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Special Article

International Autoimmune Hepatitis Group* Report: review of criteria for diagnosis of autoimmune hepatitis

*Group members: F. Alvarez, P. A. Berg, F. B. Bianchi, L. Bianchi, A. K. Burroughs, E. L. Cancado, R. W. Chapman, W. G. E. Cooksley, A. J. Czaja, V. J. Desmet, P. T. Donaldson, A. L. W. F. Eddleston, L. Fainboim, J. Heathcote, J.-C. Homberg, J. H. Hoofnagle, S. Kakumu, E. L. Krawitt, I. R. Mackay, R. N. M. MacSween, W. C. Maddrey, M. P. Manns, I. G. McFarlane, K.-H. Meyer zum Büschenfelde, G. Micli-Vergani, Y. Nakanuma, M. Nishioka, E. Penner, G. Porta, B. C. Portmann, W. D. Reed, J. Rodes, S. W. Schalm, P. J. Scheuer, E. Schrumpf, T. Seki, G. Toda, T. Tsuji, N. Tygstrup, D. Vergani and M. Zeniya

Following the identification of the hepatitis C virus (HCV) in 1989 (1), there was considerable uncertainty about criteria for diagnosis of the liver disorder which was then known as autoimmune chronic active hepatitis. In 1992, a panel of 27 physicians and pathologists with a particular interest in the syndrome was therefore convened at a meeting in Brighton, UK, to review the diagnostic criteria. That panel became the International Autoimmune Hepatitis Group (IAIHG), which shortly thereafter expanded to 40 members from 17 countries. The Group met again in Chicago in 1993 and in Copenhagen in 1994, acted as the advisory panel on autoimmune hepatitis (AIH) at the International Workshop on Terminology of Chronic Hepatitis at the World Congresses of Gastroenterology in Los Angeles in 1994 (2,3), and has since continued to monitor developments that impact on the diagnosis of the condition and to foster collaborative research.

The consensus report of the initial meeting in Brighton (4) included a descriptive set of criteria which it was recommended could be used for diagnosis in routine clinical practice to classify patients as having either "definite" or "probable" autoimmune hepatitis (AIH). Additionally, a diagnostic scoring system was devised to provide an objective method for selection of relatively homogeneous groups of patients for research purposes. It was acknowledged in that report (4) that these recommendations would require validation by prospective evaluation. In the intervening years, both the descriptive criteria and the scoring system have been widely used by many investigators and there is now sufficient published information to allow for a comprehensive review in relation to progress that has been made in understanding the clinical expression of this disease, although the pathogenesis remains obscure. During 1998, the IAIHG undertook a detailed review by correspondence between members and at a meeting of the Group in Chicago on 9th November 1998 during the 49th annual conference of the American Association for the Study of Liver Diseases. We report here the outcome of these deliberations.

Correspondence: Ian G. McFarlane, Institute of Liver Studies, King's College Hospital, Denmark Hill, London SE5 9RS, UK. Tel: 171 346 3253. Fax: 171 346 3167. e-mail: ian.mcfarlane@kcl.ac.uk

Review of Diagnostic Criteria

The descriptive criteria appear to have stood the test of time and require at most only minor modifications (see below) to bring them into line with recent developments in diagnostic modalities for liver disease generally. The review has, however, revealed that the scoring system requires some adjustments to improve specificity and simplify its use.

There are six published studies in which the scoring system has been applied to sufficient numbers of patients to allow for meaningful evaluation (5–10). Three of these (5–7) included a total of nearly 600 patients with AIH diagnosed by different criteria in different countries (Table 1). In a study of patients attending the Mayo Clinic, Czaja & Carpenter (5) employed the "conventional" clinical criteria (11) that were in use prior to publication of the "Brighton report"(4), Bianchi et al. (6) applied the IAIHG descriptive criteria to Italian patients, and in the study on Japanese patients by Toda et al. (7) AIH was diagnosed according to the Japanese Ministry of Health & Welfare criteria (7) which specify seropositivity for antinuclear antibodies (ANA). All three studies agreed that the scoring sys-

TABLE 1

Analysis of sensitivity of scoring system for diagnosis of autoimmune hepatitis

Study	Diagnostic criteria	*n*	Percent scoring as		Overall diagnostic sensitivity
			Definite AIH	Probable AIH	
Czaja & Carpenter (5)	"Conventional"	119	81.5%	18.5%	100%
Bianchi et al. (6)	IAIHG descriptive	45	68.8%	31.1%	99.9%
Toda et al. (7)	Japanese	434	54.8%	42.5%	97.3%
Total=		598			

AIH=autoimmine hepatitis. IAIHG=International Autoimmune Hepatitis Group.

TABLE 2

Specificity of scoring system for excluding autoimmune hepatitis in patients with chronic hepatitis C presenting with autoimmune features

Study	*n*	Percent scoring as		Overall diagnostic specificity
		Definite AIH	Probable AIH	
Czaja & Carpenter (5)	60	0	23.3%	76.7%
Bianchi et al. (6)	65	0	12.3%	87.7%
Toda et al. (7)	62	0	33.9%	66.1%
Miyakawa et al. (8)	25	0	8.0%	92.0%
Dickson et al. (9)	30	0	13.3%	86.7%
Total=	242			

AIH=autoimmune hepatitis.

TABLE 3

Specificity of scoring system for excluding autoimmune hepatitis in patients with biliary disorders

Study	Patient group	*n*	Percent scoring as		Overall diagnostic specificity
			Definite AIH	Probable AIH	
Czaja & Carpenter (5)	PBC PSC AIC	29	3.4%	51.7%	44.8%
Boberg et al. (10)	PSC	114	1.8%	33.3%	64.9%
Total=		143			

AIH=autoimmune hepatitis. PBC=primary biliary cirrhosis. PSC=primary sclerosing cholangitis. AIC=autoimmune cholangitis (patients with features of AIH and cholestatic biochemical profiles and/or histological or cholangiographic evidence of biliary disease).

tem has a very high degree of sensitivity, ranging from 97% to 100%, for diagnosis of AIH (Table 1).

In five of these six studies (5–9) the scoring system was also applied to a total of 242 patients with chronic hepatitis C who presented with features suggestive of AIH, including ANA, smooth muscle (SMA) or type 1 liver-kidney microsomal (anti-LKM-1) autoantibodies (Table 2). Additionally, Czaja & Carpenter (5) and Boberg et al. (10) tested the specificity of the system for *excluding* AIH in a total of 143 patients with primary sclerosing cholangitis (PSC) and other biliary disorders (Table 3). Specificity for exclusion of *definite* AIH in these 385 cases ranged from 96% to 100%. However, a variable proportion (between 8% and 52%) of patients achieved scores within the range stipulated for a diagnosis of *probable* AIH, reducing the overall specificity to between 45% and 92%. Similar findings have been reported from studies on smaller numbers of patients (12). In the majority of these cases the aggregate scores were borderline, i.e. only one or two points above the cut-off (10 points) for diagnosis of probable AIH. It was noted that indices which contributed mainly to inappropriate upgrading of scores to within the "probable" range included positive scoring for autoantibodies, mild to moderate elevations in serum immunoglobulins, low ratios of alkaline phosphatase (ALP) to aspartate (AST) or alanine (ALT) aminotransferases, concurrent immunological disorders and relevant HLA markers, together with inadequate weighting against histological evidence of biliary disease (5–10).

From the data provided for the 983 patients in the six main reports cited above (5–10), it is calculated that the overall diagnostic accuracy of the scoring system (i.e. the number of patients correctly diagnosed as having or not having definite or probable AIH as a percentage of the total number of patients studied) is 89.8%. This should be considered to be a minimal value because the calculation is based on the presumption that none of the patients with chronic hepatitis C or biliary disorders also had concomitant AIH (which is unknown).

Considerations for Revision of Diagnostic Criteria

Presenting clinical and serum biochemical features

The present review has reaffirmed that there are no particular signs, symptoms or liver test abnormalities that are of sufficient specificity to be considered part of the diagnostic criteria (4). Onset is usually insidious, with fatigue, fluctuating jaundice and arthralgia as typical features, but a substantial proportion of patients either have no obvious signs or symptoms of liver disease or have an (occasionally severe) acute presentation (13–15). There is often a history of other autoimmune disorders in the patient or first-degree relatives. The disease predominates among women, the archetypal patient being a young female with endocrine abnormalities, but it also affects males and it can present at almost any age. Distribution of age at onset was thought to be bimodal, with peaks around puberty and between the fourth and sixth decades of life (16), but it has been suggested that this impression probably relates to patterns of patient referral to specialist centres (14). In Japan, and in general gastroenterology practices elsewhere, the large majority of patients present between 50 and 70 years of age (7,14).

It is reaffirmed that hypergammaglobulinaemia with selective elevation of serum IgG is characteristic of AIH (4). Other serum biochemical abnormalities show a predominantly hepatitic pattern, but bilirubin concentrations and aminotransferase activities may range from just above the upper normal limits to more than 50 times these levels (4), with usually normal or only moderately elevated ALP, and do not reliably reflect severity of the disease. In keeping with the fluctuating nature of the condition, these biochemical indices may even spontaneously normalise despite histological evidence of continuing activity (15).

Review of the scoring system has revealed that adjustments to the scoring for ALP:AST(or ALT) ratio are necessary. During initial development of the system it was found that this parameter was essential to exclude PBC, and the ratio specified (3.0) achieved this without excluding the small proportion of AIH patients who present with cholestatic features. In retrospect, insufficient consideration was given to PSC, in which ALP activities are often only moderately raised and mild to moderate elevations of serum aminotransferase activities are frequently seen (10). In such cases the ALP:AST (or ALT) ratio falls below the cut-off that was set for negative weighting and this was a major contributory factor to the high proportion of patients with biliary diseases who achieved scores suggesting a diagnosis of "probable" AIH in the studies of Czaja & Carpenter (5) and Boberg et al. (10).

Histology

It is reaffirmed that: (a) there are no morphological features that are pathognomonic of AIH, but the characteristic histological picture is that of an interface (periportal or periseptal) hepatitis with a predominantly lymphoplasmacytic necroinflammatory infiltrate, with or without lobular (intra-acinar) involvement and portal-portal or central-portal bridging necrosis, often with the formation of liver cell rosettes and nodular regeneration (even in the early stages) in severe cases; and (b) patients in whom these features are seen together with clear evidence of bile duct damage or well-defined granulomas (see also "*Overlapping syndromes*" below) should not be regarded as having AIH (4). Other features such as lymphoid aggregates, steatosis, siderosis, cuprinosis, and bile ductule proliferation (which may occur to some degree in AIH, even in the absence of cirrhosis), are considered not to have the required specificity to exclude AIH, except where such features (and particularly combinations thereof) are sufficiently prominent to raise doubts about the diagnosis. Additionally, it is noted that the biochemical and immunological features of AIH can be seen in other disorders such as systemic lupus erythematosus in the absence of any significant liver involvement (17). It is therefore reiterated that a diagnosis of definite AIH should not be made without liver histology – and consultation with a hepatopathologist is strongly recommended (4).

Autoantibodies

It is reaffirmed that about 70–80% of AIH patients present with significant titres (1:40 or greater) of ANA or SMA (or both) and overall about 3–4% (mainly young females) have anti-LKM-1 (sometimes at titres $<$1:40), while up to 20% have none of these antibodies (4). In the context of liver disease, perinuclear staining antineutrophil cytoplasmic antibodies (pANCA) were previously thought to be particularly associated with PSC (18,19), but several recent studies have docu-

mented high titres of pANCA (detected by immunofluorescence on ethanol fixed neutrophils) in the sera of up to 90% of patients with AIH (20–24). Some progress has been made in defining sub-specificities of these four autoantibodies and identifying their target antigens (22,25–33). However, (a) sub-specificities of some antibodies (e.g. ANA) seem to have limited clinical implications in AIH (34,35) and reliance on others (e.g. anti-actin SMA) can lead to missed diagnoses in patients with AIH (36), (b) there is still ongoing debate about optimal detection techniques (23,28,30,31,37), and (c) tests for these sub-specificities are not yet widely available. For routine clinical practice, therefore, diagnosis of AIH will have to continue to rely on detection of ANA, SMA and anti-LKM-1 by conventional techniques.

Diagnosis of AIH in patients who present without ANA, SMA and anti-LKM-1 can be difficult but may be made on the basis of the combination of a hepatitic pattern of serum biochemical abnormalities, marked hypergammaglobulinaemia with selective elevation of serum IgG, typical histological findings, immunogenetic background (other autoimmune disorders in the patient or family and/or HLA typing), and appropriate investigations to carefully exclude other possible causes of liver disease. As noted in the "Brighton report" (4) several other autoantibodies are of relevance to AIH, namely those reacting with: (a) the hepatic asialoglycoprotein receptor (ASGP-R) (38,39), (b) a soluble liver antigen (SLA) (40), (c) a liver-specific cytosolic antigen (LC1) (41–44), (d) a liver-pancreas antigen (LP) (45), and (e) a glycosphingolipid (sulfatide) in hepatocyte plasma membranes (46). Tests for these are still only available in a few specialised laboratories but may continue to be used for diagnosis in ANA/SMA/LKM-1 negative cases. pANCA may be a useful addition to this repertoire.

Sub-types of AIH

There have been several proposals to classify AIH according to different autoantibody profiles (for review see (16)). Such classification can be useful for research purposes, but only the subdivision into Type 1 (ANA/SMA positive) and Type 2 (LKM-1 positive) is in common usage. However, this classification is not exclusive. While Type 2 patients can be defined in terms of a unique autoantibody profile and are almost always young females with severe disease, as noted above they represent only a small proportion of the total cases of AIH and the majority of young females with severe disease are Type 1. Additionally, long-term outcome is similar in these two groups (47). The clinical utility of this classification is therefore still uncertain (4,16,48,49).

Viral markers

Since publication of the "Brighton report" (4) there have been very marked improvements in the reliability and availability of tests for HCV, and knowledge about infections with this and other hepatotropic viruses has advanced significantly. The hepatitis G virus (GBV-C/HGV) seems not to be an aetiological factor in AIH (50,51), and routine testing for other viruses such as cytomegalovirus and Epstein-Barr virus, which only very occasionally cause hepatitis, is considered expensive and rarely necessary. It is therefore felt that for practical purposes exclusion of infection with the hepatitis A, B and C viruses by appropriate serology suffices and that AIH should not be excluded in seronegative patients who have a history of parenteral exposure to blood or blood products, or other risk factors for viral hepatitis.

Other aetiological factors

It is reaffirmed that a history of moderate to heavy alcohol intake or recent use of known hepatotoxic drugs should not exclude AIH if there is clear evidence of continuing liver damage after abstinence from alcohol or withdrawal of the drug. However, it was noted that scoring for alcohol history was unnecessarily complex (5) and that there was insufficient negative weighting in the scoring system to exclude probable AIH in patients who develop an AIH-like syndrome idiosyncratically induced by a wide range of drugs, of which the antibiotic minocycline is a recent typical example (52–54).

Response to immunosuppressive therapy

The present review reaffirms that response to immunosuppressive therapy is a characteristic of AIH (3,4) and that it is appropriate to include this as part of the assessment in the scoring system, especially if there is a relapse (necessitating continuing therapy) following an initial response. However, it is recognised that response is heavily dependent on patient compliance (which can be difficult to monitor) and that occasionally patients with classical AIH who present with severe acute disease do not respond very well to standard therapy (corticosteroids±azathioprine). Thus, whereas a rapid and sustained response may be considered to reinforce the diagnosis, a poor response should not necessarily exclude AIH. It is recommended that cholangiography should be performed in all patients with an initial diagnosis of definite or probable AIH who do not respond to corticosteroids.

Overlapping disorders

Features of AIH, particularly elevated serum IgG, autoantibodies and histologically evident interface hepatitis, occur with variable frequency and magnitude or severity in a wide range of other liver disorders, including acute and chronic viral hepatitis, PBC, PSC, Wilson's disease and alcoholic liver disease. This presents problems for diagnosis and, consequently, for clinical management because corticosteroids will often reduce the parenchymal inflammation in these disorders but are usually contraindicated. It is quite possible that, occasionally, the overlap is due to the co-existence of AIH with another disorder (55), which further complicates diagnosis and management.

Reports of the frequency of autoantibodies in chronic viral hepatitis vary widely but, overall, significant titres of ANA and/or SMA occur in 20–40% of patients with chronic hepatitis B or C and anti-LKM-1 in up to 6% of patients with chronic hepatitis C (56,57). On the other hand, pANCA is reportedly rare in chronic viral hepatitis (24) and may prove useful for distinguishing between patients with AIH and those with viral hepatitis who have autoantibodies. Recent evidence indicates that interferon therapy is generally safe in most cases of viral hepatitis with autoantibodies. However, screening for autoantibodies (particularly anti-LKM-1) before institution of therapy is recommended and patients need to be monitored carefully because occasionally interferon will unmask, or perhaps provoke, AIH or other autoimmune disorders (57–60).

Cholestatic syndromes overlapping with AIH have been variously described as: AIH/PBC, AMA-negative PBC, AMA-positive AIH, "cholestatic AIH" and AIH/PSC. They have three main features in common with AIH: elevated serum IgG, ANA and/or SMA, and histological evidence of interface hepatitis of varying severity (in addition to any biliary changes). They differ from each other with respect to the presence or absence of AMA and whether any bile duct lesions on liver biopsy are suggestive of PBC or PSC. It is noted that the terms "autoimmune cholangitis" or "autoimmune cholangiopathy" have been used most frequently to describe overlaps with PBC but they have also been applied to all of these disparate disorders (if, indeed, they are distinct) by different authorities at various times. There is still no universally agreed definition of these terms or classification of these conditions and the present review has highlighted a need for an international working party to clarify this. The previous rec-

TABLE 4

Revised descriptive criteria for diagnosis of autoimmune hepatitis

Features	Definite	Probable
Liver histology	Interface hepatitis (as defined in text) of moderate or severe activity with or without lobular hepatitis or central-portal bridging necrosis, but *without* biliary lesions or well-defined granulomas or other prominent changes suggestive of a different aetiology.	Same as for "definite".
Serum biochemistry	Any abnormality in serum aminotransferases, especially (but not exclusively) if the serum alkaline phosphatase is not markedly elevated. Normal serum concentrations of α_1-anti-trypsin, copper and ceruloplasmin.	Same as for "definite" but patients with abnormal serum concentrations of copper or ceruloplasmin may be included, *provided that Wilson's disease has been excluded by appropriate investigations.*
Serum immunoglobulins	Total serum globulin *or* γ-globulin *or* IgG concentrations greater than 1.5 times the upper normal limit.	Any elevation of serum globulin *or* γ-globulin *or* IgG concentrations above the upper normal limit.
Serum autoantibodies	Seropositivity for ANA, SMA or anti-LKM-1 antibodies at titres greater than 1:80. Lower titres (particularly of anti-LKM-1) may be significant in children. Seronegativity for AMA.	Same as for "definite" but at titres of 1:40 or greater. Patients who are seronegative for these antibodies but who are seropositive for other antibodies specified in the text may be included.
Viral markers	Seronegativity for markers of current infection with hepatitis A, B and C viruses.	Same as for "definite".
Other aetiological factors	Average alcohol consumption less than 25 g/day. No history of recent use of known hepatotoxic drugs.	Alcohol consumption less than 50 g/day and no recent use of known hepatotoxic drugs. Patients who have consumed larger amounts of alcohol or who have recently taken potentially hepatotoxic drugs may be included, *if there is clear evidence of continuing liver damage after abstinence from alcohol or withdrawal of the drug.*

TABLE 5

Revised scoring system for diagnosis of autoimmune hepatitis

Parameters/Features	Score	Notes*
Female sex	+ 2	
ALP:AST (or ALT) ratio:		
<1.5	+ 2	1
1.5–3.0	0	
> 3.0	−2	
Serum globulins *or* IgG above normal		
>2.0	+3	
1.5–2.0	+2	
1.0–1.5	+1	
<1.0	0	
ANA, SMA or LKM-1		
>1:80	+3	2
1:80	+2	
1:40	+1	
<1:40	0	
AMA positive	−4	
Hepatitis viral markers:		
Positive	−3	3
Negative	+3	
Drug history:		
Positive	−4	4
Negative	+1	
Average alcohol intake		
<25 g/day	+2	
>60 g/day	−2	
Liver histology:		
Interface hepatitis	+3	
Predominantly lymphoplasmacytic infiltrate	+1	
Rosetting of liver cells	+1	
None of the above	−5	
Biliary changes	−3	5
Other changes	−3	6
Other autoimmune disease(s)	+2	7
Optional additional parameters:		8
Seropositivity for other *defined* autoantibodies	+2	9
HLA DR3 or DR4	+1	10
Response to therapy:		
Complete	+2	11
Relapse	+3	
Interpretation of aggregate scores:		
Pre-treatment:		
Definite AIH	>15	
Probable AIH	10–15	
Post-treatment:		
Definite AIH	>17	12
Probable AIH	12–17	

* See explanatory notes in Table 6. ALP=alkaline phosphatase. AST=aspartate aminotransferase. ALT=alanine aminotransferase. ANA=antinuclear antibodies. SMA=smooth muscle antibodies. LKM-1=type 1 liver-kidney microsomal antibodies.

TABLE 6

Explanatory notes for Table 5

1	The ALP:AST (or ALT) ratio relates to the degree of *elevation above upper normal limits* (unl) of these enzymes, i.e.=(IU/l ALP÷unl ALP)÷(IU/l AST÷unl AST)
2	Titres determined by indirect immunofluorescence on rodent tissues or, for ANA, on HEp-2 cells. Lower titres (especially of LKM-1) are significant in children and should be scored at least +1.
3	Score for markers of hepatitis A, B and C viruses (i.e. positive/negative for IgM anti-HAV, HBsAg, IgM anti-HBc, anti-HCV and HCV-RNA). If a viral aetiology is suspected despite seronegativity for these markers, tests for other potentially hepatotropic viruses such as CMV and EBV may be relevant.
4	History of recent or current use of known or suspected hepatotoxic drugs.
5	"Biliary changes" refers to bile duct changes typical of PBC or PSC (i.e. granulomatous cholangitis, or severe concentric periductal fibrosis, with ductopenia, established in an *adequate* biopsy specimen) and/or a substantial periportal ductular reaction (so-called marginal bile duct proliferation with a cholangiolitis) with copper/copper-associated protein accumulation.
6	Any other *prominent* feature or combination of features suggestive of a different aetiology.
7	Score for history of any other autoimmune disorder(s) in patient or first-degree relatives.
8	The additional points for other defined autoantibodies and HLA DR3 or DR4 (if results for these parameters are available) should be allocated *only* in patients who are seronegative for ANA, SMA and LKM-1.
9	Other "defined" autoantibodies are those for which there are published data relating to methodology of detection and relevance to AIH. These include pANCA, anti-LC1, anti-SLA, anti-ASGPR, anti-LP and anti-sulfatide (see text).
10	HLA DR3 and DR4 are mainly of relevance to North European caucasoid and Japanese populations. One point may be allocated for other HLA Class II antigens for which there is published evidence of their association with AIH in other populations.
11	Assessment of response to therapy (as defined in Table 7) may be made at any time. Points should be added to those accrued for features *at initial presentation*.
12	Response and relapse as defined in Table 7.

ommendation (4) that they should not be included within the spectrum of AIH is reiterated.

Overlaps with PBC (i.e. AIH/PBC and AMA-negative PBC) are the most commonly reported, with up to 30–40% of patients with typical PBC histology having circulating ANA and/or SMA and/or some degree of interface hepatitis on liver biopsy. However, a recent study of 200 such patients concluded that the autoantibody profile is the only feature which consistently distinguishes these cases and that otherwise they have virtually identical clinical and histopathological features with those of classical PBC (61). Other studies have concluded that there are no substantial differences in the clinical spectrum or course of the disease between AMA-positive and AMA-negative PBC (62–65). Additionally, there is evidence that patients with so-called AMA-negative PBC may be found to have AMA when rigorously tested against a range of mitochondrial antigens reacting with each of the three main immunoglobulin isotypes (65–67). Genuine overlap of PBC with AIH may occur but it is recommended that this be considered

TABLE 7

Definitions of response to therapy

Response	Definition		
Complete	Either or both of the following: marked improvement of symptoms and return of serum AST or ALT, bilirubin and immunoglobulin values completely to normal within 1 year and sustained for at least a further 6 months on maintenance therapy, or a liver biopsy specimen at some time during this period showing at most minimal activity.	or	Either or both of the following: marked improvement of symptoms together with at least 50% improvement of all liver test results during the first month of treatment, with AST or ALT levels continuing to fall to less than twice the upper normal limit within 6 months during any reductions toward maintenance therapy, or a liver biopsy within 1 year showing only minimal activity.
Relapse	Either or both of the following: an increase in serum AST or ALT levels of greater than twice the upper normal limit or a liver biopsy showing active disease, with or without reappearance of symptoms, after a "complete" response as defined above.	or	Reappearance of symptoms of sufficient severity to require increased (or reintroduction of) immunosuppression, accompanied by any increase in serum AST or ALT levels, after a "complete" response as defined above.

as part of the spectrum of PBC and not as a variant of AIH. Since pANCA seems to be relatively rare in PBC (20) but occurs frequently in AIH (20–24), this autoantibody should prove useful for distinguishing between genuine cases of AIH and cases of PBC with features overlapping with those of AIH. Some studies have documented improvement of the parenchymal inflammation with corticosteroid therapy in patients with "AMA-negative PBC" (68) or classical PBC (69) (although the biliary damage persisted), but others have found corticosteroids to be ineffective (70,71).

If current recommendations that AMA (and particularly the M2 subtype that reacts with 2-oxo acid dehydrogenase complexes) should be considered virtually pathognomonic of PBC (72) and that patients with AMA should not therefore be considered to have AIH (4,49) are accepted, then "AMA-positive AIH" is a terminological contradiction. It seems likely that most (if not all) patients in this category have PBC and that failure to find histological evidence of PBC may be due to the early stage of the disease and/or to sampling error on liver biopsy.

"Cholestatic AIH" is a term that has been used to describe the approximately 10% of AIH patients who present with markedly elevated serum ALP and γ-glutamyl transferase activities without histological evidence of biliary disease. It is possible that a small minority may be cases of occult PSC or "AMA-negative PBC" but a recent long-term (median 14 years) follow-up of such cases suggests that they are not a clinically distinct subgroup, since they all responded to corticosteroid therapy with normalisation of the cholestatic indices and no evidence of development of biliary disease (73).

Overlaps between AIH and PSC are well recognised, especially in children (74–77). The comprehensive study by Boberg et al. (10) of AIH features in adults with PSC has shown that elevated serum IgG, autoantibodies and interface hepatitis occur frequently, but very few patients have combinations of these features with sufficient severity to qualify for a diagnosis of definite AIH (Table 3). Their differential diagnosis from AIH can be difficult if histological evidence of biliary changes or cholangiographic evidence of PSC is not obtained, especially since the serum ALP in PSC is often not markedly elevated (10,78). The possibility that such patients may have both AIH and PSC cannot be excluded. Due to the rarity of these cases, however, there is still uncertainty about optimal clinical management. Several case reports have documented a good response to corticosteroid therapy in terms of improvement of the parenchymal necroinflammation and normalisation of serum aminotransferases (73,79–83) but others have noted a less marked response (84).

TABLE 8

Aggregate scores after re-analysis using the revised scoring system in 40 patients with primary sclerosing cholangitis previously classified as having definite or probable autoimmune hepatitis

Classification	Aggregate score	Numbers of patients with the aggregate scores shown using	
		Original system (10)	Revised system
Definite AIH	18	1	0
	17	1	1
	16	0	1
Probable AIH	15	0	0
	14	2	0
	13	7	2
	12	7	3
	11	10	5
	10	12	0
Not AIH	<10	0	28

Data compiled from Boberg et al. (10) and from subsequent re-analysis of these data by K. Boberg (personal communication).

Revisions of Diagnostic Criteria

Descriptive criteria

The suggested minor modifications to the descriptive criteria are incorporated in Table 4. Histological features that are considered to lack sufficient specificity individually to exclude AIH have been omitted. The previous (4) separate specification for titres of autoantibodies in children is no longer considered necessary but it is noted that lower titres may be significant. Obligatory exclusion of markers of infection with hepatotropic viruses other than hepatitis A, B and C, and a history of parenteral exposure to blood products, is no longer required and the specifications relating to alcohol history have been simplified.

Scoring system

The main deficiencies of this system revealed by the present review relate to its relative complexity and its inadequate specificity with respect to excluding a diagnosis of probable AIH in other liver disorders, particularly in biliary diseases. The presentation has therefore been simplified as shown in Table 5, with explanatory notes provided separately in Table 6, and the scoring for a number of indices has been modified. The principal changes in the assigned scores relate to the ALP:AST (or ALT) ratio, drug history, liver histology and response to therapy.

The original scoring system allocated two points for ALP:AST (or ALT) ratios <3.0 and deducted two points for ratios >3.0 (4). However, as noted above, a high proportion of patients with PSC have ALP:AST (or ALT) ratios <3.0 (5,10), while a recent retrospective study of ALP:AST ratios at presentation in 100 consecutive patients with definite AIH revealed that only 5% had ratios >1.5 and none >3.0 (73). The scoring has therefore been adjusted to allocate no points for ratios between 1.5 and 3.0. This effectively deducts two points from patients with ratios between these limits, without affecting the scoring for the large majority of AIH patients. The negative score for recent or current hepatotoxic drug use has been increased from −1 to −4 to provide additional weighting against AIH-like drug-induced syndromes. To increase the weighting against biliary diseases, the negative score for AMA seropositivity has been raised from −2 to −4, and the negative scoring for histological evidence of bile duct damage has been increased from −1 to −3. Since interface hepatitis is such a characteristic of AIH, it seems logical to introduce a score of −5 for patients who do not have any evidence of this histological feature. Finally, since it is now recognised that some patients with classical AIH may not show a satisfactory response to immunosuppressive therapy for various reasons (see above), it is considered inappropriate to deduct points for "no response" or to include "treatment failure" or "partial response" in the assessment, and these three categories have been deleted.

To test these modifications, Dr. Kirsten Boberg (personal communication) has used the revised scoring system to re-analyse the previously reported (10) data on 114 PSC patients. Although there were slight reductions (by 1 and 2 points, respectively) in the scores for the two patients (1.8%) who were originally categorised as definite AIH (Table 3), both remained within the "definite" category (Table 8). However, the re-analysis revealed that of the 38 (33.3%) patients originally classified as "probable" AIH only 10 (8.8%) remained in this category, giving an overall specificity of 89.5% for exclusion of AIH in this group of PSC patients *vs.* 64.9% using the original system. Further evaluation is required to determine whether the modifications made to the scoring system also improve its specificity for excluding AIH in other liver diseases.

Application of the scoring system

The system is intended mainly for research purposes but it may also be useful (particularly for difficult cases) in routine clinical practice, in which, however, the descriptive criteria should usually suffice. Whether it might also be used as a basis for defining true "overlap" syndromes is yet to be determined. It is important to note that the scoring system is designed to be applied to features at initial presentation. Its use in other situations, such as suspected recurrence of AIH after liver transplantation or for reassessing the diagnosis in patients with long-standing disease, has not yet been validated. Additionally, it must be noted that the values assigned are purely arbitrary. They are qualitative in nature and do not reflect overall severity of disease. Scores should not therefore be subjected to mathematical manipulations for statistical analysis.

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References

1. Choo Q-L, Kuo G, Weiner AJ, Overby LR, Bradley DW, Houghton M. Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. Science 1989; 244: 359–62.
2. Ludwig J, McFarlane IG, Rakela J, Demetris AJ, Wanless IR, Panel Chairs. Terminology of chronic hepatitis, hepatic allograft rejection, and nodular lesi of the liver: summary of recommendations developed by an ternational working party. Am J Gastroenterol 1994; 89: S17/–S181.
3. Ludwig J, McFarlane IG, Rakela J, Panel Chairs. Terminology of

Chronic Hepatitis: International Working Party. Am J Gastroenterol 1995; 90: 181–9.
4. Johnson PJ, McFarlane IG. Meeting Report: International Autoimmune Hepatitis Group. Hepatology 1993; 18: 998–1005.
5. Czaja AJ, Carpenter HA. Validation of scoring system for diagnosis of autoimmune hepatitis. Dig Dis Sci 1996; 41: 305–14.
6. Bianchi FB, Cassani F, Lenzi M, Ballardini G, Muratori L, Giostra F, et al. Impact of International Autoimmune Hepatitis Group scoring system in definition of autoimmune hepatitis. An Italian experience. Dig Dis Sci 1996; 41: 166–71.
7. Toda G, Zeniya M, Watanabe F, Imawari M, Kiyosawa K, Nishioka M, et al., and the Japanese National Study Group of Autoimmune Hepatitis. Present status of autoimmune hepatitis in Japan – correlating the characteristics with international criteria in an area with a high rate of HCV infection. J Hepatol 1997; 26: 1207–12.
8. Miyakawa H, Kitazawa E, Abe K, Kawaguchi N, Fuzikawa H, Kikuchi K, et al. Chronic hepatitis C associated with anti-liver/kidney microsome-1 antibody is not a subgroup of autoimmune hepatitis. J Gastroenterol 1997; 32: 769–76.
9. Dickson RC, Gaffey MJ, Ishitani MB, Roarty TP, Driscoll CJ, Caldwell SH. The international autoimmune hepatitis score in chronic hepatitis C. J Viral Hep 1997; 4: 121–8.
10. Boberg KM, Fausa O, Haaland T, Holter E, Mellbye OJ, Spurkland A, et al. Features of autoimmune hepatitis in primary sclerosing cholangitis: an evaluation of 114 primary sclerosing cholangitis patients according to a scoring system for the diagnosis of autoimmune hepatitis. Hepatology 1996; 23: 1369–76.
11. Czaja AJ. Natural history, clinical features, and treatment of autoimmune hepatitis. Semin Liver Dis 1984; 4: 1–12.
12. Nishioka M, Morshed SA. Recent progress in autoimmune liver disease. In: Husband AJ, editor. Advances in Mucosal Immunology, vol. 1. Sydney: University of Sydney Press; 1997. p. 425–37.
13. Herzog D, Rasquin-Weber AM, Debray D, Alvarez F. Subfulminant hepatic failure in autoimmune hepatitis type 1: an unusual form of presentation. J Hepatol 1997; 27: 578–82.
14. Parker DR, Kingham JGC. Type 1 autoimmune hepatitis is primarily a disease of later life. Q J Med 1997; 90: 289–96.
15. Gordon SC. Diagnostic criteria, clinical manifestations and natural history of autoimmune hepatitis. In: Krawitt EL, Wiesner RH, Nishioka M, editors. Autoimmune Liver Diseases. 2nd ed. Amsterdam: Elsevier; 1998. p. 343–60.
16. McFarlane IG. The relationship between autoimmune markers and different clinical syndromes in autoimmune hepatitis. Gut 1998; 42: 599–602.
17. Kooy A, de Heide LJM, Engelkens HJH, Mulder AH, van Hagen M, Schalm SW. How to diagnose autoimmune hepatitis in systemic lupus erythematosus. Hepatology 1996; 23: 937–8.
18. Snook JA, Chapman RW, Fleming K, Jewell DP. Anti-neutrophil nuclear antibody in ulcerative colitis, Crohn's disease and primary sclerosing cholangitis. Clin Exp Immunol 1989; 76: 30–3.
19. Seibold F, Weber P, Klein R, Berg PA, Wiedmann KH. Clinical significance of antibodies against neutrophils in patients with inflammatory bowel disease and primary sclerosing cholangitis. Gut 1992; 33: 657–62.
20. Hardarson S, La Brecque DR, Mitros FA, Neil GA, Goeken JA. Antineutrophil cytoplasmic antibody in inflammatory bowel and hepatobiliary diseases: high prevalence in ulcerative colitis, primary sclerosing cholangitis, and autoimmune hepatitis. Clin Microbiol Immunol 1993; 99: 277–81.
21. Mulder AHL, Horst G, Haagsma EB, Limburg PC, Kleibeuker JH, Kallenberg CGM. Prevalence and characterization of neutrophil cytoplasmic antibodies in autoimmune liver disease. Hepatology 1993; 17: 411–7.
22. Vidrich A, Lee J, James E, Cobb L, Targan S. Segregation of pANCA antigenic recognition by Dnase treatment of neutrophils: ulcerative colitis, type 1 autoimmune hepatitis and primary sclerosing cholangitis. J Clin Immunol 1995; 15: 293–9.
23. Targan SR, Landers C, Vidrich A, Czaja AJ. High-titer antineutrophil cytoplasmic antibodies in type-1 autoimmune hepatitis. Gastroenterology 1995; 108: 1159–66.
24. Zauli D, Ghetti S, Grassi A, Descovich C, Cassani F, Ballardini G, et al. Anti-neutrophil cytoplasmic antibodies in type 1 and 2 autoimmune hepatitis. Hepatology 1997; 25: 1105–7.
25. Toh BH. Anti-cytoskeletal autoantibodies: diagnostic significance for liver diseases, infections and systemic autoimmune diseases. Autoimmunity 1991; 11: 119–25.
26. Worman HJ, Courvalin JC. Autoantibodies against nuclear envelope proteins in liver disease. Hepatology 1991; 14: 1269–79.
27. Takaki A, Sakaguchi K, Ogawa S, Kawamoto H, Tsuji T. Specificities and clinical significance of anti-cytoskeleton antibodies in anti-smooth muscle antibody-positive patients with chronic liver disease. Acta Med Okayama 1994; 48: 143–9.
28. Kallenberg CGM, Brouwer E, Weening JJ, Tervaert JWC. Anti-neutrophil cytoplasmic antibodies: Current diagnostic and pathophysiological potential. Kidney International 1994; 46: 1–15.
29. Wesierska-Gadek J, Penner E. Nuclear antigens. In: McFarlane IG, Williams R, editors. Molecular Basis of Autoimmune Hepatitis. Austin, Texas: RG Landes; 1996. p. 24–44.
30. Stoffel MP, Csernok E, Herzberg C, Johnston T, Carroll SF, Gross WL. Anti-neutrophil cytoplasmic (ANCA) directed against bactericidal/permeability increasing protein (BPI): a new seromarker for inflammatory bowel disease and associated disorders. Clin Exp Immunol 1996; 104: 54–9.
31. Zauli D, Cassani F, Bianchi FB. Cytoskeletal antigens. In: McFarlane IG, Williams R, editors. Molecular Basis of Autoimmune Hepatitis. Austin, Texas: RG Landes; 1996. p. 45–58.
32. Manns MP. Cytoplasmic antigens. In: McFarlane IG, Williams R, editors. Molecular Basis of Autoimmune Hepatitis. Austin, Texas: RG Landes; 1996. p. 59–74.
33. Terjung B, Herzog V, Worman HJ, Gestmann I, Bauer C, Sauerbruch T, et al. Atypical antineutrophil cytoplasmic antibodies with perinuclear fluorescence in chronic inflammatory bowel diseases and hepatobiliary disorders colocalize with nuclear lamina proteins. Hepatology 1998; 28: 332–40.
34. Czaja AJ, Cassani F, Cataleta M, Valentini P, Bianchi FB. Antinuclear antibodies and patterns of nuclear immunofluorescence in type 1 autoimmune hepatitis. Dig Dis Sci 1997; 42: 1688–96.
35. Chen M, Shirai M, Czaja AJ, Kurokohchi K, Arachi T, Arima K, et al. Characterisation of anti-histone antibodies in patients with type 1 autoimmune hepatitis. J Gastroenterol Hepatol 1998; 199: 483–9.
36. Czaja AJ, Cassani F, Cataleta M, Valentini P, Bianchi FB. Frequency and significance of antibodies to actin in type 1 autoimmune hepatitis. Hepatology 1996; 24: 1068–73.
37. Cancado EL, Vilas-Boas LS, Abrantes-Lemos CP, Novo NF, Porta G, Da Silva LC, et al. Heat serum inactivation as a mandatory procedure for antiactin antibody detection in cell culture. Hepatology 1996; 23: 1098–104.
38. Treichel U, McFarlane BM, Seki T, Krawitt EL Alessi N, Stickel F, et al. Demographics of anti-asialoglycoprotein receptor autoantibodies in autoimmune hepatitis. Gastroenterology 1994; 107: 799–804.
39. McFarlane BM. Hepatocellular membrane antigens. In: McFarlane IG, Williams R, editors. The Molecular Basis of Autoimmune Hepatitis. Austin, Texas: RG Landes; 1996. p. 75–104.
40. Czaja AJ, Carpenter HA, Manns MP. Antibodies to soluble liver antigen, P450IID6, and mitochondrial complexes in chronic hepatitis. Gastroenterology 1993; 105: 1522–8.
41. Abuaf N, Johanet C, Chretien P, Martini E, Soulier E, Laperche S, et al. Characterization of the liver cytosol antigen type 1 reacting with autoantibodies in chronic active hepatitis. Hepatology 1992; 16: 892–8.
42. Han S, Tredger M, Gregorio GV, Mieli-Vergani G, Vergani D. Anti-liver cytosolic antigen type 1 (LC1) antibodies in childhood autoimmune liver disease. Hepatology 1995; 21: 58–62.
43. Lenzi M, Manotti P, Muratori L, Cataleta M, Ballardini G, Cassani F, et al. Liver cytosolic 1 antigen-antibody system in type 2

autoimmune hepatitis and hepatitis C virus infection. Gut 1995; 36: 749–54.
44. Muratori L, Cataleta M, Muratori P, Lenzi M, Bianchi FB. Liver/kidney microsomal antibody type 1 and liver cytosol antibody type 1 concentrations in type 2 autoimmune hepatitis. Gut 1998; 42: 721–6.
45. Stechemesser E, Klein R, Berg PA. Characterization and clinical relevance of liver-pancreas antibodies in autoimmune hepatitis. Hepatology 1993; 18: 1–9.
46. Toda G, Ikeda Y, Kashiwagi M, Iwamori M, Oka H. Hepatocyte plasma membrane glycosphingolipid reactive with sera from patients with autoimmune chronic active hepatitis: its identification as sulfatide. Hepatology 1990; 12: 664–70.
47. Gregorio GV, Portmann B, Reid F, Donaldson PT, Doherty DG, McCartney M, et al. Autoimmune hepatitis in childhood: a 20-year experience. Hepatology 1997; 25: 541–7.
48. Maddrey WC. How many types of autoimmune hepatitis are there? Gastroenterology 1993; 105: 1571–4.
49. Desmet VJ, Gerber M, Hoofnagle JH, Manns M, Scheuer PJ. Classification of chronic hepatitis: diagnosis, grading and staging. Hepatology 1994; 19: 1513–20.
50. Heringlake S, Tillman HL, Cordes-Temme P, Trautwein C, Hunsmann G, Manns MP. GBV-C/HGV is not the major cause of autoimmune hepatitis. J Hepatol 1996; 25: 980–4.
51. Gerken G. Distinction between autoimmune and viral liver diseases. In: Berg P, Lohse AW, Tiegs G, Wendel A, editors. Autoimmune Liver Disease. London: Kluwer; 1997. p. 86–92.
52. Gough A, Chapman S, Wagstaff K, Emery P, Elias E. Minocylcine induced autoimmune hepatitis and systemic lupus erythematosus-like syndrome. Br Med J 1996; 312: 169–72.
53. Malcolm A, Heap TR, Eckstein RP, Lunzer MR. Minocycline induced liver injury. Am J Gastroenterol 1996; 91: 1641–3.
54. Goldstein PE, Devier J, Cremer M. Acute hepatitis and drug-related lupus induced by minocycline treatment. Am J Gastroenterol 1997; 91: 143–6.
55. Colombato LA, Alvarez F, Côté J, Huet MP. Autoimmune cholangiopathy: the result of consecutive primary biliary cirrhosis and autoimmune hepatitis ? Gastroenterology 1994; 107: 1839–43.
56. Czaja AJ, Carpenter HA, Santrach PJ, Moore SB. Immunologic features and HLA associations in chronic viral hepatitis. Gastroenterology 1995; 108: 157–64.
57. Cassani F, Cataleta M, Valentini P, Muratori P, Giostra F, Francesconi R, et al. Serum autoantibodies in chronic hepatitis C: comparison with autoimmune hepatitis and impact on disease profile. Hepatology 1997; 26: 561–6.
58. Calleja JL, Albillos A, Cacho G, Abreu L, Esartin P. Interferon and prednisone therapy in chronic hepatitis C with non-organ-specific antibodies. J Hepatol 1996; 24: 308–12.
59. Gregorio GV, Jones H, Choudhuri K, Vegnente A, Bortolotti F, Mieli-Vergani G, et al. Autoantibody prevalence in chronic hepatitis B virus infection: effect of interferon alpha. Hepatology 1996; 24: 520–3.
60. Dalekos GN, Wedemeyer H, Obermayer-Straub P, Kayser A, Barut A, Frank H, et al. Epitope mapping of cytochrome P4502D6 autoantigen in patients with chronic hepatitis C during α-interferon therapy. J Hepatol 1999; 30: 366–75.
61. Goodman ZD, McNally PR, Davis DR, Ishak KG. Autoimmune cholangitis. A variant of primary biliary cirrhosis: clinicopathological and serologic correlations in 200 cases. Dig Dis Sci 1995; 40: 1232–42.
62. Inverizzi P, Crosignani A, Battezzati PM, Covini G, De Valle G, Larghi A, et al. Comparison of the clinical features and clinical course of antimitochondrial antibody-positive and -negative primary biliary cirrhosis. Hepatology 1997; 25: 1090–5.
63. Michieletti P, Wanless IR, Katz A, Scheuer P, Yeaman S, Bassendine M, et al. Antimitochondrial antibody negative primary biliary cirrhosis: a distinct clinical syndrome of autoimmune cholangitis. Gut 1994; 35: 260–5.
64. Kim WR, Poterucha JJ, Jorgensen RA, Batts KP, Homburger HA, Dickson ER, et al. Does antimitochondrial antibody status affect response to treatment in patients with primary biliary cirrhosis ? Outcomes of ursodeoxycholic acid therapy and liver transplantation. Hepatology 1997; 26: 22–6.
65. Kinoshita H, Omagari K, Whittingham S, Kato Y, Ishibashi H, Sugi K, et al. Autoimmune cholangitis and primary biliary cirrhosis – an autoimmune enigma. Liver 1999; 19: 122–8.
66. Heathcote J. Overlap syndromes of autoimmune hepatitis, primary biliary cirrhosis and primary sclerosing cholangitis. In: Krawitt EL, Wiesner RH, Nishioka M, editors. Autoimmune Liver Diseases, 2nd ed. Amsterdam: Elsevier; 1998. p. 449–56.
67. Neuberger J, Thomson R. PBC and AMA – what is the connection? Hepatology 1999; 29: 271–6.
68. Ben-Ari Z, Dhillon AP, Sherlock S. Autoimmune cholangiopathy: part of the spectrum of autoimmune chronic active hepatitis. Hepatology 1993; 18: 10–15.
69. Mitchison HC, Palmer JM, Bassendine MF, Watson AJ, Record CO, James OFW. A controlled trial of prednisolone treatment in primary biliary cirrhosis. Three-year results. J Hepatol 1992; 15: 336–44.
70. Taylor SL, Dean PJ, Riely CA. Primary autoimmune cholangitis: an alternative to antibmitochondrial antibody-negative primary biliary cirrhosis. Am J Surg Pathol 1994; 18: 91–9.
71. Duclos-Valee JC, Hadenque A, Ganne-Carrie N, Robin E, Degott C, Erlinger S. Primary biliary cirrhosis-autoimmune hepatitis overlap syndrome. Corticoresistance and effective treatment by cyclosporine A. Dig Dis Sci 1995; 40: 1069–73.
72. Metcalf J, Mitchison HC, Palmer JM. Natural history of early primary biliary cirrhosis. Lancet 1996; 348: 1399–402.
73. McNair ANB, Moloney M, Portmann BC, Williams R, McFarlane IG. Autoimmune hepatitis overlapping with primary sclerosing cholangitis in five cases. Am J Gastroenterol 1998; 93: 777–84.
74. Wilschanski M, Chait P, Wade JA, Davis L, Corey M, St. Louis P, et al. Primary sclerosing cholangitis in 32 children: clinical, laboratory, and radiographic features, with survival analysis. Hepatology 1995; 22: 1415–22.
75. Protzer U, Dienes HP, Bianchi L, Lohse AW, Helmreich-Becker I, Gerken G, et al. Post infantile giant cell hepatitis in patients with primary sclerosing cholangitis and autoimmune hepatitis. Liver 1996; 16: 274–82.
76. Mieli-Vergani G, Vergani D. Autoimmune hepatitis in children. In: Krawitt EL, Wiesner RH, Nishioka M, editors. Autoimmune Liver Diseases, 2nd ed. Amsterdam: Elsevier; 1998. p. 425–32.
77. Roberts EA. Primary sclerosing cholangitis in children. In: Krawitt EL, Wiesner RH, Nishioka M, editors. Autoimmune Liver Diseases, 2nd ed. Amsterdam: Elsevier; 1998. 433–47.
78. Balasubramaniam K, Wiesner RH, LaRusso NF. Primary sclerosing cholangitis with normal alkaline phosphatase activity. Gastroenterology 1988; 95: 1395–8.
79. Rabinowitz M, Demetris AJ, Bou-Abboud CG, Van Thiel DH. Simultaneous occurrence of primary sclerosing cholangitis and autoimmune chronic active hepatitis in a patient with ulcerative colitis. Dig Dis Sci 1992; 37: 1606–11.
80. Leggett BA, Hallam A, Powell EE, Powell LW. Autoimmune chronic active hepatitis evolving to primary sclerosing cholangitis: evidence for a common pathogenesis [abstract]. Hepatology 1992; 16: 191A.
81. Lawrence SP, Sherman KE, Lawson JM, Goodman ZD. A 39 year old man with chronic hepatitis. Semin Liver Dis 1994; 14: 97–105.
82. Wurbs D, Klein R, Terracciano LM, Berg PA, Bianchi L. A 28-year-old woman with a combined hepatitis cholestatic syndrome. Hepatology 1995; 22: 1598–805.
83. Gohlke F, Lohse AW, Dienes HP, Löhr H, Märker-Hermann E, Gerken G, et al. Evidence for an overlap syndrome of autoimmune hepatitis and primary sclerosing cholangitis. J Hepatol 1996; 24: 699–705.
84. Roberts S, Poterucha JJ, Gores GJ, Czaja AJ. Overlap between type 1 autoimmune hepatitis and primary sclerosing cholangitis [abstract]. Hepatology 1995; 22: 129A.