antibodies and is then particularly useful to establish the diagnosis. The pANCA is found in 50–96% of patients with AIH-1. Approximately 10% of AIH patients do not have any of these antibodies at presentation, and therefore, their absence should not preclude the diagnosis [6,11]. Importantly, most of the antibodies may also be detected in patients with other liver diseases [10]. Even anti-SLA/LP is not entirely specific for AIH and has also been detected in cases of PBC or PSC, albeit in association with features of AIH [19–23]. A definitive diagnosis of AIH cannot be established without a liver biopsy [7,10]. However, none of the histopathological findings are specific, and in particular, interface hepatitis can be part of the disease spectrum of other hepatic disorders [6,10]. The diagnosis of AIH should not be made when definite bile duct pathology or granulomas are present [7], but some coincidental biliary injury may be observed [5,7,15,24–26]. In a review of histological bile duct abnormalities, the presence of fibrous or polymorph cholangitis did not distinguish patients with chronic hepatitis from patients with PBC or PSC [27]. Moreover, as many as 20 (24%) out of 84 patients who were considered classical AIH cases, had biliary changes, including destructive cholangitis in 6 (30%), ductopenia in 4 (20%), and non-destructive cholangitis in 10 (50%) [28]. These patients were anti-mitochondrial antibody (AMA) negative and did not exhibit any distinctive clinical features or treatment response. When the possibility of concurrent PBC in AIH patients with bile duct injury was later specifically addressed, it was concluded that such patients lack the features of PBC [29].

The presence of some degree of biliary involvement in AIH should therefore not necessarily lead to a change in diagnosis [10,29], but an adequate cholangiographic examination should be considered in such patients. Histological biliary changes, including bile duct damage, acute and/or chronic cholangitis, and biliary pattern of periportal hepatitis, have also been noted in 31% of children with AIH [13].

**PBC: diagnosis and features that may overlap with those of AIH**

The “typical” PBC patient is female in the age group 30–65 years, presenting with biochemical signs of cholestasis and the presence of AMA, being asymptomatic or suffering from fatigue or pruritus [30]. PBC is not diagnosed in children. The diagnosis can be made in patients who have elevated ALP levels of at least 6 months’ duration, in combination with the presence of AMA (≥1:40) [31,32]. A liver biopsy is not required, but may be useful to assess inflammatory activity and to stage the disease [31]. Serum aminotransferase levels usually are only slightly elevated, whereas the IgM concentration typically is increased.

AMA in high titers is present in approximately 95% of PBC patients. These AMAs are directed against acetyltransferases of the inner mitochondrial membrane; more that 90% of sera have specificity for the E2 subunit of the pyruvate dehydrogenase complex (PDC-E2). This AMA pattern is highly specific for PBC. Positive ANA titers are found in at least 1/3 of cases [31,33]. Antibodies against the nuclear pore membrane glycoprotein (anti-gp210) and against the nuclear protein Sp100 (anti-Sp100) have a high specificity (>95%) for PBC [34]. A liver biopsy is necessary for the diagnosis of PBC to be established in the absence of AMA [35]. The AMA negative PBC patients appear to have a disease
that otherwise is identical to the AMA positive cases [36]. AMA positivity, generally in low titer and considered non-specific, is occasionally observed in patients who otherwise fulfil the diagnostic criteria of AIH [37–41]. Specific AMA, e.g. anti-PDH-E2, can be detected in a minority of AIH cases [15].

The presence of degenerating biliary epithelium with focal bile duct obliteration and formation of granuloma, termed a “florid duct lesion”, is highly suggestive of PBC, but is not invariably present. Granulomatous cholangitis was present in only 32% of 258 biopsies of PBC patients [42]. Severe lymphocytic interface hepatitis is present in up to 25–30% of PBC cases [15,43,44]. The histological picture thus may not always be distinct from other conditions like AIH and PSC. In the assessment of a liver biopsy, limitations due to biopsy size and sampling error should always be kept in mind.

**PSC: diagnosis and features that may overlap with those of AIH**

The “typical” PSC patient is a 30–40 year old male with inflammatory bowel disease (IBD) who presents with serum markers of cholestasis [31,45]. About half of the patients are asymptomatic at presentation [46]. When present, the most common symptoms are fatigue, pruritus, right upper abdominal pain, and jaundice. PSC differs from AIH and PBC in that 2/3 of the patients in most populations are male. Median age at diagnosis is between 30 and 40 years, but PSC may be diagnosed at all ages including

### Table 1. Features of AIH, PBC, and PSC.

<table>
<thead>
<tr>
<th>Feature</th>
<th>AIH</th>
<th>PBC</th>
<th>PSC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td>Females: 60-75%</td>
<td>Females: &gt;90%</td>
<td>Females: 30-35%</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>All age groups. Median age approx. 45 years</td>
<td>Typically age group 30-65 years. Not diagnosed in children</td>
<td>Typically 30-50 years, but all age groups</td>
</tr>
<tr>
<td><strong>Aminotransferases</strong></td>
<td>Markedly elevated, often 3–10-fold, but may be normal or only minimally elevated</td>
<td>Normal or slightly elevated</td>
<td>Normal or slightly elevated</td>
</tr>
<tr>
<td><strong>Alkaline phosphatase</strong></td>
<td>Elevated levels may be seen</td>
<td>Moderately - markedly elevated</td>
<td>Moderately - markedly elevated (typically at least 3 x ULN; but variable levels, may even be normal)</td>
</tr>
<tr>
<td><strong>Bilirubin</strong></td>
<td>Variable increase</td>
<td>Variable increase, but normal in majority at diagnosis</td>
<td>Variable increase, but normal in majority at diagnosis</td>
</tr>
<tr>
<td><strong>Immunoglobulins</strong></td>
<td>Hypergammaglobulinemia, especially elevated IgG (generally elevated 1.2-3.0 x ULN)</td>
<td>IgM increased in most patients</td>
<td>IgG increased in up to 61%</td>
</tr>
<tr>
<td><strong>Autoantibodies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANA</td>
<td>Significant titres (≥1:40) of ANA and/or SMA in 70-80%</td>
<td>ANA in &gt;30% (anti-gp210 and anti-Sp100 highly specific)</td>
<td>ANA in 8-77%</td>
</tr>
<tr>
<td>SMA</td>
<td></td>
<td>SMA may be present</td>
<td>SMA in 0-83%</td>
</tr>
<tr>
<td>Anti-LKM</td>
<td>Anti-LKM in 3-4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-SLA/LP</td>
<td>Anti-SLA/LP in 10-30%</td>
<td>Anti-SLA/LP may be detected</td>
<td>Anti-SLA/LP may be detected</td>
</tr>
<tr>
<td>pANCA</td>
<td>pANCA in 50-96% (often atypical, pANNA) Conventional autoantibodies not detected in up to 10%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AMA</td>
<td>AMA in low titre occasionally seen (AMA anti-PDC-E2 pattern rarely detected)</td>
<td>AMA in 90-95% (AMA anti-PDC-E2 pattern highly specific)</td>
<td>AMA occasionally positive</td>
</tr>
<tr>
<td><strong>Liver biopsy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interface hepatitis</td>
<td>Typical finding*</td>
<td>In a proportion of cases**</td>
<td>In a variable number of cases***</td>
</tr>
<tr>
<td>Portal inflammation</td>
<td>Portal plasma cell infiltrate</td>
<td>Portal lymphocytic infiltrate</td>
<td>Portal lymphocytic infiltrate</td>
</tr>
<tr>
<td>Biliary changes</td>
<td>In a proportion of cases</td>
<td>Typical</td>
<td>Typical</td>
</tr>
<tr>
<td>Granulomas</td>
<td>Atypical Suggestive of PBC, but invariably present</td>
<td>Atypical, but may be observed</td>
<td></td>
</tr>
<tr>
<td>Cholangiography</td>
<td>Normal or signs of liver cirrhosis</td>
<td>Normal or signs of liver cirrhosis</td>
<td>Characteristic findings, diagnostic of PSC. Normal cholangiography in small duct PSC</td>
</tr>
<tr>
<td>IBD</td>
<td>Rarely associated with AIH. PSC should be excluded</td>
<td>Rarely associated with PBC</td>
<td>Present in up to 80%</td>
</tr>
</tbody>
</table>

---

1. A diagnosis of definite AIH should not be concluded without a liver biopsy.
2. A liver biopsy is not required in AMA positive cases. In early disease, characteristic features are uncommon.
3. A liver biopsy is not necessary for the diagnosis of large duct PSC, but required for the diagnosis of small duct PSC.
The diagnosis is confirmed by characteristic cholangiographic findings [45]. A high-quality magnetic resonance cholangiography (MRC) is recommended as the initial diagnostic procedure [31,47]. PSC is associated with IBD, most often ulcerative colitis, in approximately 80% of cases in patients of northern European heritage. IBD has also been described in patients with AIH and PBC, so the association is not entirely linked to PSC [48–50]. However, PSC should be carefully looked for in patients that present with IBD and liver pathology.

Elevated serum ALP (typically at least a 3-fold increase) is the characteristic biochemical finding in PSC [45,46,51]. Aminotransferase levels are often moderately elevated. Bilirubin concentration is normal in the majority of patients at diagnosis, but typically increases or fluctuates during disease progression. IgG and IgM are elevated in up to 61% and 45% of cases, respectively [45,52]. Positive titers of auto-antibodies are common, including ANA (8–77%), SMA (0–83%), and pANCA (26–94%) [45,53,54]. Antibody titers are usually lower than in AIH, but their presence may contribute to a diagnostic dilemma, at least until cholangiography confirms or excludes PSC.

Typical liver histological findings in PSC are portal tract inflammation with infiltration of lymphocytes in the bile ducts and ductular proliferation [55]. Periductal fibrosis is suggestive of PSC, but is not always present, indeed in some cases, the liver biopsy may be normal. Moreover, interface hepatitis may be observed, raising the possibility of the diagnosis of AIH. When liver biopsies from 105 PSC patients were assessed using the original IAIHG scoring system, biliary changes were predominant, however, 35 (33%) cases achieved positive scores for histological features which were similar to those of AIH [52]. A liver biopsy is not necessary to diagnose PSC in the presence of an abnormal cholangiogram [31,47].

**Associated disorders in AIH, PBC, and PSC**

Other diseases with autoimmune features are primarily associated with AIH [11], but can also be diagnosed in combination with PBC [30] or PSC [56] and therefore, do not provide a clue in the differential diagnosis between the three disorders. Raynaud’s phenomenon, sicca syndrome, scleroderma, and CREST syndrome are predominantly related to PBC [5].

**Characteristics of the “overlaps” described in patient series**

In the majority of cases, the so-called “overlap syndromes” are between AIH and PBC or AIH and PSC (Fig. 1). The overlapping features include symptoms, clinical findings, biochemical tests, a variety of immunological findings, as well as histology. Several types of relationship between the autoimmune liver disorders in the same patient have been described:

1. Sequential presentation of two disorders: this contention has been supported by reports of cases with consecutive occurrence of characteristics of two diseases.
2. The concomitant presence of two distinct disorders: autoimmune diseases are often associated with one another (in about 5–10% of cases), and it can be argued that an individual who has developed one autoimmune liver disease is predisposed to develop another one as well.

3. The existence of a continuum of pathological changes between two disorders, without strict boundaries and with “overlaps” localized in the center.
4. “Overlap syndromes” are distinct entities on their own, with a variety of autoimmune manifestations presenting in a susceptible individual.
5. The presence of one primary disorder that also has one or more characteristics of another: this contention has been supported by a majority of investigators.

**Overlap between PBC and AIH**

Patients with overlapping features between PBC and AIH have long been recognized [57,58]. Subsequent patient series have been described from different parts of the world [22,23,44,59–71]. The patients have been identified in several ways. Some studies have required the presence of at least two out of three specific criteria of each disorder [61]. The PBC criteria include (i) ALP levels at least twice- or γ-glutamyl transpeptidase (γGT) levels at least five times the upper limit of normal, (ii) positive AMA, and (iii) a liver biopsy showing florid bile duct lesion, and the AIH criteria comprise (i) alanine transaminase (ALT) levels at least five times the upper limit of normal, (ii) IgG levels at least twice the upper limit of normal or positive anti-SMA, and (iii) a liver biopsy with moderate or severe periportal or periseptal lymphocytic piecemeal necrosis.

These criteria were incorporated in the recent European Association for the Study of the Liver (EASL) guidelines for management of cholestatic liver diseases, but with the emphasis that histological evidence of interface hepatitis is mandatory for the diagnosis of PBC–AIH overlap [31].
Position Paper

Table 2. Selected studies of PBC–AIH and PSC–AIH overlap conditions.

<table>
<thead>
<tr>
<th>Criterium for diagnosis of overlap condition</th>
<th>Reference</th>
<th>No. of patients</th>
<th>Proportion (%) of patients with overlapping features</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least 2 of 3 criteria of PBC and AIH</td>
<td>[61,63]</td>
<td>130 - 331</td>
<td>4.8 – 9.2% PBC-AIH</td>
</tr>
<tr>
<td>Revised IAIHG criteria applied to PBC patients</td>
<td>[23,44,66,70,71]</td>
<td>137 - 368</td>
<td>2.1 – 19% PBC-AIH</td>
</tr>
<tr>
<td>Revised IAIHG criteria applied to PSC patients</td>
<td>[71,70,82,83]</td>
<td>113 - 221</td>
<td>7.4 – 14% PSC-AIH</td>
</tr>
</tbody>
</table>

*Presenting the results of application of the revised IAIHG scoring system to the group of PSC patients previously scored [52] according to the original IAIHG system.

In the two largest studies using the combination of AIH- and PBC criteria, the prevalence of PBC–AIH overlaps among PBC patients was in the range 4.8–9.2% [61,63] (Table 2). In studies applying the revised IAIHG scoring system, the findings of PBC–AIH overlaps have varied considerably, from 2.1% to 19% (Table 2). After elimination of scores for either female gender or the presence of other autoimmune disorders in one of the studies that identified 19% with overlap, the prevalence was reduced to 4% [44]. This observation illustrates that several parameters in the scoring system award positive scores for features that are common to both AIH and PBC and thus lack discriminative power.

Several reports have pointed out that overlap cases do not present features that differ significantly from the classical disorders. In an assessment of variant syndromes according to the original IAIHG scoring system among 225 patients with AIH, PBC, or PSC, 18% of the patients presented with features characteristic of a second autoimmune liver disease [62]. However, no specific characteristics could be identified that would distinguish these variants as distinct clinical entities. In a study from Germany, 20 patients who were suggested to have an “overlap syndrome” of PBC and AIH, were compared with 20 patients with typical AIH and typical PBC, respectively [22]. Overlap cases were selected either on the basis of biochemical and serological findings, or on histological features. The authors concluded that all overlaps were PBC cases who had developed a more hepatic picture and that this condition should be termed “PBC with secondary AIH” [22].

A change in diagnosis may be observed during follow-up. Among 35 patients with variant forms of PBC that were identified in a Swedish study, transitions between the variant forms of PBC over time were observed, but the diagnosis remained unchanged in 16 out of the 25 AIH–PBC overlap cases [69]. In contrast, in a study from Japan, most patients with AIH–PBC overlap evolved into either AIH or PBC, with only 0.8% of patients diagnosed as “strict” AIH–PBC overlaps [66].

The simplified IAIHG scoring system is based on the presence of auto-antibodies, IgG, histological features of AIH, and the exclusion of viral hepatitis [8]. By application of this score to 368 PBC patients, the proportion classified as PBC–AIH overlaps was reduced from 12% by the revised IAIHG criteria [7] to 6% [71]. This is another example of how the frequencies of overlap conditions are dependent upon the definitions of disease entities. Prognosis was worse in patients that fulfilled the new criteria as compared with those who only fulfilled the old ones, and the authors suggested that the simplified scoring system is more specific in recognizing patients with PBC–AIH “overlap syndrome”. A scoring system for PBC that can be used in combination with the revised IAIHG score to distinguish PBC from PBC–AIH overlap has also been proposed [64].

In PBC patients, features of AIH have also been described to develop in a sequential manner [9,72,73]. Among 282 PBC patients, AIH developed in 12 (4.3%) patients after 6 months to 13 years [73]. The development of AIH could not be predicted from baseline characteristics and initial response to ursodeoxycholic acid (UDCA). Alternatively, PBC may occur after the diagnosis of AIH [74].

AMA negative PBC

Some patients have clinical and histopathological features of PBC, but lack AMA and most often have ANA. This group has, by some, been claimed to represent a separate entity, often named “autoimmune cholangitis”. However, the majority view is that these patients have a variant of PBC, best regarded as AMA negative PBC [3,31,61,75–77].

Overlap between PSC and AIH

The diagnosis of large duct PSC should always be established on typical cholangiographic findings. Other features may be less characteristic. In a patient with a confirmed diagnosis of PSC, concurrent features resembling AIH may lead to classification of an overlap PSC–AIH. This condition seems to occur particularly often in children, where it has been extensively studied. Such patients may benefit from concomitant immunosuppressive therapy [13].

Large duct PSC–AIH overlap

Overlapping features between PSC and AIH have been described in case reports and small series [78–81], but also in larger groups of PSC patients [23,52,62,82–84] (Table 2). When 114 PSC patients were assessed using the original IAIHG scoring system, 2% were scored as definite- and 33% as probable AIH [52]. After the application of the revised scoring system to the same patients, 2% were still scored as definite AIH, but the proportion of probable AIH was reduced to 9% [7]. Similar results were obtained from a study of 211 PSC patients who, using the original system were scored as definite AIH in 2% of cases and probable in 19%, whereas the revised system reduced the proportion of probable AIH to 6% [82]. In the largest PSC patient series evaluated according to the revised system, overall 7–14% of patients scored for features of AIH (Table 2).

Patients with an original diagnosis of AIH who later undergo cholangiography and prove to have PSC, are also often considered “overlap syndromes” [83–85]. We would recommend classifying these patients as PSC, as initially, cholangiographic features of PSC were not excluded. AIH is more rarely diagnosed in patients with an original diagnosis of PSC [83,86].
Patients who present with clinical features and a liver biopsy compatible with PSC but with a normal cholangiogram are classified as small duct PSC [87]. These patients have IBD in the majority (50–88%) of cases. In an early study of 17 patients diagnosed with AIH and ulcerative colitis, a diagnosis of PSC was made in 5 (42%) among 12 cases who underwent cholangiography [49]. Patients with and without cholangiographic abnormalities were otherwise indistinguishable. It could be surmised that the 7 cases without cholangiographic PSC represent small duct PSC with overlapping features with AIH [46]. Alternatively, it could be argued that they are AIH with some bile duct changes and an association with ulcerative colitis. A recent study concluded that small duct PSC is prevalent among patients with overlapping AIH and PSC. Seven (27%) among 26 PSC patients who fulfilled criteria of AIH (the revised IAIHG system but not deducting scores for bile duct changes) had small duct PSC [88]. The diagnosis of small duct PSC was based on a normal MRC in 6 out of the 7 cases, and it cannot be excluded that the performance of ERC may have revealed large duct disease in some of these patients.

PSC is strongly associated with IBD, unlike AIH. The prevalence of IBD in patients with overlap PSC–AIH has been reported to be higher than in patients with AIH only [62] and corresponding to that in PSC [82,83,89], making PSC the likely primary disorder in these cases. The concurrence of AIH and ulcerative colitis should raise the possibility of PSC. Studies of MRC in AIH patients have been controversial, finding cholangiographic changes suspicious of PSC to be rare [90] as well as more frequent (10%) [91]. PSC should be considered in AIH patients with pruritus, cholestatic liver tests, histological bile duct changes, and in those who show a poor response to therapy.

**PSC and AIH in children**

Characteristics of AIH appear to be considerably more frequent in PSC presenting in childhood and adolescents than in adults. Several similarities with AIH were noted in 13 children with PSC in an early report [92] and subsequently described in nine (28%) among 32 children with PSC [93]. In a prospective study including 55 children who presented with evidence of liver disease and positive test for one or more circulating auto-antibodies, 27 (49%) patients proved to have bile duct abnormalities consistent with PSC, and the remaining 28 (51%) were diagnosed with AIH [13]. Of note, 35% among the PSC patients did not have histological biliary changes and most likely would have been diagnosed with AIH if cholangiography had not been carried out. Half (52%) of the 27 PSC patients satisfied the IAIHG criteria for definite- and half (48%) those of probable AIH. IBD was more frequent in this group than in patients with AIH only. The authors introduced the term “autoimmune sclerosing cholangitis” (ASC) to designate the group of children with PSC who also have findings in keeping with AIH. They suggested that AIH and ASC are within the spectrum of the same disease process [13].

ASC appears to be a childhood counterpart of the AIH–PSC overlap condition in adults, but having the same prevalence as AIH type 1 in children [94]. Other investigators have classified pediatric patients as having an AIH–PSC “overlap syndrome” [95]. In a long-term follow-up study of 52 children with PSC, 35% (14/40 with biopsies) met the IAIHG criteria for definite or probable AIH [96]. These authors suggested that the expression of PSC in children is skewed toward a hepatitic presentation instead of the predominantly cholestatic profile in adults. Notwithstanding, the possibility of PSC should be considered in all children with AIH.

**Overlap between PBC and PSC**

Overlap between PBC and PSC has only been described in a few patients [97,98]. The two conditions can be clearly distinguished in the large majority of cases. However, liver histology may be similar [42], including granulomas as a feature of PSC [99], and AMA may occasionally be positive in PSC.

**International study of patients with autoimmune liver disorders**

On behalf of the IAIHG, an international working party applied the IAIHG scoring system on a large group of patients (n = 479) within the spectrum of autoimmune liver diseases from four different countries [70]. Among these, 7% of PBC- and 14% of PSC patients scored as probable or definite AIH, although they were not clinically considered overlap cases. On the other hand, only 7 (29%) patients with a clinically defined overlap of AIH–PBC (n = 18) or AIH–PSC (n = 6) scored as probable or definite AIH. The low sensitivity of the scoring system for clinically defined “overlap syndromes” is in keeping with results of a previous study [100]. Based on the IAIHG scoring system, specific differences between the clinical overlaps and other patients within the spectrum of autoimmune liver disease with a single diagnosis could not be defined, and this study did not support the contention of “overlap syndromes” as distinct diagnostic entities. A recent study [101] concluded that the criteria previously suggested by Chazouillères et al. [61] could identify patients with a clinical diagnosis of PBC–AIH “overlap syndrome” with high sensitivity (92%) and specificity (97%) and that these criteria performed better than the revised [7] and the simplified [8] IAIHG scoring system in this regard. Still, these criteria do not represent international consensus.

**Are there shared pathogenetic factors that predispose to overlapping features between autoimmune liver diseases?**

PSC, AIH, and PBC are all complex traits in which several genes act in concert with environmental factors to increase the risk of disease [102]. Diseases that share genetic susceptibility factors could be more likely to develop in the same individual. Alternatively, genes that are associated with one particular disorder could affect the clinical expression when also present in a patient with another primary disease.

AIH, PBC, and PSC are associated with human leukocyte antigen (HLA) genes on chromosome 6 [11,103–105]. Due to the lack of precise classifications of patients with overlapping features and the rarity of such conditions, systematic genetic studies of sufficient numbers have been impossible to perform. The findings from previous studies provide variable results and hence firm conclusions cannot be made. The characteristic HLA
manifestations of the primary disease [106]. Thus, patients were commonly shared and did not affect the clinical patients with AIH, PBC, or PSC, demonstrated that HLA risk factors were commonly shared and did not affect the clinical manifestations of the primary disease [106]. Thus, patients with shared HLA associations did not have characteristics of “overlap syndromes”. In a study in children, HLA-DR3 was more frequent in AIH than in patients characterized as ASC, but the finding was not statistically significant (p = 0.07) [13].

The genetic characteristics of autoimmune liver diseases will be further clarified by genome-wide association studies [107,108]. Diseases can then be compared in a much more sophisticated and direct way. It is reasonable to speculate that if overlaps do indeed represent independent clinical entities, their genetic susceptibility will differ from that of AIH, PBC or PSC.

Unique serological profiles in patients considered to be overlaps could support the idea that they are disease entities on their own, and antibody profiles could serve as diagnostic markers. In a recent study, anti-dsDNA antibodies were significantly more frequent in 15 PBC–AIH overlap cases (60%) than in 120 PBC (4%) and 120 AIH (26%) patients (<0.0001 and 0.01, respectively) [109]. The concomitant presence of AMA and anti-dsDNA was highly specific (98%) for the overlap condition, being observed in 47% of overlaps as compared to only 2% of controls. A difference in immunoreactivity to a distinct subset of AMA between patients with PBC and PBC–AIH “overlap syndrome” has also been suggested to be of potential importance in differentiating these groups [110]. Further serological studies are required to ascertain the significance of the above observations or to clarify other possible differences in immune-mediated damage to liver cells and/or biliary epithelium.

Are “overlap syndromes” important to recognize in order to decide on therapy?

Immunosuppression (primarily oral corticosteroids) is a standard and highly effective therapy in AIH, and UDCA is recommended to reduce disease progression in PBC [31]. UDCA has not been proven to have a beneficial effect on prognosis in PBC [31]. There have been no large, randomized treatment studies in patients with features of PBC- or PSC and AIH, merely retrospective reports on experiments in small patient samples. Currently, there are no evidence-based recommendations for treatment of either PBC- or PSC–AIH overlap conditions.

Treatment of PBC patients with features of AIH

Several studies have demonstrated a positive response to immunosuppressive therapy in patients with overlapping features between PBC and AIH [22,61,62,73,109,111,112], but it has also been suggested that treatment solely with UDCA alone is sufficient [63]. In a study of 12 patients defined as PBC–AIH “overlap syndrome”, nine obtained remission during corticosteroid therapy [62]. This response was comparable with that in patients with definite AIH. The PBC–AIH patients even had a lower frequency of progression to cirrhosis compared with the AIH cases. Response to corticosteroids was associated with a serum ALP level of less than 2-fold the reference value. Among 5 patients initially treated with UDCA alone and 6 with prednisolone alone, 9 patients (3 UDCA, 6 prednisolone) had persistently abnormal liver tests [61]. They were subsequently given a combination of UDCA and prednisolone for a median of 18 months, which resulted in an overall improvement. In another study, 20 PBC patients with features of AIH were followed for an average of 6.4 years, 16 among them being treated with steroids ± azathioprine in addition to UDCA with excellent biochemical response [22]. Favorable biochemical response to a combination of UDCA and immunosuppressive agents has also been reported by others [69,73,112,113]. A case report has suggested a beneficial effect of cyclosporine A in patients resistant to UDCA and prednisolone [114].

Different treatment regimens were retrospectively compared in a long-term follow-up (median 7.5 years) of 17 PBC–AIH overlap patients strictly defined by the criteria previously proposed by this group [61,111]. First-line treatment was UDCA alone (11 patients) or UDCA combined with immunosuppressive agents (6 patients, 4 receiving azathioprine in addition to corticosteroids). In the UDCA group, biochemical response and stable or decreased fibrosis were observed in 3/11 patients, while the remaining 8/11 patients were non-responders with increased fibrosis in 4. In the group receiving both UDCA and immunosuppression, 4/6 patients (all non-cirrhotic) achieved a complete biochemical response along with unchanged fibrosis, suggesting that combined therapy is the best option.

In a histopathological analysis of liver biopsies from PBC patients obtained before and after 4 years of therapy with UDCA, the severity of lymphocytic piecemeal necrosis and the lobular inflammation at entry was significantly associated with the progression of fibrosis [43]. These results suggested that PBC patients who share the histological features of both AIH and PBC are more likely to have a rapid progression of fibrosis than those who do not and that these patients may need a combination of UDCA and corticosteroids. Other reports have also supported an effect of interface hepatitis and serum aspartate transaminase (AST) levels on prognosis in PBC [115,116]. A worse clinical outcome in patients with overlapping features of PBC and AIH (n = 26; mean follow-up 6.1 years) compared with patients with PBC only (n = 109; mean follow-up 5.4 years) has also been observed [117]. On the contrary, Joshi et al. [63] found that 12 PBC patients who had features of AIH had a similar biochemical and serologic response to UDCA as ordinary PBC patients treated in the same manner for 24 months. They also noted that features of AIH in PBC may be transient in some patients. In a comparison of patients with PBC–AIH (n = 10) with a group of “pure” AIH (n = 238), the PBC–AIH cases responded less well to standard AIH therapy, however, this did not affect survival [68].

With the reservation that this strategy is not evidence-based, the recent EASL guidelines recommend combined therapy with UDCA and corticosteroids in patients with PBC–AIH overlap [31]. As an alternative approach, it is suggested that UDCA can be the initial therapy and corticosteroids be added if an adequate biochemical response has not been obtained within a time frame of 3 months.
Treatment of PSC patients with features of AIH

Various results of therapy have been reported in patients with combined features of PSC and AIH. Clinical and biochemical improvement after treatment with corticosteroids and azathioprine, sometimes combined with UDCA, were noted in a small number of patients in early reports [78,80,81]. One patient had no significant effect of prednisone and azathioprine, but responded to cyclosporine A [79]. Compared with patients with classical AIH, however, patients with AIH and PSC obtained remission significantly less frequently (2/9 patients) and reached the end-points of death from liver failure or liver transplantation significantly more often [62]. Treatment failure was also frequent (4/5 patients) in another report [49]. In a study of 9 AIH–PSC patients, all were reported to respond to immunosuppressive therapy. Long-term remission was obtained in 3 cases, but 3 underwent liver transplantation after 4 months and 7 and 9 years, respectively [83]. In another study, partial response was obtained in 3 out of 4 PSC–AIH patients treated with steroids [82]. Judged from the effect on aminotransferases, a good response was also concluded in 16/24 overlap cases treated with corticosteroids and azathioprine (tacrolimus in one) [88]. In a prospective study of 7 patients with AIH–PSC “overlap syndrome” treated with prednisolone (initial dose 0.5 mg/kg/day, tapered to 10–15 mg/day) and azathioprine (50–75 mg/day) plus UDCA (15–20 mg/kg/day), a favorable biochemical response was noted [84]. Moreover, the patients had an improved survival as compared with a parallel group of 34 patients with classical PSC on UDCA therapy (follow-up 7–8 years). A retrospective study of PSC patients treated with corticosteroids also concluded that a subgroup seems to respond favorably and may obtain improved long-term survival [118]. As compared with patients with AIH and AIH–PBC on similar immunosuppressive therapy, however, PSC–AIH patients had a significantly reduced survival (hazard ratio 2.08 and 2.14, respectively), even though the majority had a good initial response [68]. A similar observation was also made in a study identifying 8 cases with findings consistent with PSC by MRC carried out in 79 adult AIH patients [91]. Likewise, progressive disease was observed in 16 patients with features of both PSC and AIH despite combined immunosuppressive and UDCA therapy and initial biochemical improvement [119]. In summary, the studies would suggest that the prognosis of PSC–AIH patients may be better than in patients with classical PSC, but worse than in patients with AIH alone [91,119,120].

The response to immunosuppressive therapy appears to be better in children with PSC–AIH overlap (or ASC) than in adults [13,121]. In 23/27 children with ASC treated with immunosuppression (most also receiving UDCA) response to therapy was satisfactory and similar to that observed in AIH.

The EASL guidelines recommend that patients with AIH–PSC “overlap syndrome” are treated with UDCA and immunosuppressive therapy, but emphasize that this is not evidence-based [31]. The American Association for the Study of Liver Diseases (AASLD) guidelines on PSC also recommend the use of corticosteroids and other immunosuppressive agents in patients with PSC–AIH overlap [47].

Discussion and conclusions

Most diseases have a spectrum of clinical manifestations with imprecise boundaries, and overlapping features between conditions are seen within all fields of medicine. In some situations, for example research purposes, a strict classification is needed with inclusion of only patients with an unquestionable diagnosis. However, in clinical practice, it is preferable to have a small number of categories based on simple diagnostic criteria so that most patients can be easily subdivided into few and large groups, making the diagnosis easy and reproducible. As a consequence, some degree of heterogeneity among patients within each group has to be accepted. The introduction of new sets of classifications requires a rationale, for example in terms of defining groups according to specific pathogenetic traits, specific diagnostic tests, indications for therapy or implications for prognosis.

It is established that some patients, who satisfy established criteria for PBC or PSC, also can have biochemical, serological, and/or histological features overlapping with those of AIH on a continuous scale. On the basis of the current, very limited knowledge about the etiopathogenesis of the 3 disorders, definition of diagnostic criteria for overlap conditions can only be arbitrary.

The IAIHG scoring system has been widely applied to PBC and PSC patients, and a numerical expression of similarities with AIH has been obtained. However, the scoring system was developed to diagnose AIH and to increase the discrimination of AIH from potential differential diagnoses. Therefore, the wide application of the scoring system to identify a subgroup of patients thereby defined as “overlaps” is inappropriate. Even if a scoring system with higher specificity for AIH could be produced and the number of PBC and PSC patients obtaining a certain level of scores reduced, the question remains whether the results would be clinically relevant. The observation that patients clinically considered to be overlaps only achieve a score diagnostic of AIH in a limited number of cases, supports the contention that the IAIHG scoring system should not be used to define such cases [70].

Patients with overlapping features between PBC- or PSC and AIH are often treated with a combination of UDCA and immunosuppressive agents, based on several reports indicating beneficial effects. The addition of corticosteroids and/or other immunosuppressive agents has recently been recommended in PBC–AIH patients in the EASL guidelines and in PSC–AIH cases in both EASL- and AASLD guidelines [31,47]. Due to the lack of proper studies, this strategy is not evidence-based, and it seems unreasonable to define new diagnostic groups on this ground.

The IAIHG suggests that patients with overlapping features between AIH, PBC, and PSC are not categorized as separate diagnostic entities, but are considered to be parts of the respective “classical” diseases. Nevertheless, specific therapeutic considerations may be required in such patients.

Algorithms for the therapeutic approach to patients with overlapping features have been proposed [122], but based on the paucity of current evidence it is difficult to set rigid guidelines. In most cases, however, it should be possible to define one primary disorder and prescribe the appropriate treatment. A suggested outline for clinical assessment and therapeutic approach to patients with PBC or PSC with features of AIH is presented in Fig. 2.

In patients with a predominance of cholestatic findings supporting a diagnosis of PBC, UDCA should be the primary choice. PBC with features of AIH can improve with UDCA alone, but the addition of immunosuppressive medication may improve
the therapeutic response. Patients with large duct PSC should be treated according to general guidelines with endoscopic therapy when indicated [31, 47]. In PSC with features of AIH, immunosuppressive treatment should also be considered. As a rule, the dominant clinical feature should be treated first and therapy should be individualized, tailored to each patient, and adjusted according to the response. Importantly, care must be taken not to expose PBC- or PSC patients thought to have an overlap with AIH to the risk of side effects of steroids if this cannot be justified by the beneficial effect [123]. Future studies should aim to identify the subgroups of patients who will benefit from immunosuppressive treatment. It is also possible that one in the future will be able to identify subgroups within the spectrum of autoimmune liver diseases.

In conclusion, we propose that patients with autoimmune liver disease should be categorized as AIH, PBC, and PSC/small duct PSC, respectively. The IAIHG scoring system should not be used to establish subgroups of patients. Patients with PBC and PSC with features of AIH should be considered for immunosuppressive treatment.

**Conflict of interest**

The authors who have taken part in this study declared a relationship with the manufacturers of the drugs involved. GH has received an unrestricted grant from Axcan Pharma and MM has a financial interest with Falk Pharma: Consulting; Advisory Arrangements: Speaker’s bureau; Grants/contracts: research; Grants/contracts: unrestricted. The remaining authors have no disclosures.

**Acknowledgments**

We gratefully acknowledge the contribution of Prof. Hans-Peter Dienes, Institute for Pathology, University Medical Centre,
Cologne, Germany, concerning discussions on issues related to histopathology.

References


[40] Boberg KM, Fusa O, Haaland T, Holter E, Melbye OQ, Spurkland A, et al. Features of autoimmune hepatitis in primary sclerosing cholangitis: an evaluation of 114 primary sclerosing cholangitis patients according to a

Journal of Hepatology 2011 vol. 54 | 374–385

838


Donaldson PT. Genetics of autoimmune and viral liver diseases; understanding the issues. J Hepatol 2004;41:327–332.


