Diagnosis and management of the overlap syndromes of autoimmune hepatitis

Albert J Czaja MD

The overlap syndromes of autoimmune hepatitis (AIH) are hybrid conditions that cannot be assimilated into classical diagnostic categories (1-6). Patients with AIH may exhibit features of primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), or a cholestatic syndrome in the absence of objective features of PBC or PSC (6). The common clinical feature of these atypical phenotypes is the presence of a cholestatic component (7,8), and the major clinical relevance of these syndromes is their failure to respond in a consistent fashion to conventional corticosteroid therapy (2,6,8). The overlap syndromes are clinical descriptions rather than distinct pathological entities. They are important in clinical practice because they are relatively common, have uncertain clinical outcomes and require non-standard treatments (2,6,9).

The exclusion of cholestatic features from the classical definition of AIH does not exclude them from clinical experience, and multiple international organizations have designated ‘overlap syndromes’ (2,6,9). These overlap syndromes have uncertain clinical outcomes and require non-standard treatments (2,6,9).

The overlap syndromes are clinical descriptions rather than distinct pathological entities, and the dominant component of the disease determines its designation and therapy. Cholestatic findings in autoimmune hepatitis influence the response to immunosuppressive therapy alone or in combination with low-dose ursodeoxycholic acid. The overlap syndrome with primary sclerosing cholangitis or with cholestasis without diagnostic features is commonly treated with immunosuppressive therapy and ursodeoxycholic acid. Responses are variable and commonly incomplete (20% to 100% improvement) depending on the degree of cholestasis.

The exclusion of cholestatic features from the classical definition of AIH does not exclude them from clinical experience, and multiple international organizations have designated ‘overlap syndromes’ (2,6,9). These overlap syndromes have uncertain clinical outcomes and require non-standard treatments (2,6,9).
## TABLE 1

<table>
<thead>
<tr>
<th>Overlap syndrome</th>
<th>Laboratory features</th>
<th>Serological features</th>
<th>Histological features</th>
<th>Cholangiographic findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AIH-PBC</strong></td>
<td>Consistent with Paris criteria* (19, 30) Mild forms may have AP ≤2×ULN (2, 8)</td>
<td>AMA positive (2)</td>
<td>Interface hepatitis (30)</td>
<td>Normal (6)</td>
</tr>
<tr>
<td></td>
<td>AST/ALT=ULN (2) γ-globulin and IgG =ULN (2) AP or GGT=ULN (2)</td>
<td>AMA negative (2)</td>
<td>Destructive cholangitis (florid duct lesions) (30)</td>
<td>Bile duct strictures (2, 18, 20, 72)</td>
</tr>
<tr>
<td><strong>AIH-PSC</strong></td>
<td>AST/ALT=ULN (2) γ-globulin and IgG =ULN (2) AP or GGT=ULN (2)</td>
<td>AMA negative (2)</td>
<td>Interface hepatitis (34)</td>
<td>Normal (2, 11, 27)</td>
</tr>
<tr>
<td><strong>AIH-cholestatic syndrome</strong></td>
<td>AST/ALT=ULN (2) γ-globulin and IgG =ULN (2) AP or GGT=ULN (2)</td>
<td>AMA negative (2)</td>
<td>Destructive cholangitis or bile duct loss (11, 27)</td>
<td>Normal (2, 11, 27)</td>
</tr>
</tbody>
</table>

**Overlap syndrome laboratory features**

<table>
<thead>
<tr>
<th><strong>Serological features</strong></th>
<th><strong>Histological features</strong></th>
<th><strong>Cholangiographic findings</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>AST/ALT&gt;ULN (2)</td>
<td>Interface hepatitis (30)</td>
<td>Normal (6)</td>
</tr>
<tr>
<td>γ-globulin and IgG &gt;ULN (2)</td>
<td>Destructive cholangitis (florid duct lesions) (30)</td>
<td>Bile duct strictures (2, 18, 20, 72)</td>
</tr>
<tr>
<td>AP or GGT&gt;ULN (2)</td>
<td>Interface hepatitis (34)</td>
<td>Normal (2, 11, 27)</td>
</tr>
</tbody>
</table>

**Numbers in parentheses refer to references. *Paris criteria endorsed by the European Association for the Study of the Liver require interface hepatitis and either serum alanine aminotransferase (ALT) level ≥5-fold upper limit of normal range (ULN), serum immunoglobulin G (IgG) level ≥2-fold ULN or smooth muscle antibodies, and two of three features of primary biliary cirrhosis (PBC) including serum alkaline phosphatase (AP) level ≥2-fold ULN or serum gamma glutamyl transferase (GGT) ≥5-fold ULN, antimitochondrial antibodies (AMA) and destructive cholangitis. AST Serum aspartate aminotransferase level; PSC Primary sclerosing cholangitis**

Reports attest to their occurrence in otherwise classical disease (5, 6, 9, 18-24). This realization has indicated the need to recognize these variant syndromes and manage them effectively. The goal of the present review was to meet this need.

### TYPES OF OVERLAP SYNDROMES OF AIH

The overlap syndromes of AIH imply that the predominant disease is AIH and that the concurrent cholestatic features are background components (5, 6). In this context, AIH has three cholestatic phenotypes that may be intermixed with its classical hepatic features (Table 1). Patients may have antimitochondrial antibodies (AMA) and histological findings of bile duct injury or loss that suggest PBC (AIH-PBC overlap) (5, 6). They may have absence of AMA and endoscopic retrograde (ERC) and magnetic resonance (MRC) cholangiograms that suggest PSC (AIH-PSC overlap) (5, 6). They may also have a cholestatic syndrome characterized by the absence of AMA, normal ERC or MRC, and histological features of bile duct injury or loss (AIH-cholestatic syndrome) (6, 11, 12). The AIH-cholestatic syndrome may include patients with AMA-negative PBC or small-duct PSC (6, 11, 25-27).

Patients with the AIH-PBC overlap syndrome are different from patients with predominantly PBC and incidental features of AIH (PBC-AIH overlap syndrome) (6). Similarly, patients with the AIH-PSC overlap syndrome are different from patients with predominantly PSC and incidental features of AIH (PSC-AIH overlap syndrome) (6). The predominant disease in the overlap syndrome determines its principal clinical manifestations and outcome (5, 6). In contrast to patients with the AIH-PBC overlap syndrome, patients with the PBC-AIH overlap syndrome frequently have cirrhosis, portal hypertension, gastrointestinal bleeding, ascites and esophageal varices (28, 29). Similarly, patients with the PSC-AIH overlap syndrome (20) may respond less well to conventional corticosteroid therapy than patients with the AIH-PSC overlap syndrome (18). The overlap syndromes of AIH are important to distinguish from the overlap syndromes of PBC and PSC, and the various mixtures of AIH, PBC and PSC must be categorized according to their major component and not consolidated into categories that give equal weight to each constituent (2, 4-6).

### DIAGNOSTIC CRITERIA FOR THE OVERLAP SYNDROMES OF AIH

The diagnosis of the overlap syndromes of AIH has not been codified; however, the importance of having prominent features of classical AIH and secondary objective findings of PBC or PSC has been emphasized by the IAIHG (5), the European Association for the Study of the Liver (EASL) (30) and the American Association for the Study of Liver Diseases (31). The AIH component must be established by demonstrating satisfaction of the codified diagnostic criteria for this disease based on clinical features or scoring systems (either the original comprehensive or simplified systems) (7, 32). The definite or probable diagnosis of AIH according to these criteria is a requisite for the syndrome (33), and the predominant histological features should be interface hepatitis with or without plasma cells (34).

### Diagnostic criteria for the AIH-PBC overlap syndrome

The minimum diagnostic criteria for the AIH-PBC overlap syndrome are the presence of AMA and histological findings of bile duct injury or loss in otherwise classical AIH (Table 1) (2, 6). The serum alkaline phosphatase level and the histological findings of destructive cholangitis indicate the strength of the association with PBC, and they direct the management strategy (19, 35). Other histological findings may include portal or acinar granulomas, cholelithiasis and nondestructive lymphocytic cholangitis (34, 36). The ‘Paris criteria’ provide an objective basis for making the diagnosis of the overlap syndrome with PBC and they ensure uniformity of the diagnosis (Table 1) (19, 30, 35). They encompass patients with the strongest manifestations of the AIH-PBC overlap syndrome.

The Paris criteria for the AIH-PBC overlap syndrome require two of three features associated with AIH selected from the following: serum alanine aminotransferase level ≥5-fold ULN, immunoglobulin G level ≥2-fold ULN or the presence of smooth muscle antibodies, and interface hepatitis on histological examination (19). They also require two of three features associated with PBC selected from the following: serum alkaline phosphatase level ≥2-fold ULN or γ-glutamyl transferase (GGT) level ≥5-fold ULN, AMA, and florid duct lesions or destructive cholangitis on histological examination (19). The Paris criteria have a sensitivity of 92% and specificity of 97% using clinical judgment as the gold standard (37), and they have been endorsed by the EASL with the stipulation that all patients with this syndrome have interface hepatitis (5, 30).

### Diagnostic criteria for the AIH-PSC overlap syndrome

Cholangiographic changes indicating focal strictures and dilations of the biliary tree are characteristic of PSC by ERC or MRC, and patients with classical AIH and these radiological findings warrant the diagnosis of the AIH-PSC overlap syndrome (Table 1) (2, 5, 6). Histological changes may disclose interface hepatitis with or without plasma cells, portal edema or fibrosis, ductopenia, ductular tortuosity, ductular proliferation, cholestatic stasis or, rarely, obliterative fibrous cholangitis (34, 36). Concurrent inflammatory bowel disease is common in adults with this overlap syndrome (38), but its absence does not preclude the diagnosis (39). Routine cholangiography has not been promulgated for adults with classical AIH in the absence of inflammatory bowel disease (40), and the detection of the AIH-PSC overlap syndrome in adults is typically driven by the presence of chronic ulcerative colitis, marked cholestatic features or poor treatment response (2, 6, 38). Children with AIH frequently have ‘autoimmune sclerosing cholangitis’ in the
absence of inflammatory bowel disease; the threshold for cholangiography may be lower in this population (41,42).

Diagnostic criteria for the AIH-cholestatic overlap syndrome

The diagnosis of the AIH-cholestatic overlap syndrome implies the absence of serological and histological features diagnostic of PBC and the presence of a normal cholangiogram (Table 1). The designation may encompass patients with AMA-negative PBC or small duct PSC (27,43), and the heterogeneity of this category is suggested by the diversity of histological manifestations. Patients with this syndrome may have a dense lymphoplasmacytic portal infiltrate with interface hepatitis and bile duct injury suggestive of PBC, or portal fibrosis, portal edema and ductopenia reminiscent of PSC (34). The AIH-cholestatic overlap syndrome probably existed earlier under the rubric of ‘autoimmune cholangitis’ (11,43-48).

FREQUENCIES OF THE OVERLAP SYNDROMES OF AIH

The frequencies of the overlap syndromes in patients with AIH vary widely depending on the diagnostic criteria that are applied. In a compilation of reported experiences (6), 7% to 13% of patients with AIH have overlapping features of PBC; 6% to 11% of patients have features of PSC, and 5% to 11% have a cholestatic syndrome in the absence of PBC and large duct PSC. The estimated overall frequency of an overlap syndrome in a well-defined cohort of patients with classical AIH is 14% to 18% (2.9). The presence of inflammatory bowel disease in patients with AIH favours the existence of the AIH-PSC syndrome, and 41% of adults with AIH and chronic ulcerative colitis have cholangiographic features of PSC (38). This finding has justified a recommendation that cholangiography be considered in all adults with AIH and inflammatory bowel disease (6,38).

Endoscopic cholangiography in children with AIH has disclosed biliary changes of ‘autoimmune sclerosing cholangitis’ in 50% (41), and MRI in adults with AIH has disclosed biliary changes of PSC in 10% (39). Most children and adults with AIH who have cholangiographic abnormalities were female, and they had no clinical evidence of inflammatory bowel disease. These observations suggested that patients with otherwise classical AIH could have an unsuspected biliary disease in the absence of inflammatory bowel disease and that this occurrence was underestimated.

Importantly, these observations did not include a disease-control population to establish the disease specificity of the radiological findings. A subsequent French study performed MRC in adults with AIH and adults with nonautoimmune chronic liver disease, and it found that the frequency of bile duct changes was similar between the patient groups (44% versus 59%) and that PSC was rare in AIH (2%) (40). The hepatic fibrosis score was the only independent predictor of the biliary changes by MRC (OR 2.4 [95% CI 1.4 to 1.7]), and advanced hepatic fibrosis rather than an unsuspected PSC was most closely associated with the MRC changes (40). These findings do not justify the routine performance of cholangiography in adults with classical AIH and no inflammatory bowel disease.

PATHOGENIC HYPOTHESES FOR THE OVERLAP SYNDROMES OF AIH

The overlap syndromes of AIH are clinical descriptions rather than valid pathological entities, and their true nature is uncertain (6,49). The overlap syndromes may simply represent a classical disease with variant or atypical manifestations (30). They could represent a transition stage in the evolution of classical PBC or PSC in which mixed features are present during an early formative period (34,36). They could represent two diseases in the same individual, or they could be separate pathological entities with their own yet undiscovered and distinctive pathogenic mechanisms (49).

Overlap syndromes as variants of classical AIH

The autoimmune liver diseases undoubtedly have blurred outer boundaries of diagnosis that cannot be rigidly defined, and the distinction between a hepatic PBC and cholestatic AIH may be difficult (21,50). The overlap syndromes of AIH may be at the fringe of the diagnosis of AIH, but still be within the domain of that disease (Table 2). The original goal of the IAIHG was to develop diagnostic criteria that identified a homogeneous population that could be assimilated into clinical studies (7,15). The failure of some forms of AIH to satisfy the current diagnostic criteria for AIH does not exclude them from the diagnosis. The overlap syndromes of AIH may, in part, be consequences of diagnostic criteria that are inadequate, misapplied or invalid (6,51,52). Furthermore, the diagnostic scoring systems of the IAIHG are not discriminatory diagnostic indexes, and the declaration that patients with PBC or PSC have AIH based on these scoring systems is presumptuous.

Overlap syndromes as transitional stages

The autoimmune liver diseases can evolve through different stages, and they may have mixed features at early stages of development (Table 2). Observations during these transitional stages may confound the diagnosis and suggest an overlap syndrome that actually represents an immature classical disease (6). Spontaneous transitions from AIH to PBC (53), AIH to PSC (54) and PBC to AIH (55,56) may be examples of this evolutionary pathway. Furthermore, serological markers, especially antinuclear and smooth muscle antibodies, are common findings in PBC, PSC and AIH that can suggest concurrent diseases (57), and AMA in 13% of patients with classical AIH can mistakenly suggest an association with PBC (58). Hypergammaglobulinemia and the human leukocyte antigen (HLA) DRB1*03 occur frequently in white North American and northern European patients with AIH, PBC or PSC (59), and the histological features of AIH may be difficult to distinguish from stage 2 PBC or the early portal inflammatory changes of PSC (34). The clinical, serological and histological features that

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Pathogenic hypotheses for the overlap syndromes of autoimmune hepatitis (AIH)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothesis</td>
<td>Theoretical bases</td>
</tr>
<tr>
<td>Classical AIH with atypical features</td>
<td>AIH features not disease specific (52)</td>
</tr>
<tr>
<td></td>
<td>AIH features occur in multiple acute and chronic liver diseases (16)</td>
</tr>
<tr>
<td>Diagnostic scoring systems are based on classical AIH and not valid in atypical phenotypes (7,32)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Transitional stage in evolution to classical PBC or PSC</td>
<td>Autoimmune liver diseases evolve through early formative stages that have mixed features (34,59)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Concurrent separate diseases</td>
<td>Common genetic factors in AIH, PBC and PSC may predispose to concurrent separate diseases (59)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Unrecognized new disease</td>
<td>Promiscuous immune response can target multiple targets in liver and biliary tree and create various phenotypes (63,75)</td>
</tr>
</tbody>
</table>

Numbers in parentheses refer to references. PBC Primary biliary cirrhosis; PSC Primary sclerosing cholangitis.
Overlap syndromes as concurrent diseases

The overlap syndromes of AIH may represent two diseases (AIH and PBC or PSC) occurring simultaneously in the same individual (49) (Table 2). This hypothesis is justified by the presence of highly disease-specific findings of PBC or PSC in some patients with otherwise classical AIH (6,49) and the concurrence of PBC and PSC (60-62). Furthermore, AIH, PBC and PSC share genetic factors that may predispose susceptible individuals to develop concurrent separate diseases (59,63). Cholangiographic changes that include focal biliary strictures and dilations (31) and histological findings of destructive cholangitis or obliterator fibrous cholangitis (10,64) are so disease-specific for PBC and PSC that their presence in patients with AIH supports the possibility of coexistent diseases. It also challenges the validity and the primacy of the diagnosis of concurrent AIH in patients with these predominant features. Because the diagnostic manifestations of AIH lack disease specificity, their occurrence in patients with unequivocal features of PSC or PBC may reflect variants of PSC or PBC rather than a concurrent AIH. Validation of the two-disease hypothesis in AIH requires the identification of a disease-specific feature of AIH that can be assessed in patients with definite PBC or PSC.

Overlap syndromes as distinct diseases

The overlap syndromes of AIH could represent distinct pathological entities with disease-specific pathogenic mechanisms, genetic predispositions, outcomes and treatment requirements (6). Self-antigens or foreign antigens that mimic self-antigens could initiate promiscuous immune responses that overcome self-tolerance and target hepatocytes, intrahepatic bile ducts and the extrahepatic biliary tree in genetically susceptible individuals (63,65). Different patterns of injury within the liver and contiguous structures could reflect this unfocused and poorly regulated immune response and create a phenotype with mixed features. Rather than two diseases occurring simultaneously in one person, the mixed phenotype could reflect a single complex disease with distinctive yet undiscovered immune regulatory defects and genetic predispositions (6,63). There have been no studies to advance or discount this conjecture.

TREATMENT AND OUTCOMES OF THE OVERLAP SYNDROMES OF AIH

The overlap syndromes of AIH have a variable response to conventional corticosteroid therapy (2) and they have a higher probability of recurrence after liver transplantation than patients with classical AIH (five-year probability of recurrence: 53% versus 17%) (66). This variability of response and behaviour may, in part, relate to the degree of variance of the overlap syndrome from classical AIH (6). Serum alkaline phosphatase level and the histological findings of bile duct injury or loss are the principal indicators of this variance, and the strength of the cholestatic component, as reflected in these indexes, directs the management strategy (4,8,19). Treatments are empirical and highly individualized, but they typically include corticosteroids alone or in combination with low-dose ursodeoxycholic acid (13 mg/kg to 15 mg/kg daily) (2,4-6,9).

Treatment and outcome of the AIH-PBC overlap syndrome

Patients with features of AIH and PBC who have a serum alkaline phosphatase level less than two-fold ULN respond as well to corticosteroid therapy as patients with classical autoimmune hepatitis (2) (Table 3). This combination significantly improves the serum alkaline phosphatase (P<0.05), GGT (P<0.02) and alanine aminotransferase (P<0.02) levels (19), prevents progressive hepatic fibrosis (P<0.04) (19,35), and induces clinical and laboratory improvement more frequently than treatment with corticosteroids or ursodeoxycholic acid alone (9). In some patients, the resemblance to PBC may be so strong that treatment with ursodeoxycholic acid alone (13 mg/kg to 15 mg/kg daily) is sufficient (67). Combined therapy has been endorsed by the EASL for patients satisfying the Paris criteria with the recognition that this recommendation is not strongly evidence based (5,30).

Can J Gastroenterol Vol 27 No 7 July 2013

420
The overlap syndromes of AIH are clinical descriptions that have depending on the predominant manifestations (4,6). Therapy usually involves corticosteroids alone or in combination with low-dose ursodeoxycholic acid (13 mg/kg/day to 15 mg/kg/day) (3). Unfortunately, corticosteroid treatment does not prevent progression of the cholangiopathy in some children (41) and the transplant-free survival in these children is shorter than that in similar treated children without the biliary changes (68).

Treatment options for adults with the AIH-PSC overlap syndrome are limited (41) (Table 3). Mycophenolate mofetil has been ineffective in children with AIH and sclerosing cholangitis (69) and adults with classic PSC (70), and the reported experiences with the calcineurin inhibitors (cyclosporine and tacrolimus) in the treatment of the AIH-PSC overlap syndrome have been sparse (5,27,71). Conventional corticosteroid regimens have been effective to 100% of patients (2,18,20,27,38), and corticosteroids in combination with low-dose ursodeoxycholic acid have had similar inconsistent results (27,72). Despite these limitations, combined therapy with corticosteroids and low-dose ursodeoxycholic acid has been endorsed by the EASL and the American Association for the Study of Liver Diseases with the recognition that this recommendation is not strongly evidence based (5,30,31).

Prednisone or prednisolone (0.5 mg/kg/day tapered to 10 mg/day to 15 mg/day) and azathioprine (50 mg/day to 75 mg/day) in combination with ursodeoxycholic acid (15 mg/kg/day to 20 mg/kg/day) has been associated with a better survival in adults with the AIH-PSC overlap syndrome than that in adults with classic PSC (72), and a similar dosing schedule may be considered in adults with this overlap syndrome (Table 3). High-dose ursodeoxycholic acid (28 mg/kg/day to 30 mg/kg/day) should not be used because individuals with classical PSC who have been treated in this fashion have experienced increased frequencies of death from hepatic failure, need for liver transplantation and serious complications of advanced liver disease (73). High serum concentrations of the toxic metabolite lithocholic acid may have contributed to these dire consequences (74).

Treatment and outcome of the AIH-cholestatic overlap syndrome

Patients with the AIH-cholestatic overlap syndrome respond less well to conventional corticosteroid therapy than patients with classical AIH, and they respond as poorly as patients with AIH and large-duct PSC (2). Improvement to normal or near-normal laboratory tests and liver tissue was not achieved in six patients during conventional corticosteroid therapy, and the frequencies of disease progression and liver transplantation were 17% and 33%, respectively (2). A similarly poor response to conventional corticosteroid therapy has been reported in patients classified as having AIH and small-duct PSC, and they responded more poorly to corticosteroid therapy than patients with large-duct PSC (27).

Treatment options for patients with the AIH-cholestatic overlap syndrome are also limited (Table 3). Corticosteroid regimens have been generally ineffective, and therapies with low-dose ursodeoxycholic acid alone or in combination with corticosteroids have had variable results (2,11,27). No treatment has been preferred or endorsed by a liver society. Therapy usually involves corticosteroids alone or in combination with low-dose ursodeoxycholic acid (13 mg/kg/day to 15 mg/kg/day) depending on the predominant manifestations (4,6).

**CONCLUDING VIEWPOINTS**

The overlap syndromes are not valid pathological entities, but their recognition is important because they can influence management strategies (6,23). They should be sought in all patients with AIH who are refractory to conventional corticosteroid therapy, have cholestatic features, or concurrent inflammatory bowel disease. They cannot be assimilated into conventional diagnostic categories and should maintain separate classifications that emphasize their predominant component (5,6). Current designations that imply the simultaneous occurrence of two diseases in the same individual are presumptuous, and they should be modified to emphasize the predominant component of the syndrome and the modifying cholestatic feature that denotes the atypicality and influences the treatment strategy (5,6). Terms such as ‘AIH with destructive cholangitis’ or ‘AIH with biliary sclerosis’ may be more accurate and clinically valuable than terms such as ‘AIH-PBC’ or ‘AIH-PSC overlap syndrome’. The international liver societies and liver interest groups must standardize diagnostic criteria and designations that accurately reflect the clinical relevance and nature of these syndromes as currently understood.

**DISCLOSURES:** Presented, in part, during the Canadian Digestive Diseases Week and annual winter meeting of the Canadian Association for the Study of the Liver, Victoria, British Columbia, March 3, 2013. This review did not receive financial support from a funding agency or institution, and Albert J Czaja has no conflict of interests to declare.
REFERENCES
Submit your manuscripts at http://www.hindawi.com