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Primary sclerosing cholangitis and overlap features of autoimmune hepatitis: A coming of age or an age-ist problem?

Amanda Ricciuto¹, Binita M. Kamath¹, Gideon M. Hirschfield^{2,†}, Palak J. Trivedi^{3,4,5,6,*}

Summary

Autoimmune liver diseases are siloed into three syndromes that define clinical practice. These classifiers can, and are, challenged by variant presentations across all ages, something inevitable to disease definitions that rely on interpreting (inherently variable) semi-quantitative/qualitative clinical, laboratory, pathological or radiological findings. Furthermore this categorisation is premised on an ongoing absence of definable disease aetiologies. Clinicians thus encounter individuals with biochemical, serological, and histological manifestations that are common to both primary sclerosing cholangitis (PSC) and autoimmune hepatitis (AIH), often labelled as 'PSC/AIH-overlap'. In childhood the term 'autoimmune sclerosing cholangitis (ASC)' may be used, and some propose this to be a distinct disease process. In this article we champion the concept that ASC and PSC/AIH-overlap are not distinct entities. Rather, they represent inflammatory phases of PSC frequently manifesting earlier in the disease course, most notably in younger patients. Ultimately, disease outcomes remain similar to those of a more classical PSC phenotype observed in later life. Thus, we argue that it is now time to align disease names and descriptions used by clinicians across all patient subpopulations, to help unify care. This will enhance collaborative studies and ultimately contribute to rational treatment advances.

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Autoimmune liver disease concepts

Sophisticated immunologic privilege protects the liver from a varied portal venous antigen load and enables it to perform a continuous metabolic role in xenobiotic biotransformation. A tolerising hepatic immunoregulatory network of resident and traversing immune cells, alongside a carefully orchestrated bi-directional entero-hepatic 'collaboration' contributes to healthy homeostasis. When loss of immunologic tolerance occurs, a family of harmful autoimmune liver diseases (AILD) are seen. Although enigmatic in aetiology, and lacking in definable triggers, AILD is the result of a combination of genetic risk and environmental exposures (exposome) that are largely beyond the control of the individual.¹ Conceptually, diseases manifest as i) corticosteroid responsive relapsing-remitting hepatitis ["AIH"]; ii) sclerosing medium-large bile duct cholangitis ["PSC"]; and iii) lymphocytic, granulomatous, small bile duct cholangitis ["PBC"].

Age at the time of disease presentation has proved an interesting dynamic in understanding AILD: primary biliary cholangitis (PBC) does not occur at a meaningful frequency in childhood; but primary sclerosing cholangitis (PSC), autoimmune hepatitis (AIH), and variants thereof, do. This has divided the descriptive literature, depending on whether studies have a paediatric or adult focus.

Our personal perspectives are that autoimmune sclerosing cholangitis (ASC) and PSC/AIH 'overlap syndromes' represent temporal phases along a fundamental PSC continuum. It is our contention, that as non-distinct entities, patients are experiencing a clinico-pathological process aligned to the ultimate natural history of PSC.

Being critical about aetiology

Whilst defined disease triggers are lacking, we continue to be reliant on advances in knowledge gained from fundamental science, clinical presentation, treatment response and long-term follow-up studies. Genome-wide association studies are one robust approach to identifying risk factors for AILD. Such studies remain hypothesis free and are worth interrogating not just for specific risk alleles, but as importantly for mechanistic themes. Human leucocyte antigen (HLA) risks exist for all AILDs. Of interest, despite AIH seemingly being the most responsive to immunosuppression, it is associated with a relative paucity of identifiable non-HLA risk loci compared to PBC and PSC, which are largely non-overlapping genetically.

Another relevant concept that challenges the existing dogma arises from observations linking bile acid signalling and

Keywords: Autoimmune cholangitis; autoimmune liver disease; colitis; inflammatory bowel disease; overlap syndrome.

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immune cell function. The gut microbiome and bile acids may modulate immunoregulatory cell function,²⁻⁵ and by analogy cholestasis from bile duct injury could contribute to immune-mediated injury in the liver that manifests histologically and biochemically as a hepatitis, with some initial corticosteroid responsiveness. Thus, although the term “primary” in PSC derives from uncertainty surrounding pathogenesis, it does not exclude an important immunological role in the disease, which results in biliary and (often co-existent) gut inflammation. Whilst age at presentation may modulate the intensity and pattern of PSC presentation, for many, long-term follow-up is a better reflection of natural history.

The concept that ASC or PSC/AIH-overlap have distinct characteristics to PSC has practical implications for patient care, treatment, risk stratification and counselling. Additionally, overlap labels may limit participation in PSC trials.

Challenging historical paradigms

Overlapping features between PSC and AIH were originally reported in the 1980-1990s, first among children and soon after in adults. Overlap presentations have since been conceptualised in a number of ways (Fig. 1), however, it was a UK prospective study that first applied the term ‘autoimmune sclerosing cholangitis’, in reference to 27/55 children with AIH in whom features of biliary disease were observed on cholangiography.⁶ Biochemical

improvements under immunosuppressive treatment, with or without ursodeoxycholic acid, occurred in >80% of patients, accompanied by a significant decrease in histological inflammatory activity over a median follow-up of 6 years (range 2-16 years). The authors report that ASC is as common as AIH in children, represents a unique entity to PSC, and is part of the spectrum of AIH. However, histological confirmation of disease was not an explicit inclusion criterion, with eligibility requiring a biochemical and/or serological profile compatible with AIH. The study assumes at its outset that PSC is incompatible with AIH-like laboratory parameters, a challengeable premise given that hypergammaglobulinemia and autoantibody positivity are common in PSC.⁷ Moreover, half of the ASC group showed features of cholangiographic progression over a median of 5 years (range 1-9) despite medical therapy.⁶

Many subsequent adult studies invoking the International AIH Group (IAIHG) scoring system, to add a label of AIH to patients with known PSC, declare those with enough points as having overlap syndrome. However, IAIHG scoring was not designed for this purpose, its goal instead being to ensure homogeneity in AIH clinical research. A study using the original scoring system found that 33% of 114 adult patients with PSC identified by endoscopic retrograde cholangiopancreatography scored positively for at least probable AIH, with the most common contributors being elevated serum IgG values (61%),

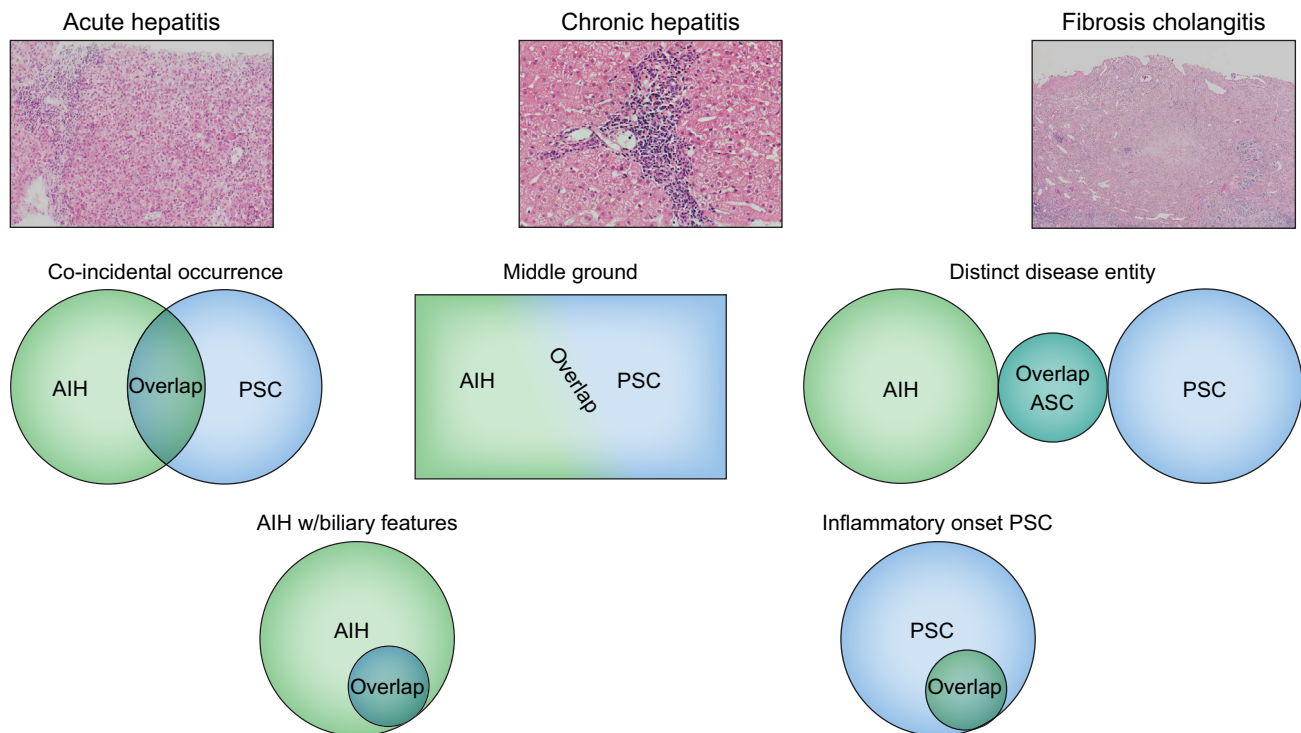


Fig. 1. Trying to understand the nature of PSC/AIH-overlap syndromes. Pathological processes in immune-mediated liver disease exist across a continuum, both spatially and temporally, and injury can range from a predominantly acute hepatitis, chronic hepatitis that can be primary or secondary, and fibrosing cholangiopathy. The challenge remains that neither AIH nor PSC has an absolute diagnostic test, with labels being attributed based on the presence (and relative absence) of disease-specific markers. To this effect, overlap presentations have historically been conceptualised in a number of ways, as either the coincidental occurrence of two diseases within the same individual, the ‘middle ground’ on a continuum bound by two different autoimmune liver diseases, a unique disease entity separate from AIH and PSC (for instance, ASC), or a disease state that falls along the spectrum of, and that can be diagnosed as, AIH or PSC predominant based on its overriding features – such as AIH with biliary features, or inflammatory onset PSC. AIH, autoimmune hepatitis; ASC, autoimmune sclerosing cholangitis; PSC, primary sclerosing cholangitis.

Table 1. Paediatric studies reporting comparative outcomes in patients with PSC/AIH-overlap.

Study	Study groups	Observation period	Treatments evaluated	Outcome assessment	PSC/AIH vs. PSC	PSC/AIH vs. AIH
Hensel 2021 ¹⁵ Retrospective	<ul style="list-style-type: none"> n = 59 ASC (↑ IgG values, positive autoantibodies and histological features of AIH in addition to cholangiopathy on imaging and/or histology score of ≥7 on ESPGHAN ASC criteria)⁹ n = 23 PSC 	Mean 6.8 (SD 3.3) years	All received UDCA; corticosteroids + azathioprine	Liver-related complications (portal hypertension, biliary complications, LTx, death)	4/59 (7%) vs. 2/23 (9%) (p = n.s.)	—
Deneau 2017 ²⁰ Retrospective	<ul style="list-style-type: none"> n = 260 PSC/AIH (large or small duct PSC and probable or definite AIH as per simplified IAIHG score) n = 521 PSC 	Median 4.4 (IQR 2-7.9) years	n.a.	5-year LTx-free survival 5-year event-free survival HPB cancer	90% vs. 87% (p = n.s.) 69% vs. 71% (p = n.s.) Adjusted HR 0.89 (0.67-1.2) 0% vs. 1.5% (n = 8 CCAs)	— — —
Deneau 2013 ³⁷ Retrospective	<ul style="list-style-type: none"> n = 12 ASC (large or small duct PSC and AIH as per simplified IAIHG score) n = 29 PSC n = 44 AIH 	Mean 5.9 (range 0.4-17.8) years	n.a.	5-year LTx-free survival 5-year event-free survival HPB cancer	90% (95% CI 47-99%) vs. 78% (95% CI 54-91%) (p = n.s.) 75% (95% CI 30-93%) vs. 75% (95% CI 30-93%) vs. 73% (95% CI 42-79%) (p = n.s.) 0% vs. 6.9% (n = 2 CCAs)	90% (95% CI 47-99%) vs. 87% (95% CI 71-95%) (p = n.s.) 87% (95% CI 71-95%) vs. 75% (95% CI 30-93%) vs. 85% (95% CI 67-93%) (p = n.s.) 0% vs. 0%
Feldstein 2003 ³⁸ Retrospective	<ul style="list-style-type: none"> n = 14 PSC/AIH (cholangiographic abnormalities and probable or definite AIH as per revised IAIHG score) n = 38 PSC 	Mean 6.6 (SD 4.4) years	Immunosuppression ± UDCA	LTx-free survival	No significant difference (log-rank p = 0.2)	—
Gregorio 2001 ⁶ Prospective	<ul style="list-style-type: none"> n = 27 ASC (clinical and/or biochemical evidence of liver disease plus serological profile compatible with AIH plus ERCP findings of PSC) n = 28 AIH 	Median 7 (range 2-16) years	Most received steroids ± azathioprine + UDCA	Biochemical Histological ERCP 10-year LTx-free survival HPB cancer	— — — — —	>80% vs. 100% normalized AST, GGT, ALP ↓ in histological inflammatory activity index from median 7 (range 2-11) to 2 (1-6) (p = 0.003) vs. 10 (3-12) to 2 (0-6) (p<0.001) 8/17 (47%) vs. 1/17 (6%) progressed 65% vs. 100% (p = 0.053) 0% vs. 0%

aHR, adjusted hazard ratio; AIH, autoimmune hepatitis; ALP, alkaline phosphatase; ASC, autoimmune sclerosing cholangitis; AST, aspartate aminotransferase; CCA, cholangiocarcinoma; ERCP, endoscopic retrograde cholangiopancreatography; GGT, gamma-glutamyltransferase; HPB, hepatobiliary; HR, hazard ratio; IAIHG, International Autoimmune Hepatitis Group; LTx, liver transplantation; PSC, primary sclerosing cholangitis; n.a., not applicable; n.s., not significant; UDCA, ursodeoxycholic acid.

Table 2. Adult studies reporting comparative outcomes in patients with PSC/AIH-overlap.

Study	Population (PSC/AIH definition)	Follow-up duration	Treatments evaluated	Outcomes	PSC/AIH vs. PSC	PSC/AIH vs. AIH
Weismüller 2017 ²³ Retrospective	<ul style="list-style-type: none"> • n = 470 PSC/AIH (large or small duct PSC plus biochemical, serological and/or histological features of AIH) • n = 6,651 PSC 	53,893 PY	N/A	LTx-free survival HPB cancer	IR: 4.7 vs. 5.62/10,000 PY difference (log-rank $p = n.s.$) IR: 0.43 vs. 1.52 (log-rank $p < 0.001$)	—
Lüth 2009 ³¹ Retrospective	<ul style="list-style-type: none"> • n = 16 PSC/AIH (definite AIH as per revised IAIHG score plus large or small duct PSC) • No comparator group 	Median 12 (range 1.5-18.5) years	Steroids ± azathioprine ± UDCA	Biochemical Histological LTx	14/16 (88%) ALT normalization 12/16 (75%) cirrhosis on repeat biopsy 1/16 (6%)	—
Olsson 2009 ³³ Retrospective	<ul style="list-style-type: none"> • n = 26 PSC/AIH (based on revised IAIHG score plus histological diagnosis of AIH and PSC ± cholangiographic abnormalities; 27% small duct) • No comparator group 	Mean 71 (SD 56) months in large duct; 120 (SD 56) months in small duct group	Most received steroids ± azathioprine ± UDCA	Biochemical LTx Death HPB cancer	16/24 (67%) experienced ≥50% ↓ in aminotransferases (better response in large duct) 5/26 (19%) (all large duct) 2/26 (8%) (all large duct) 1/26 (4%) (large duct)	—
Al-Chalabi 2008 ³⁹ Retrospective	<ul style="list-style-type: none"> • n = 16 PSC/AIH (definite AIH based on revised IAIHG score, typical AIH features on liver biopsy plus cholangiographic abnormalities) • n = 238 AIH 	Median 10.5 (range 2-25) years in PSC/AIH; 11 (range 1-35) years in AIH group	Most received steroids ± azathioprine ± UDCA	Biochemical Histological LTx-free survival HPB cancer	— — — —	88% vs. 96% ($p = 0.059$) complete biochemical response (as per revised IAIHG criteria) 10/13 (77%) vs. 105/129 (81%) improvement in necroinflammatory activity ($p = 0.24$) HR 2.08 7/16 (44%) vs. 57/238 (24%) LTx ($p = 0.24$) 2/16 (12%) vs. 8/238 (3%)
Floreani 2005 ²⁴ Retrospective	<ul style="list-style-type: none"> • n = 7 PSC/AIH (ERCP abnormalities of PSC plus definite AIH as per revised IAIHG score, with requirement for ANA or SMA positivity, and piecemeal necrosis, rosetting, moderate-severe periportal or periseptal lobular inflammation on liver biopsy) • n = 34 PSC 	Mean 93 (SD 66) months in PSC/AIH; 98 (SD 66) months in PSC group	Immunosuppression + UDCA	Biochemical LTx Overall survival HPB cancer	Significant reduction in AST ($p < 0.05$) vs. no change 1/7 (14%) vs. 6/34 (18%) 100% vs. 43% at 21 years 0 vs. 5/34 (15%)	—
Abdo 2002 ⁴⁰ Retrospective	<ul style="list-style-type: none"> • n = 6 PSC/AIH (AIH with subsequent PSC development – definite AIH as per revised IAIHG score, initially without PSC on ERCP/liver biopsy, subsequent development of cholangiographic abnormalities) • No comparator group 	Mean 6 years	Steroids ± azathioprine ± UDCA	Biochemical	Initially complete biochemical normalization, followed by subsequent signs of PSC and treatment resistance	—
McNair 1998 ³² Retrospective	<ul style="list-style-type: none"> • n = 5 PSC/AIH (definite AIH as per original IAIHG score plus cholangiographic abnormalities) • No comparator group 	Range 2-21 years	Steroids ± azathioprine ± UDCA	Biochemical Histological	5/5 biochemical response 4/5 improvement of inflammatory component but progression of biliary lesions	—
Czaja 1998 ⁴¹ Retrospective	<ul style="list-style-type: none"> • n = 14 PSC/AIH (cholangiographic abnormalities plus probable or definite AIH as per a modified AIH score based on but distinct from original IAIHG score) • n = 146 AIH 	Mean 62 (SD 38) months in PSC/AIH; 94 (SD 10) months in AIH group	Most received steroids ± azathioprine ± UDCA	Biochemical LTx/death	— —	2/9 (22%) vs. 55/86 (64%) biochemical remission ($p = 0.03$) 3/9 (33%) vs. 7/86 (8%) ($p = 0.05$)

(continued on next page)

Table 2. (continued)

Study	Population (PSC/AIH definition)	Follow-up duration	Treatments evaluated	Outcomes	PSC/AIH vs. PSC	PSC/AIH vs. AIH
Gohike 1996 Retrospective	<ul style="list-style-type: none"> n = 3 PSC/AIH (histological changes of AIH plus ERCP abnormalities compatible with PSC) No comparator group 	Range 7-11 years	Steroids ± azathioprine ± UDCA	Biochemical Histological	Normalization or significant improvement in ALT, IgG and ANA/SMA Resolution or improvement of parenchymal inflammation; persistence of periductular fibrosis	—

AIH, autoimmune hepatitis; ANA, anti-nuclear antibody; CCA, cholangiocarcinoma; ERCP, endoscopic retrograde cholangiopancreatography; HPB, hepatobiliary; HR, hazard ratio; IAIHG, International Autoimmune Hepatitis Group; LTx, liver transplantation; n.a., not applicable; PSC, primary sclerosing cholangitis; PY, person-years; SMA, anti-smooth muscle antibody; UDCA, ursodeoxycholic acid.

positive anti-nuclear antibody (ANA) and/or anti-smooth muscle antibodies (22%) and AIH-like histological features (33%). The finding of elevated AIH scores in this PSC cohort prompted development of revised scoring criteria,⁸ which introduced point deductions for biliary features on histopathology. These simplified criteria were designed with an inherently different purpose than the preceding AIH scoring system, namely to identify patients who may benefit from a trial of immunosuppressive therapy. The simplified IAIHG criteria led to an increase in specificity from 65% to 90%, and the proportion of cases labelled as probable AIH declined from 33% to 9%.⁹ The prevalence of AIH overlap in PSC is dependent on the method by which it is diagnosed. To this effect, the IAIHG explicitly recommend against using their scoring system to establish overlap subgroups.¹⁰ Interestingly, in validating the 2008 simplified AIH scoring algorithm, a small number of PSC/AIH-overlap patients (n = 2) were included in the AIH case group, and PSC patients in the control group (n = 23).¹¹ However, sample sizes were too small to allow for a meaningful assessment of the score's ability to distinguish PSC/AIH from PSC.

In a similar manner, alanine aminotransferase (ALT) activity is often purported as the biochemical hallmark of AIH, yet can be elevated >2-3x the upper limit of normal in most adults participating in PSC clinical trials.^{12,13} Preliminary data from the UK (n = 116) also show that young presenting age associates with lower serum alkaline phosphatase (ALP) and elevated aspartate aminotransferase (AST) values (Spearman's *rho* according to age = 0.239 and 0.252, respectively; *p* = 0.011 and 0.008, respectively).¹⁴ The revised IAIHG scoring system, putatively designed to ensure patients with PSC do not score too highly for AIH, have been applied in most adult studies. This contrasts with the lion's share of paediatric literature, with most paediatric studies using the 2008 simplified criteria that disregards point deductions for biliary features (Tables 1 and 2). Whilst a dedicated paediatric score has been proposed to discriminate ASC from AIH,¹⁵ the tool has yet to be validated and cannot differentiate ASC from PSC. This is because the point threshold is easily attainable in the presence of ANA and elevated IgG values alone, which are observed in ~80% and >60% of adults with PSC, respectively.⁷ Inflammatory bowel disease (IBD), which develops in >70% of patients with PSC, is itself associated with elevated IgG values.¹⁶ Anti-nuclear antibodies are also found in approximately 40% of patients with IBD,¹⁷ and in >65% of individuals who undergo treatment with anti-tumour necrosis factor agents.^{18,19}

Despite these observations, PSC presentations that manifest with one or more feature of AIH, be that biochemical, serological, or histological, continue to be labelled as overlap syndromes. As such, the label of 'overlap' has been a source of consternation for decades and has driven practical management questions from the juxtaposition of two conditions that differ in epidemiology, treatment, and prognosis.

Epidemiological insights

In children, the incidence and prevalence of ASC is estimated to be 0.1 and 0.6/100,000, respectively, as compared to PSC (0.2 and 1.5) and AIH (0.4 and 3.0).¹ Across global paediatric series,²⁰ up to one-third of children with PSC were reported to have AIH overlap (probable or definite as per the simplified AIH

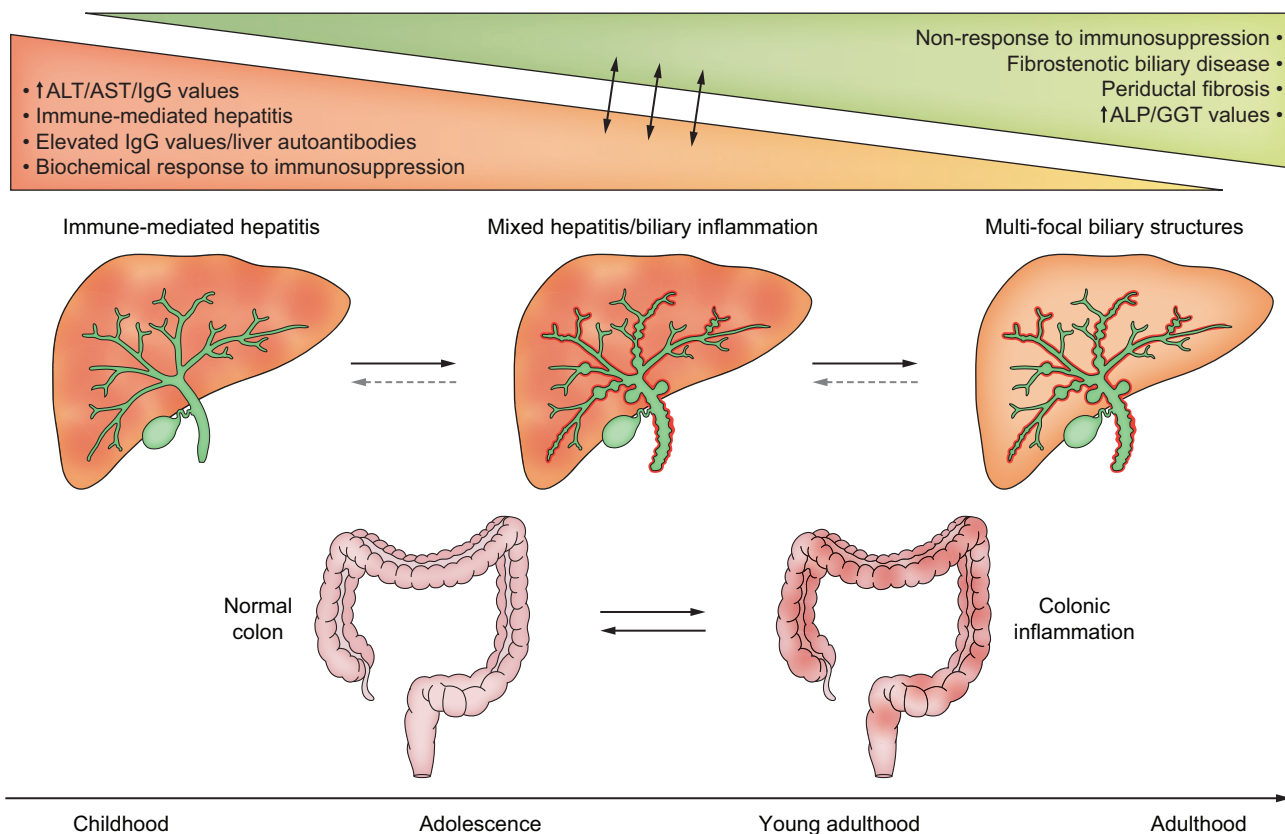


Fig. 2. Temporal evolution of immune-mediated hepatitis to PSC. Approximately 50% of children with immune-mediated hepatitis (elevated IgG values, elevated transaminases, interface activity) demonstrate signs of biliary disease as they grow older. Either concurrently or sequentially, signs of inflammatory bowel disease also develop, and sclerosing cholangitis emerges as the dominant clinical entity. The latter is associated with a loss of response to immunosuppression, and in some cases, a waning of hepatic inflammatory activity. This intermediate phenomenon of ‘ASC’ does not represent a distinct disease to PSC. However, it requires an acceptance that autoimmune disease phenotypes are not always static, can vary according to age, and tend to evolve over time. With age as a continuum, the evolution from an AIH-type picture to PSC being the predominant disease is not unique to children, with different phases of the disease process recognised amongst adolescents and the young adult population. Disease progression may not be linear, and inflammatory or secondary “AIH-like” flares can be observed along the journey that patients experience. AIH, autoimmune hepatitis; ALP, alkaline phosphatase; ALT, alanine aminotransferase; ASC, autoimmune sclerosing cholangitis; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase; PSC, primary sclerosing cholangitis.

score), which is similar to the proportion of adults reported in a single-centre study from Norway ($n = 114$, median age = 31 years) using the original IAIHG scoring system.⁸ However, more contemporary studies using the revised scoring system report features of AIH in between 6% and 14% of adults with PSC (Table 2). Reciprocally, the prevalence of features of PSC in AIH cohorts varies from 2–10% in adults^{21,22} to 50% in children.⁶

Proponents of the notion that PSC/AIH-overlap and ASC are distinct to PSC point to differences in phenotypic characteristics and responses to immunosuppression, although clinical comparisons are dependent on the way in which diagnoses have been made. When PSC/AIH-overlap presentations were compared to AIH in the original study, IBD was more common (44% vs. 18%), alongside perinuclear anti-neutrophil cytoplasmic antibody positivity (74% vs. 36%), more elevated cholestatic parameters (ALP/AST ratio 3.96 vs. 1.14) and lower AST values (102 vs. 333 IU/L). As the incidence and prevalence of PSC rise,¹ phenotypic understandings have seemingly evolved, with an increasing proportion of adults and children with PSC/AIH-overlap being diagnosed with IBD (75% and >60%, respectively).^{20,23,24} Colonic findings also appear to be similar between ASC and PSC, with extensive colitis worse in

the right colon along with rectal sparing.²⁵ Moreover, a single-centre study in children found that 40% of those with ASC have small bowel aphthous ulcers.²⁶

In a large paediatric PSC consortium ($n = 781$), PSC/AIH overlap (compared to PSC) occurred more often in patients of female sex (45% vs. 36%), was less commonly associated with IBD (63% vs. 82%), more often associated with non-IBD autoimmune comorbidities, and manifested with greater IgG values (23 vs. 17 g/L), seropositivity for ANA and anti-neutrophil cytoplasmic antibody, and baseline elevations in serum ALT activity (299 vs. 161 U/L).²⁰ Data from an Italian series also highlight that histologically evident biliary lesions are more common in children with AIH and IBD than in those with AIH alone (8/12 vs. 6/38).²⁷ In turn, adults with PSC/AIH-overlap tend to be younger at diagnosis than those with more typical manifestations of PSC (mean 32 vs. 39 years old, respectively).²³ However, data from the International PSC Study Group also show that the proportion of patients labelled with PSC/AIH-overlap who develop IBD increases over time, from 44% to 60% over a median follow-up of 14.4 years – in support of PSC being the underlying disease process. This observation highlights how disease labels cannot be static and must evolve

in line with clinical changes; a concept widely accepted across other areas of medicine, with IBD being the exemplar. For instance, children with young age onset IBD often cannot be classified under the Crohn's disease or ulcerative colitis labels until later life.²⁸ Additionally, a change in disease label is evident in up to 9% of adults within the first 5 years of an IBD diagnosis.²⁹

Implications for the patient and clinician

In contrast to recommendations for classical PSC, some paediatric and adult guidelines endorse immunosuppressive therapy for PSC/AIH-overlap, given that several small, uncontrolled studies show high rates (>70%) of biochemical improvement ± reduction of parenchymal inflammation with immunosuppressive treatment.^{30–33} However, this is despite overt progression of biliary lesions and/or fibrosis on liver biopsy.^{30,32} In one study of 16 adults with PSC/AIH-overlap, those with large duct involvement displayed the greatest improvements in biochemistry. However, adverse events (transplant, death and cancer) also occurred uniquely within the large duct subgroup,³³ illustrating a disconnect between biochemical evolution and eventual outcome. Standalone case studies that report a survival advantage following immunosuppressive treatment do not provide direct 'head-to-head' comparisons to non-treated patients with PSC,³⁴ and quote time-to-event estimates that are no different to population-based PSC cohorts.³⁵

Series from across Europe and North America validate the fact that despite biochemical improvement, transplant-free survival is similar in PSC/AIH-overlap and classical PSC groups, but lower than that expected for AIH (Tables 1 and 2). International, multicentre data estimate the 5-year transplant-free survival rate to be between 71–85% and 61–92% from the point of first diagnosis, for classical PSC and PSC/AIH-overlap, respectively.²³ In turn, the paediatric literature cites 5-year event-free survival rates of 69% and 67% for PSC/AIH-overlap and large duct PSC, respectively (hazard ratio 0.89; 95% CI 0.67–1.2).²⁰

Long-term immunosuppression risks patient harm. Additionally, the diagnostic label of AIH overlap is a common exclusion criterion for interventional PSC clinical trials. Given the dynamic nature of AILD, with the potential (perhaps even expectation) of AIH in the young patient to evolve to a predominantly biliary stricturing disease over time, a label of ASC should not be misconstrued as a hard indication to continue immunosuppression indefinitely. In turn, AIH remission targets should not be applied to patients with PSC/AIH-overlap when determining suitability to withdraw immunosuppression. One may postulate that whilst immunosuppression alleviates parenchymal inflammation, this does not favourably influence bile duct injury or fibrosis. Whilst it can be appropriate to initiate a trial of immunosuppression at presentation, clinical review with close longitudinal follow-up of cholangiographic appearances will be key in long-term management, and guide de-escalation of immunosuppression over time. This contrasts with the AIH paradigm of lifelong immunosuppression for the majority.

Reframing paradigms

We propose that the clinical profiles of PSC/AIH-overlap and ASC are not distinct, but rather represent an 'inflammatory' phase of PSC that manifests earlier in the disease course, which then converges toward a more classic PSC phenotype in older age (Fig. 2).

Firstly, like other immune-mediated conditions including IBD, AILD presentations are heterogeneous, with cross-sectional and longitudinal intra-patient variability. In Crohn's disease, it is well-recognised that patients can progress from an inflammatory to a fibrostenotic phase over time. We acknowledge, however, that this progression may not be linear, with inflammatory or secondary "AIH-like" flares possible (and perhaps to be expected) along the way, particularly in younger patients. Whilst our limited grasp of PSC pathogenesis precludes a refined understanding of this heterogeneity, age at disease onset appears to be a common theme. This is like the pattern of young age onset PBC, which can manifest with elevated serum aminotransferase values and moderate-severe interface hepatitis. The assumption that PSC must conform to a singular static prototype, and that any deviation mandates a separate diagnosis is also not consistent. For instance, in chronic hepatitis B virus infection it is readily accepted that there are distinct phases of the immune response, with transition between inflammatory and non-inflammatory presentations and variation in immune response by age. In all examples, it is accepted that different disease phases arise from common pathophysiological drivers. The rate of hepatitis B flares on discontinuation of anti-viral therapy, including the self-resolution of hepatitis activity in many, should serve as an interesting comparator to AILD activity. To use a further IBD analogy, the entity of IBD-unclassified is perceived by many IBD specialists to be a placeholder until the 'true' IBD type manifests in later life.³⁶ Similarly, in PSC, greater tolerance for temporary diagnostic uncertainty may be an asset, as it fosters a flexible and unbiased approach towards reaching a more definitive diagnostic label longer-term.

To this end, there is an urgent need for greater collaboration between paediatric and adult practitioners and researchers, to define long-term natural history, but also to streamline the work-up of individuals of all ages presenting with AILD, which currently varies between centres and physicians. For example, given the strong association between gut inflammation and AILD, and the potential effects of immunosuppressive therapies on the liver, routine screening for IBD with ileocolonoscopy in children and young adults presenting with AIH should be considered. Alongside long-term cohort studies – ideally bridging the artificial divide that exists between paediatric and adult care – there is a need for prospective observational clinical trials and higher quality population-based data. This is with the overarching goal of better describing the natural history of all AILD phenotypes and the optimal use of therapies. With this, we hope to eventually leave the age of uncertainty behind us and to move towards an age of opportunity for clinicians and patients.

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Abbreviations

AIH, autoimmune hepatitis; AILD, autoimmune liver diseases; ALP, alkaline phosphatase; ANA, anti-nuclear antibody; ASC, autoimmune sclerosing cholangitis; HLA, human leucocyte antigen; IAIGH, International AIH Group; IBD, inflammatory bowel disease; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis.

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Conflict of interest

The authors report no conflicts of interest as relates to the conduct of this study. Unrelated to this study PT has received grant support from the Wellcome Trust, the Medical Research Foundation, GlaxoSmithKline, Guts UK, PSC Support, LifeArc, NIHR, Intercept Pharma, Dr Falk Pharma, Gilead Sciences, and Bristol Myers Squibb. He has also received speaker fees from Intercept and Dr Falk, and advisory board/consultancy fees from Intercept, Dr Falk, Albireo, Ipsen and GlaxoSmithKline. GMH has received consultancy and speaker fees from Intercept, Cymabay, GSK, Dr. Falk, Ipsen, Mirum, Escent, HighTide and Gilead; BMK has received consultancy fees from Mirum Pharmaceuticals, Inc., Albireo Pharma, Inc., Audentes Therapeutics, Inc., and Third Rock Ventures.

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

Authors' contributions

Study concept and commission: GMH; Manuscript preparation: AR, BMK, GMH and PT; Manuscript finalisation: GMH and PT; Manuscript approval: all authors.

Supplementary data

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Author names in bold designate shared co-first authorship

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