



به نام خدا

Autoimmune liver disease (overlap syndrome)

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Diagnosis and Management of Pediatric Autoimmune Liver Disease: ESPGHAN Hepatology Committee Position Statement

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ABSTRACT

82. Francavilla R, Castellaneta S, Davis T, et al. Serological markers of coeliac disease in children with autoimmune hepatitis. *Acta Endoscopica* 2001;3:281–2.
83. Najafi M, Sadjadei N, Eftekhari K, et al. Prevalence of celiac disease in children with autoimmune hepatitis and vice versa. *Iran J Pediatr* 2014;24:723–8.



Definition

- The term overlap syndrome is employed to describe variant forms that display characteristics of both AIH and PSC, which is also called autoimmune sclerosing cholangitis (ASC) mainly observed in children and young adults.



- Autoimmune liver disease encompasses autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC) and ‘overlap syndromes’ of AIH with PBC or PSC.
- However, in children only AIH-PSC overlap syndrome, also known as ‘autoimmune sclerosing cholangitis’ (ASC), has been recognized
- *SLE??*
- **ESPGHAN guideline** → In children and adolescents, there are 3 liver disorders in which liver damage is likely to arise from an autoimmune attack: autoimmune hepatitis (AIH), autoimmune sclerosing cholangitis (ASC), and de novo AIH after liver transplant



PSC

- Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease that is characterized by inflammation and fibrosis of the intrahepatic and/or extrahepatic biliary ducts and is commonly associated with inflammatory bowel disease (IBD), primarily ulcerative colitis (UC).
- The natural history of PSC is progression to advanced fibrosis and end-stage liver disease requiring liver transplantation (LT).
- PSC is also associated with an increased risk of hepatobiliary and colorectal cancer, particularly in adults.



AIH and PSC can occur sequentially .(AIH $\Leftrightarrow$ PSC)

Sclerosing cholangitis may also complicate a wide variety of disorders, including primary and secondary immunodeficiencies, Langerhans cell histiocytosis, psoriasis, cystic fibrosis, reticulum cell sarcoma, and sickle cell anemia.



ASC is as prevalent as AIH-1 (only one prospective study)

In this study, clinical features of ASC compared to AIH include:

1. 50% of the patients with ASC are male.
2. Abdominal pain, weight loss, and intermittent jaundice, are frequent presenting symptoms in both ASC and AIH-1.
3. IBD affects about 45% of children with ASC, and about 20% of those with AIH.
4. Virtually all ASC patients are seropositive for ANA and/or SMA.
5. 90% of children with ASC have greatly increased serum IgG levels.
6. Standard liver function tests do not help in discriminating between AIH and ASC at presentation.
7. The IAIHG scoring systems do not discriminate between AIH and ASC.
8. pANCA is present in 75% of patients with ASC in comparison with 45% of patients with AIH type 1 and 10% of those with AIH type 2.



Epidemiology

- The reported prevalence of AIH-PSC overlap in adults is 1.7–10% in AIH .
- However, the prevalence of ASC in children is reported to be much higher (20–49%).....(33-50%).
- ASC has been proposed as an overlap syndrome of AIH with features of sclerosing cholangitis, which **affects males and females equally**.
- Peak of incidence in the older child, typically in pre-pubertal age .



Clinical presentation

- These conditions can present insidiously or with a picture of acute hepatitis.
- **Gregorio et al 'proposed the term autoimmune sclerosing cholangitis (ASC) for children with radiographic features suggestive of sclerosing cholangitis and with a biopsy revealing interface hepatitis, associated with the presence of high levels of antibodies and immunoglobulin G in the serum.**

TABLE 1. The baseline clinical characteristics of patients with a known diagnosis of autoimmune hepatitis and the comparison between those who developed autoimmune sclerosing cholangitis during the follow-up (ASC group) and those who did not (AIH group)

	Total (134)	AIH group (106)	ASC group (28)	<i>P</i>
Score diagnosis: AIH definitive	73	57	16	
AIH likely	61	49	12	0.83
Female sex*	98 (73.1%)	82 (77.3%)	16 (57.1%)	0.04
Age at diagnosis, [†] y	10.41 (7.4–12.5)	10.5 (7.3–12.8)	10.7 (8.4–11.5)	0.76
Clinical presentation				
Prolonged acute hepatitis*	50 (37.3%)	42 (39.6%)	8 (28.6%)	0.38
Chronic form*	52 (38.8%)	38 (35.8%)	14 (50%)	0.19
Liver failure*	20 (14.9%)	18 (17%)	2 (7.1%)	0.24
Silent*	11 (8.2%)	5 (4.7%)	6 (21.4%)	0.01
Other*	1 (0.74%)	1 (0.94%)	0	1
Other autoimmune manifestations				
Hemolytic anemia*	3 (2.2%)	3 (2.8%)	0	0.49
Thyroiditis*	4 (2.9%)	4 (3.7%)	0	0.38
Vitiligo*	3 (2.2%)	1 (0.9%)	2 (7.1%)	0.11
Arthritis and/or arthralgia*	10 (7.5%)	8 (7.54%)	2 (7.1%)	0.65
Acneiform lesions*	4 (2.9%)	3 (2.8%)	1 (3.5%)	0.61
Autoimmune disease in relatives*	49 (36.6%)	39 (36.8%)	10 (35.7%)	0.57
Liver disease in relatives*	14 (10.4%)	11 (10.4%)	3 (10.7%)	0.76

AIH = autoimmune hepatitis; ASC = autoimmune sclerosing cholangitis.

AIH group: patients who did not develop ASC during follow-up; ASC group: patients who developed ASC during follow-up.

Less frequent autoimmune manifestations: psoriasis (1 patient), uveitis (1 patient), idiopathic thrombocytopenic purpura (1 patient), systemic lupus erythematosus (1 patient), celiac disease (1 patient), and inflammatory bowel disease (1 patient).

* Number (frequency, %).



Diagnosis

- Almost all patients with ASC have autoimmune serology and histological characteristics similar to AIH-1).
- ASC is serologically (ANA/SMA) and histologically similar to autoimmune hepatitis type 1, but in addition has bile duct damage demonstrable by cholangiography, often already at presentation.
- Positivity for peripheral anti-nuclear neutrophil antibodies is more frequent in ASC than AIH. Rare patients with ASC are anti-LKM-1-and Anti-LC-1 positive.
- ASC is more frequently associated to IBD than AIH.
- De novo AIH after LT is characterized by autoantibody seropositivity (ANA, SMA, and typical or atypical antiLKM-1).
- *Almost all patients with ASC have autoimmune serology and histological characteristics similar to AIH-1 (. Of note, alkaline phosphatase and gamma glutamyl transpeptidase levels—usually elevated in cholestatic disease—are often normal or only mildly increased in the early disease stages of ASC, although the alkaline phosphatase/AST ratio is significantly higher in ASC than in AIH*

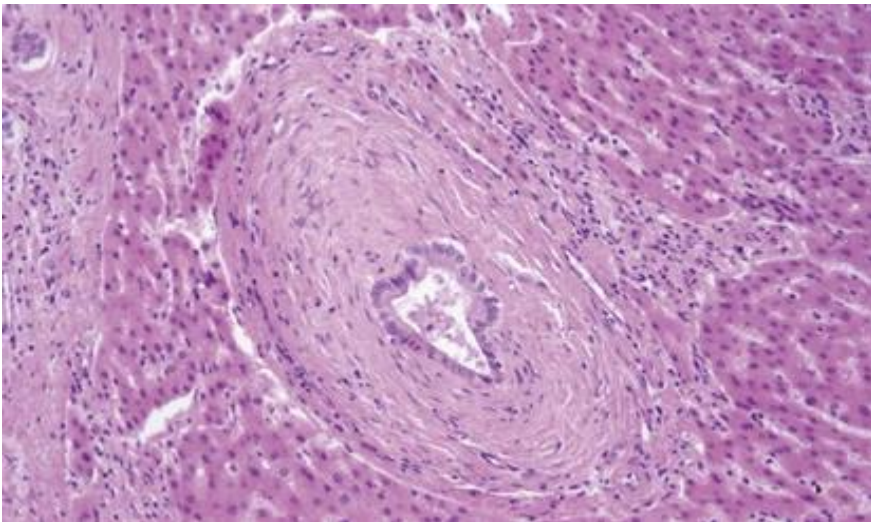


Liver biopsy

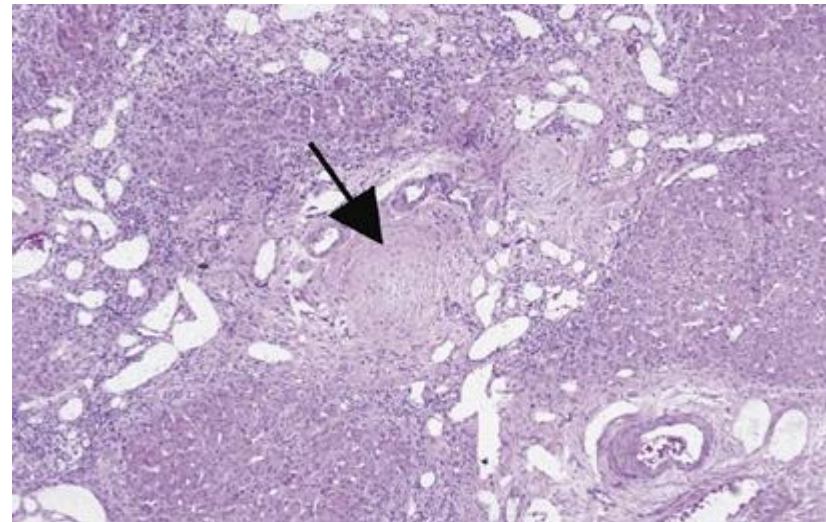
- The characteristic histological feature, common to AIH, ASC, and de novo AIH after transplantation, is interface hepatitis
- Interface hepatitis is characterized by a dense inflammatory infiltrate composed of lymphocytes and plasma cells, which crosses the limiting plate and invades the surrounding parenchyma.
- Biliary features include bile duct damage and proliferation, and cholangitis. (the disease process may be patchy 😞)
- Approximately 25% of children with ASC reportedly have no histological biliary features and are diagnosed based on cholangiography alone.



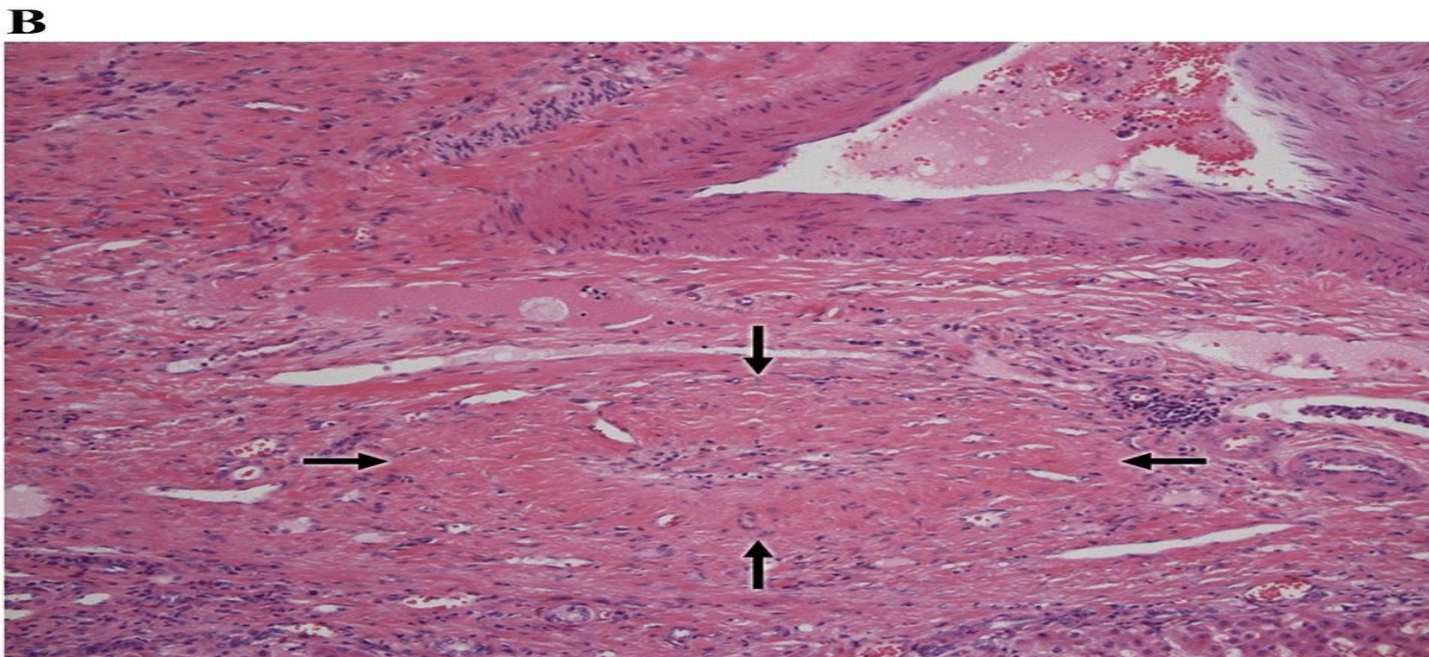
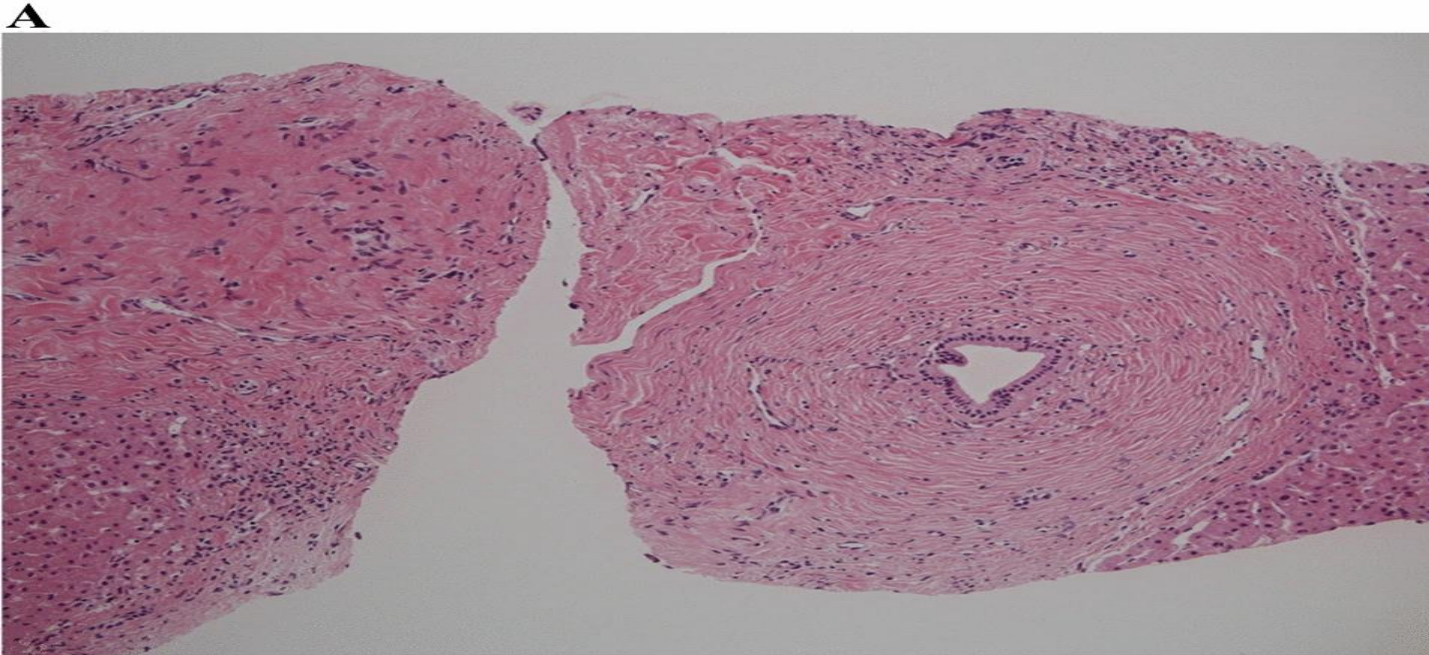
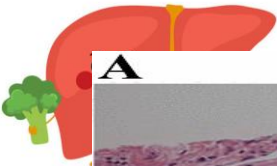
- Histology is also the criterion standard for evaluating the extent of fibrosis and helps in identifying overlap syndromes as well as the possible presence of concomitant diseases, such as nonalcoholic fatty liver disease .
- Although inflammatory changes surrounding the bile ducts are present also in a small proportion of patients with classical AIH, when conspicuous, they suggest an overlap with sclerosing cholangitis.



Concentric periductal fibrosis with bile duct distortion.



PSC. Nodular almost acellular scars mark areas of destroyed bile ducts



Histology of the liver biopsy.

A Onion-skin lesion (hematoxylin and eosin staining), concentric fibrosis around the bile duct epithelium.

B Fibrous obliterative cholangitis (arrows, hematoxylin and eosin staining), fibrous occlusion of the bile duct lumen due to the progression of an onion-skin lesion



Magnetic Resonance Cholangiopancreatography (MRC)

- The guidelines of American Association for the Study of Liver Disease (AASLD) as well as the clinical practice guidelines of European Association for the Study of the Liver recommend, “all children with AIH should undergo cholangiographic studies to exclude PSC”.
- ESPGHAN hepatology committee's position statement also recommend cholangiographic studies in all children with AIH .
- High sensitivity (84%) and accuracy (84-94 %)
- **It is considered the "gold standard" for diagnosis**



Technique

- Magnetic resonance cholangiopancreatography or MRCP uses a powerful magnetic field, radio waves and a computer to evaluate the liver, gallbladder, bile ducts, pancreas and pancreatic duct for disease. It is noninvasive and does not use ionizing radiation.
- Patients are fasted for 4 h prior to the study in order to reduce fluid secretions within the stomach and duodenum, reduce bowel peristalsis and promote gallbladder distension.
- **The MRCP test doesn't use contrast**
- Gadolinium: Po /Inj (maybe): When given intravenously, show hepato-biliary excretion.
- Sedation
- It makes use of heavily T2-weighted pulse sequences, thus exploiting the inherent differences in the T2-weighted contrast between stationary fluid-filled structures in the abdomen (which have a long T2 relaxation time) and adjacent soft tissue (which has a much shorter T2 relaxation time). Static or slow-moving fluids within the biliary tree and pancreatic duct appear of high signal intensity on MRCP, whilst surrounding tissue is of reduced signal intensity.

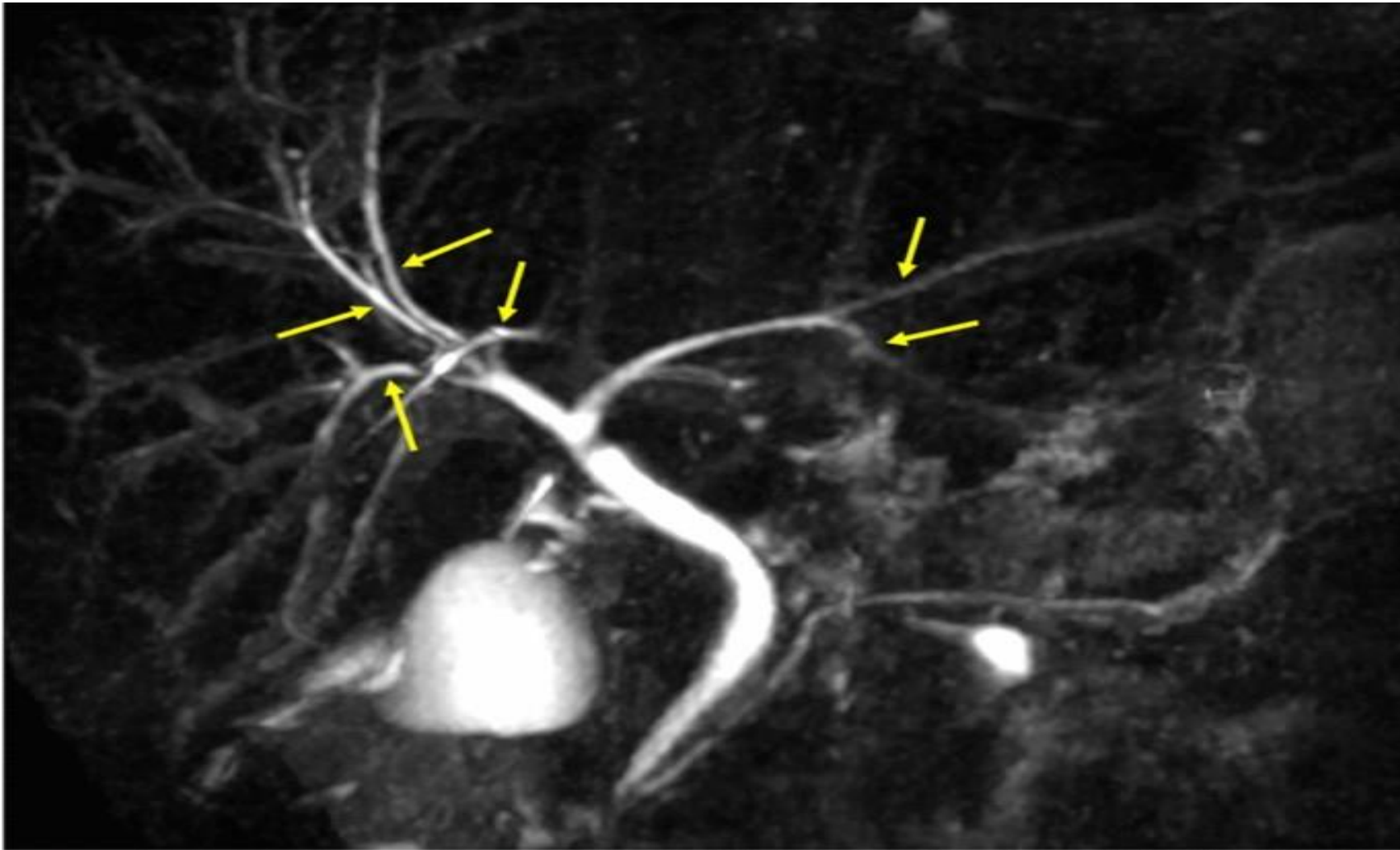


IHDs

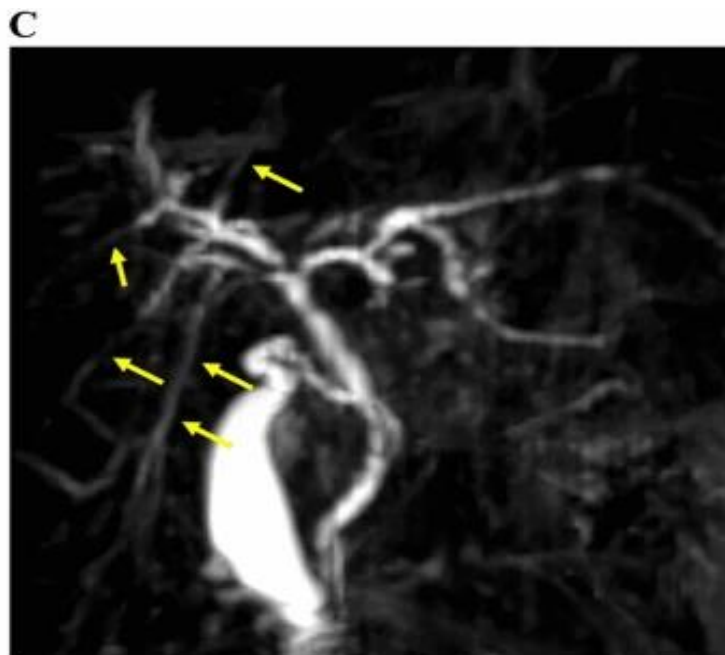
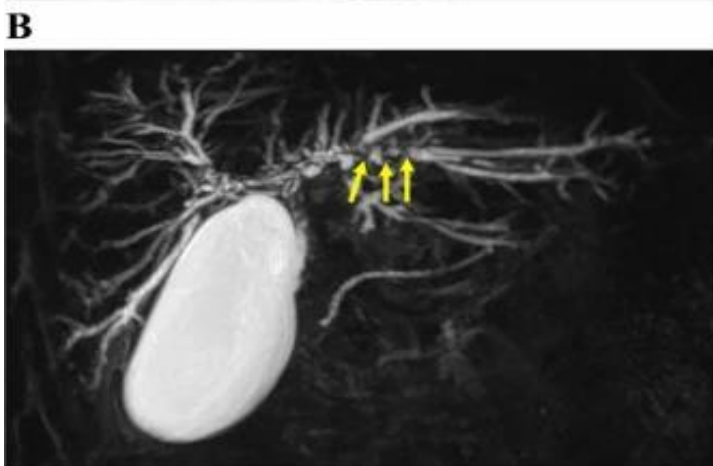
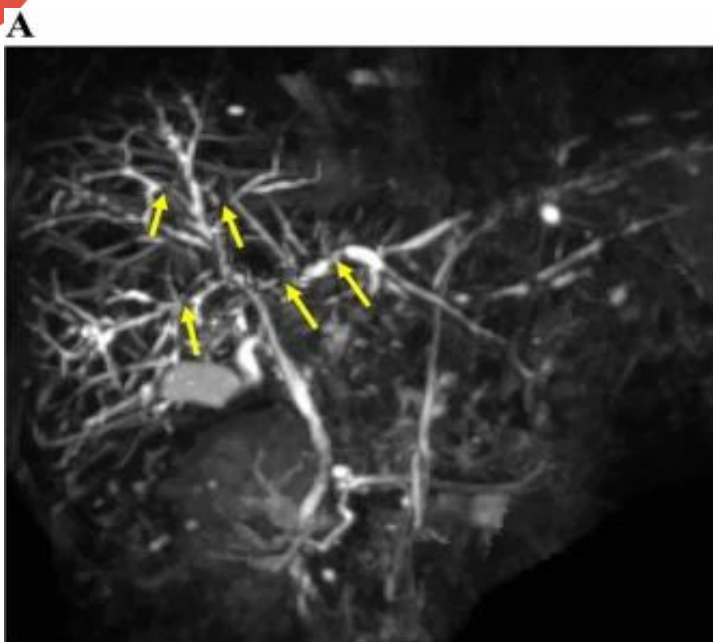
- No abnormalities
- Minimum stenosis with biliary ducts of regular diameter or minimally dilated
- Multiple stenosis and saccular dilations with reduction of intraparenchymal arborization (aspect as “bare tree”)
- Closed stenosis to carrefour with obstruction or lack of visualization of one of the main hepatic ducts

EHDs

- No abnormalities
- Wall irregularity in absence of significant stenosis
- Segmental stenosis
- Entire stenosis of the CBD
- Irregularities in diameter, nodularity, and pseudodiverticular formations



Maximum intensity projection image of a normal biliary tree. Arrows: tertiary (sub-segmental) branches

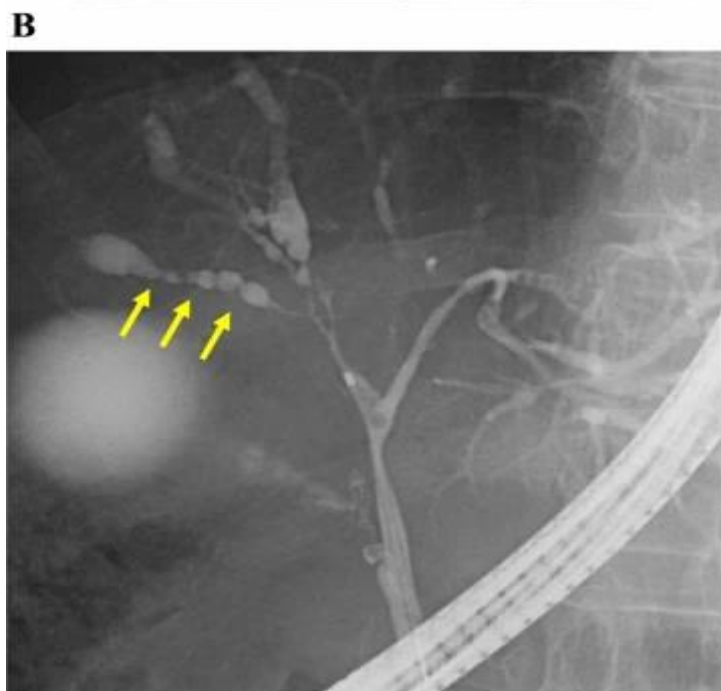
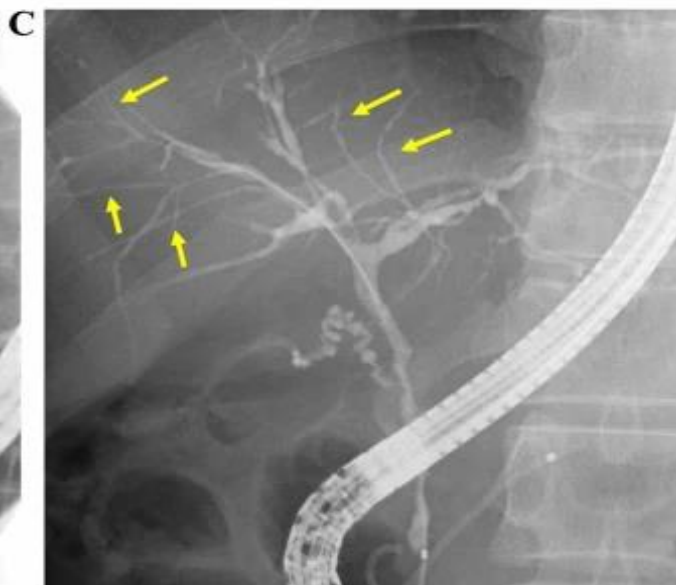
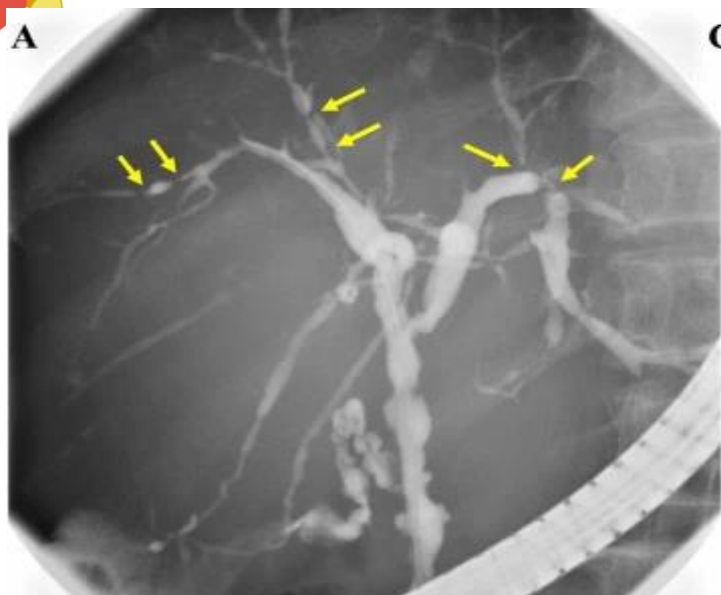
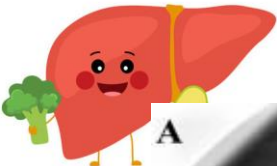


A: Multifocal band-like strictures (arrows) are multiple short strictures (1–2 mm)

B: Beaded appearance (arrows), a short, annular stricture alternating with normal or minimally dilated segments.

C: Pruned-tree appearance (arrows), defined as a narrowing of the intrahepatic duct, and reduced arborization of the intrahepatic duct and pruning.

D: Diverticulum-like outpouching (arrows) is outpouching resembling diverticula, often protruding between adjacent strictures



Characteristic biliary findings on endoscopic retrograde cholangiography.

A Multifocal band-like strictures (arrows).

B Beaded appearance (arrows).

C Pruned-tree appearance (arrows).

D Diverticulum-like outpouching (arrows)



Feature	AIH	PBC	PSC
Gender	Females: 60-75%	Females: >90%	Females: 30-35%
Age	All age groups. Median age approx. 45 years	Typically age group 30-65 years. Not diagnosed in children	Typically 30-50 years, but all age groups
Aminotransferases	Markedly elevated, often 3–10-fold, but may be normal or only minimally elevated	Normal or slightly elevated	Normal or slightly elevated
Alkaline phosphatase	Elevated levels may be seen	Moderately - markedly elevated	Moderately - markedly elevated (typically at least 3 x ULN; but variable levels, may even be normal)
Bilirubin	Variable increase	Variable increase, but normal in majority at diagnosis	Variable increase, but normal in majority at diagnosis
Immunoglobulins	Hypergammaglobulinemia, especially elevated IgG (generally elevated 1.2-3.0 x ULN)	IgM increased in most patients	IgG increased in up to 61% IgM increased in up to 45%
Autoantibodies			
ANA	Significant titres ($\geq 1:40$) of ANA and/or SMA in 70-80%	ANA in >30% (anti-gp210 and anti-Sp100 highly specific)	ANA in 8-77%
SMA		SMA may be present	SMA in 0-83%
Anti-LKM	Anti-LKM in 3-4%		
Anti-SLA/LP	Anti-SLA/LP in 10-30%	Anti-SLA/LP may be detected	Anti-SLA/LP may be detected
pANCA	pANCA in 50-96% (often atypical, pANNA) Conventional autoantibodies not detected in up to 10%		pANCA in 26-94%
AMA	AMA in low titre occasionally seen (AMA anti-PDC-E2 pattern rarely detected)	AMA in 90-95% (AMA anti-PDC-E2 pattern highly specific)	AMA occasionally positive
Liver biopsy			
Interface hepatitis	Typical finding*	In a proportion of cases**	In a variable number of cases***
Portal inflammation	Portal plasma cell infiltrate	Portal lymphocytic infiltrate	Portal lymphocytic infiltrate
Biliary changes	In a proportion of cases	Typical	Typical
Granulomas	Atypical	Suggestive of PBC, but invariably present	Atypical, but may be observed
Cholangiography	Normal or signs of liver cirrhosis	Normal or signs of liver cirrhosis	Characteristic findings, diagnostic of PSC. Normal cholangiography in small duct PSC
IBD	Rarely associated with AIH. PSC should be excluded	Rarely associated with PBC	Present in up to 80%



Treatment

- AIH has two serologic patterns of presentation; type 1 (AIH-1) and type 2 (AIH-2), but treatment approaches are consistent, and are usually effective.
- In contrast, treatment options for autoimmune biliary disease continues to lack the efficacy of AIH management, and often progressive biliary involvement portends a poorer outcome



- There is currently no effective treatment for patients with PSC, which could prevent gradual progression of liver disease to biliary cirrhosis and chronic liver failure.
- Liver transplantation remains the only treatment, and about 17%-21% of patients with PSC and approximately the same number of children with ASC undergo this operation in the course of the disease.
- Immunosuppressive therapy is effective for ASC; however, there is no definite evidence that the long-term prognosis of patients with ASC is better than that of patients with PSC.

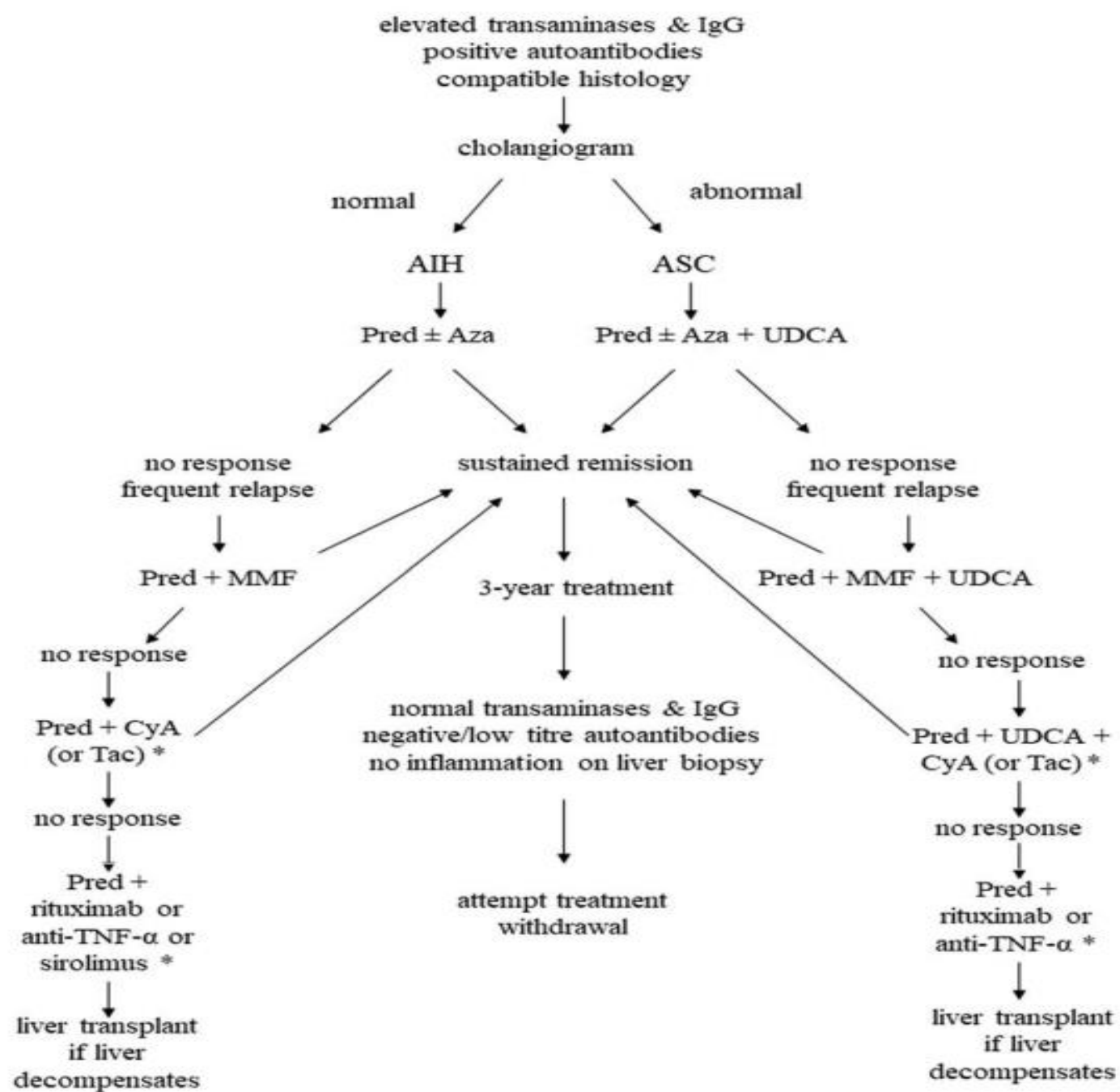


FIGURE 1. Flow chart for treatment decision making in children with autoimmune liver disease. * Second- and third-line treatments to be decided and monitored only in specialized pediatric hepatology centers. (Modified from (62)).

TABLE 1. Immunosuppressive treatment regimens for juvenile autoimmune liver disease

	Initial regimen		Maintenance			Definition of remission	Treatment length	Before attempting treatment withdrawal
	Predni(so)lone	Azathioprine	Prednis(ol)one	Azathioprine	Azathioprine mono-therapy (in AIH-1)			
AIH	2 mg · kg ⁻¹ · day ⁻¹ (up to 60 mg/daily) decreased weekly in parallel to transaminase levels decrease to a minimum maintenance dose of 2.5 to 5 mg daily	1–2 mg · kg ⁻¹ · day ⁻¹ added gradually if transaminase levels plateau or increase. Alternatively, added in all patients after 2 weeks of predniso(lo)ne treatment	0.1–0.2 mg · kg ⁻¹ · day ⁻¹ or 5 mg/day	1–2 mg/kg/day if required	1.2–1.6 mg/kg/day	Normal transaminase and IgG levels; - Negative or low titer (< 1:20) ANA/ SMA -negative anti-LKM-1/anti-LC-1	3 y Before considering suspension	Remission for at least 3 years + follow up liver biopsy showing no inflammatory changes
ASC	Predniso(lo)ne ± azathioprine as above, plus ursodeoxycholic acid 15 mg/Kg/day		Predniso(lo)ne ± azathioprine as above, plus ursodeoxycholic acid 15 mg · kg ⁻¹ · day ⁻¹			As above	As above	As above

AIH = autoimmune hepatitis; ANA = anti-nuclear antibody; ASC = autoimmune sclerosing cholangitis; SMA = anti-smooth muscle antibody.



TABLE 2. Alternative treatments for juvenile autoimmune liver disease

Agent	Pros	Cons
Mycophenolate mofetil	Favorable toxicity profile Experience in the transplant setting	Contradictory reports regarding its efficacy Teratogenicity
Tacrolimus	Potent immunosuppressant Experience in the transplant setting	Anecdotal experience Unclear efficacy Renal toxicity
Cyclosporine	Potent immunosuppressant Experience in the transplant setting	Unclear benefit over standard treatment Cosmetic effects Renal toxicity
Budesonide	High first pass metabolism in the liver	Ineffective in cirrhotic patients Less effective as first line treatment compared to standard treatment
Rituximab	Relatively favorable toxicity profile	Infectious complications Anecdotal experience Unclear efficacy
Infliximab	Potent immunomodulatory properties Effective in inflammatory bowel disease	Unclear efficacy in liver disease Infectious complications Paradoxical development of AIH
Ursodeoxycholic acid	Putative immunomodulatory capacities Choleretic	Efficacy yet to be demonstrated

AIH = autoimmune hepatitis.



- **Ursodeoxycholic acid (UDCA)** treatment was added to immunosuppression in the prospective study, but whether it has any role in arresting the progression of the bile duct disease remains to be established. In adults with primary sclerosing cholangitis, high-dose UDCA has been reported as more beneficial than standard doses, but a randomized double-blind controlled study shows that high-dose UDCA has a negative long-term effect. It is prudent, therefore, to use doses not >15 mg/kg/day
- Antibiotics, particularly **vancomycin** have shown potential benefits, particularly in children with IBD but phase III studies are lacking.
- **Metronidazole**
- MTZ therapy could result in long-term benefit in early-stage PSC or ASC.
- 2 cycles of 14-day treatment.
- Biochemical data (CRP, AST, ALT, and gamma-glutamyl transferase levels) decreased following metronidazole (MTZ) in remission patients; these decreases were higher in remission than in relapse patients.
- MTZ therapy could result in long-term benefit at early-stage autoimmune sclerosing cholangitis or primary sclerosing cholangitis.
- The mean plasma relative abundance of hydrophilic bile acids significantly increased to a greater extent in remission versus relapse patients post-MTZ therapy.



- Parenchymal inflammation responds satisfactorily to standard immunosuppressive treatment with steroids azathioprine both in AIH and ASC, but in ASC, the bile duct disease progresses in about 50% of cases, leading to end-stage liver disease requiring transplantation more frequently than in AIH.
- ASC is more frequently associated to IBD than AIH.
- Deterioration of liver disease, as well as the risk of disease recurrence after transplant, is correlated to the activity of the intestinal disease. The minority of patients who do not respond to standard treatment, and those who relapse frequently, should be offered alternative immunosuppression, the efficacy of which is still anecdotal (including in order of priority MMF, calcineurin inhibitors, rituximab, anti-TNF-a).



Prognosis

- Relapse affects approximately 40% of patients while on treatment and is frequently due to non-adherence, particularly in adolescents. It is prudent to treat children for at least 2 to 3 years before attempting treatment withdrawal, which should be considered only if transaminase and IgG levels have been normal and autoantibody negative or low titer (1:20 by immunofluorescence) for at least a year. Before withdrawal, liver biopsy should be repeated to exclude residual inflammatory changes. Both AIH and ASC can recur after LT, recurrence being more common in ASC than in AIH.
- De novo AIH after LT for non-autoimmune conditions responds to the classical treatment of AIH, but not to standard antirejection treatment.



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