
2023
SCSG
LIVER SYMPOSIUM
DECEMBER 9-10, 2023

Difficult Cases in Autoimmune Hepatitis

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December 10, 2023

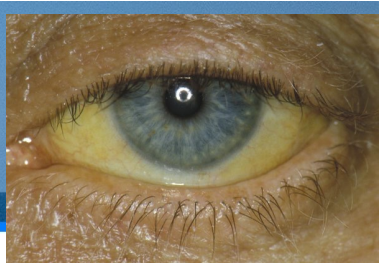
Disclosures

- Speakers’ Bureau: Intercept, Gilead

Objectives

- Update on the diagnosis and treatment of autoimmune hepatitis (AIH)
- Drug induced autoimmune like hepatitis (DI-ALH)

Case Presentation



29-year-old man with no past medical history presents to the ER

He was in his usual state of good health until 1 week prior to admission when he developed malaise, nausea, vomiting and then jaundice.

He denied sick contacts, recent travel and antibiotic exposure. He takes no prescribed outpatient medications, however, one month ago started green tea extract.

He drinks on average 1-3 alcohol beverages per day and denies illicit drug use.

Case Presentation

Urine toxicology negative

Ultrasound: liver 19.6 cm (mildly enlarged), no gallstones.

CT abdomen w contrast: normal liver parenchyma, no biliary dilatation, contracted gallbladder.

INR	1.6
Cr	0.68
Total Bilirubin	28.3
Direct bilirubin	20.7
Alkaline Phosphatase	110
AST	2640
ALT	2811
AFP	45

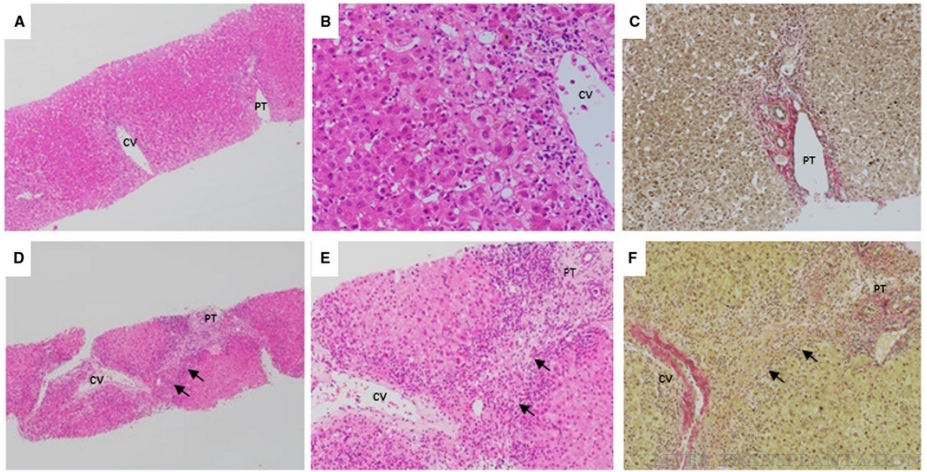
Case Presentation: More Labs

- Viral work-up: HIV negative, Hep E IgM/IgG negative, HCV RNA negative, HBcIgM negative, HBsAb positive, HBsAg negative, EBV and CMV PCR negative
- Metabolic work-up: ferritin 6171, % sat 24, ceruloplasmin 24, A1AT phenotype MM
- Autoimmune work-up: ANA 1:160, SMA 1:640, LKM negative, **IgG serum 3180**

Case Presentation

Liver biopsy

- Severe acute hepatitis with extensive bridging necrosis, plasma cells, no fibrosis



Rahim MN et al. *Liver Transpl*. 2019 Jun;25(6):946-959.

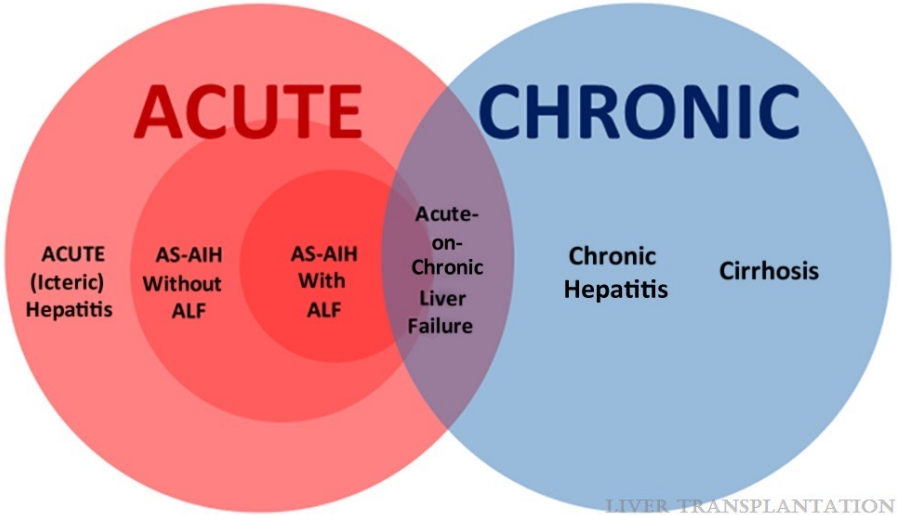
Diagnosis

Autoimmune hepatitis (AIH)

OR

Drug induced autoimmune like hepatitis (DI-ALH)

The Many Clinical Faces of AIH …



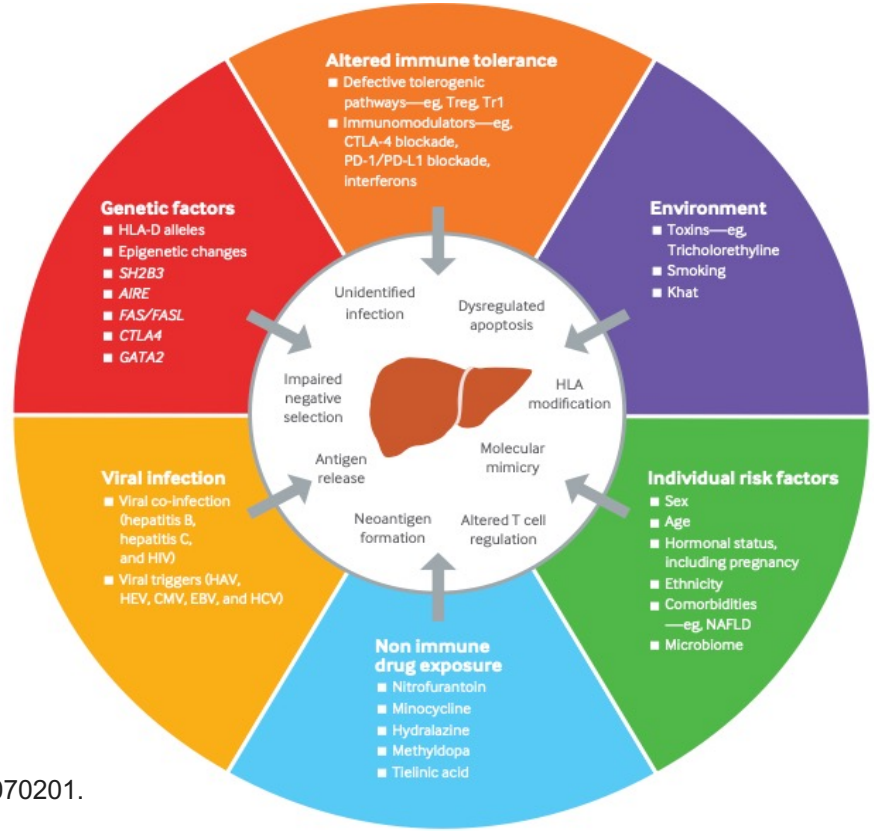
Acute AIH	Icteric No coagulopathy No encephalopathy
AS-AIH	Icteric Coagulopathic (INR ≥1.5) No encephalopathy
AS-AIH with ALF	Icteric Coagulopathic (INR ≥1.5) Encephalopathic

LIVER TRANSPLANTATION

AS: acute severe; ALF: acute liver failure.

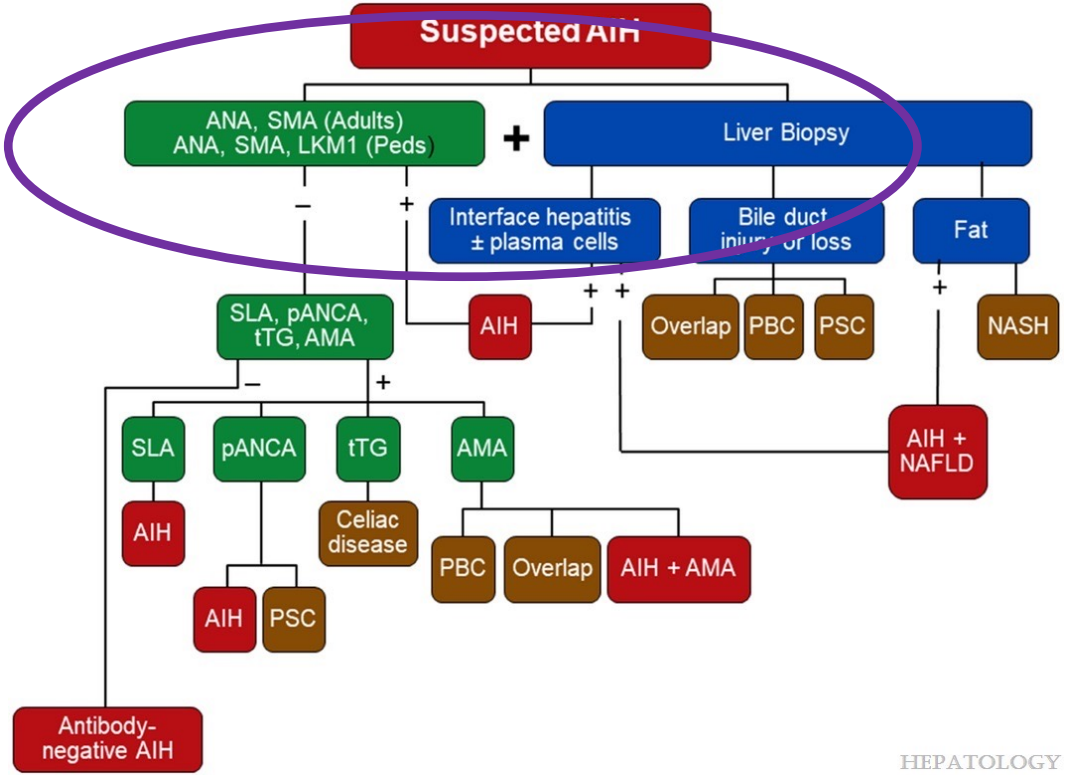
Rahim MN, Liberal R, Miquel R, Heaton ND, Heneghan MA. *Liver Transpl*. 2019 Jun;25(6):946-959.

Pathophysiology of AIH



Muratori L et al. *BMJ*. 2023 Feb 6;380:e070201.

Diagnosis of AIH: Serum Markers



Mack CL et al. *Hepatology.* 72(2):p671-722, August 2020.

Diagnosis of AIH: Serum Markers Can Be Tricky

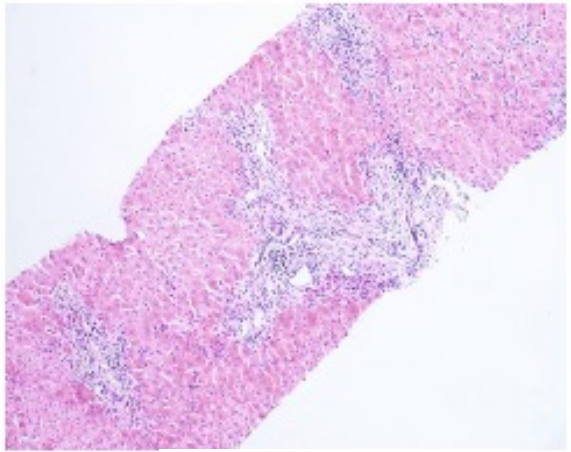
Table 4: Proportion of patients with AIH with positive auto-antibodies compared with their prevalence among healthy population. Auto-antibodies are compared with the proportion of those who are positive for genetic tests in both groups. Adapted from reference 2.

Test: antibodies	% positive in AIH cases	% positive in 'normal' population
ANA 1:60	68%-75%	15% (< 40 ♀) - 24% (> 40 ♀)
ASMA	52%-59%	Up to 43%
IgG >1600 mg/dL	86%	5%
Anti-LKM	4%-20%	1%

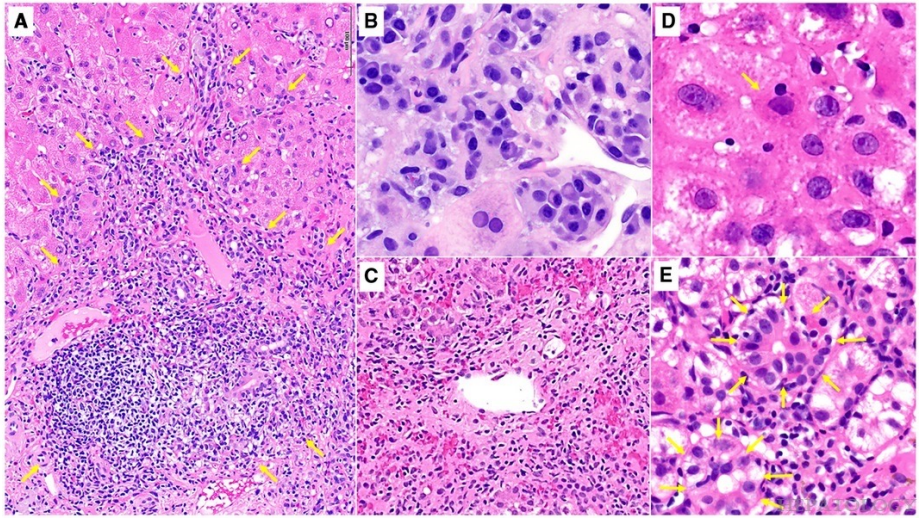
Abbreviations: AIH, autoimmune hepatitis; ANA, anti-nuclear antibody; anti-LKM, anti-liver-kidney-microsomal antibody; ASMA, anti-smooth muscle antibody; DILI, drug-induced liver injury; HLA, human leukocyte antigen; IgG, immunoglobulin

Andrade RJ et al. *J Hepatol*. 2023 Sep;79(3):853-866.

Diagnosis of AIH: Histological Features on Biopsy



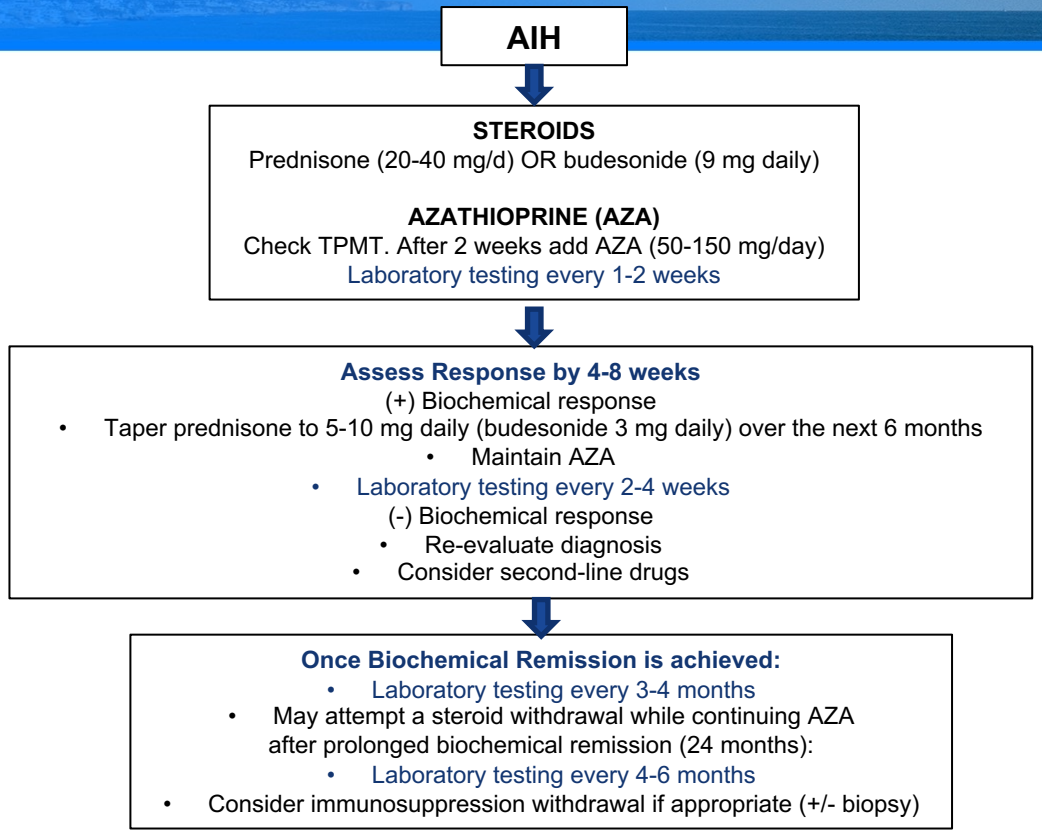
Interface hepatitis



(A) Lymphoplasmacytic inflammatory infiltration of the portal tract and interface hepatitis involving >50% of the portal tract circumference
(B) Plasma cell predominance in a portal inflammatory infiltrate
(C) Perivenulitis of a central vein
(D) A hepatocyte undergoing emperipolesis
(E) Rosettes of regenerating hepatocytes

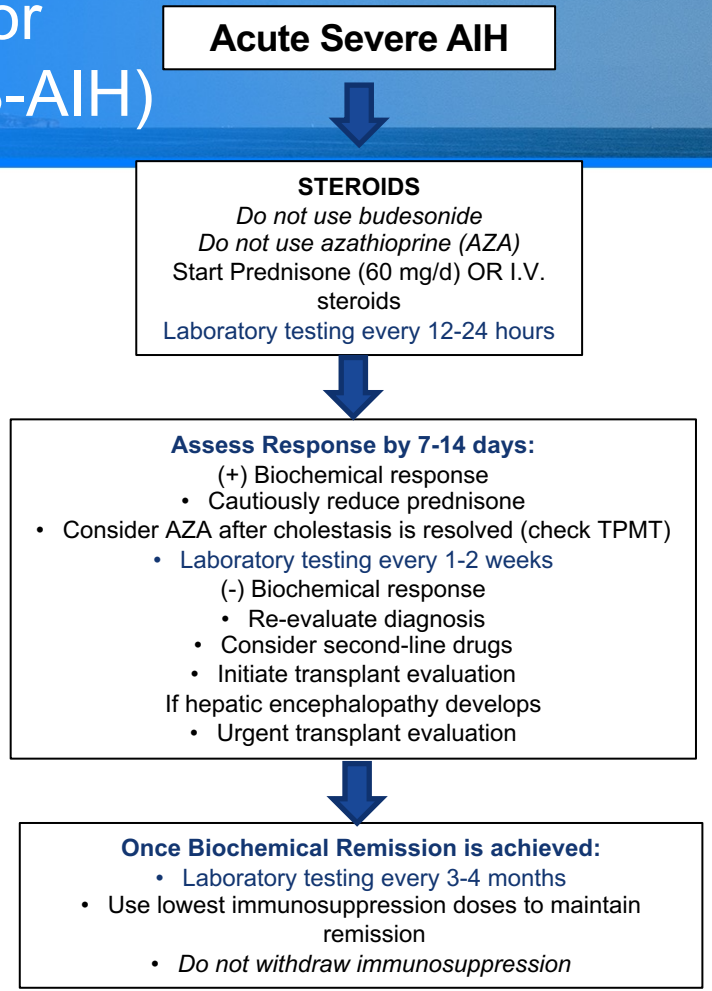
Sucher E et al. *J Immunol Res*. 2019 Nov 25;2019:9437043; Mack CL et al. *Hepatology.* 72(2):p671-722, August 2020.

Treatment Algorithm for AIH



Mack CL et al. *Hepatology.* 72(2):p671-722, August 2020.

Treatment Algorithm for Acute Severe AIH (AS-AIH)



- High INR at initiation of corticosteroids and an insufficient improvement in INR and bilirubin days after administration of the medication are predictive factors for LT or death in patients with AS-AIH*
- If no improvement and/or hepatic encephalopathy, stop steroids

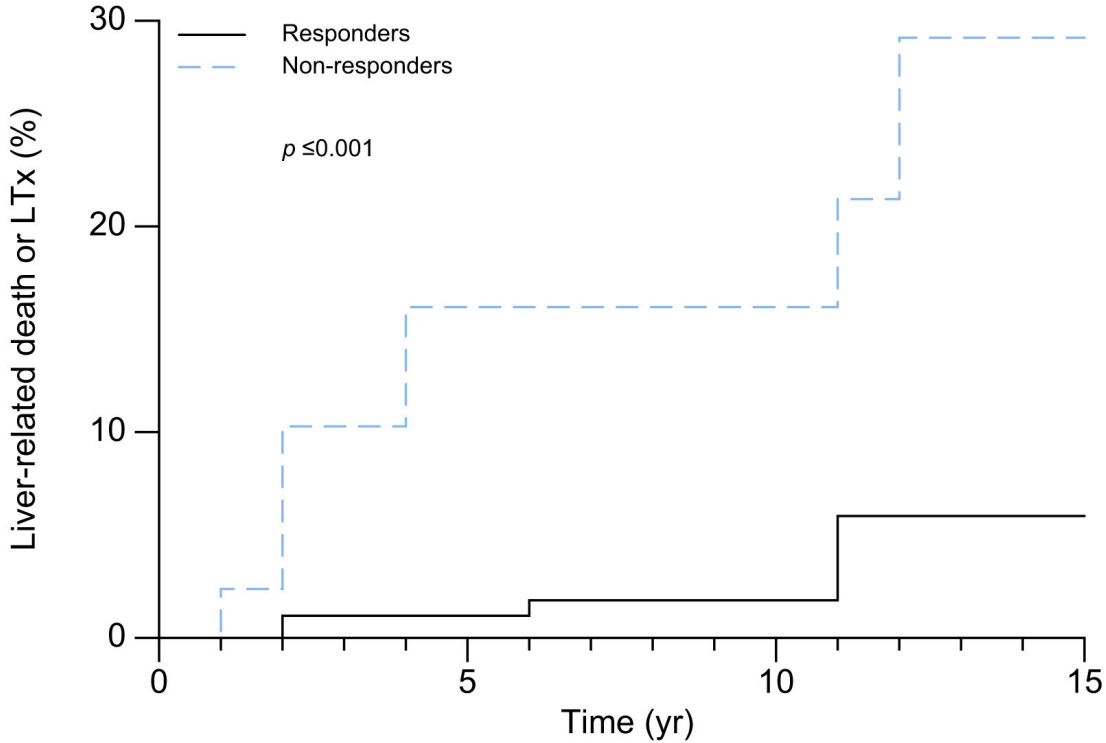
Mack CL et al. *Hepatology.* 72(2):p671-722, August 2020;
De Martin E et al. *J Hepatol*. 2021 Jun;74(6):1325-1334.

Treatment Goals: Consensus by the International Autoimmune Hepatitis Group

Endpoint	Definition
Complete biochemical response	**normalization** of serum transaminases and IgG below the upper limit of normal (6 months after initiation of treatment)
Insufficient response	lack of complete biochemical response (6 months after initiation of treatment)
Non-response	< 50% decrease of serum transaminases within 4 weeks after initiation of treatment
Remission	complete histological resolution of disease
Intolerance to treatment	any adverse event possibly related to treatment as assessed by the treating physician leading to potential discontinuation of the drug

Pape S et al. *J Hepatol*. 2022 Apr;76(4):841-849.

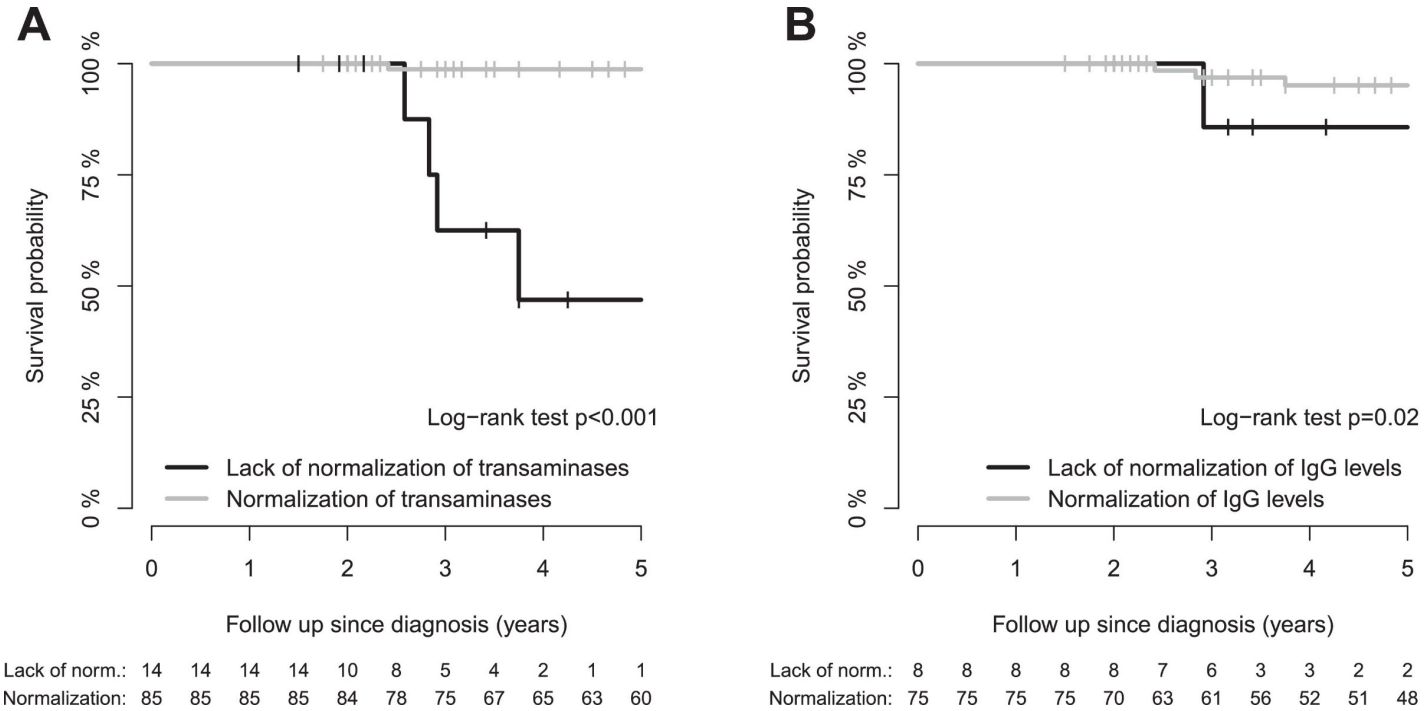
Why Is Normalization of AST and ALT important in AIH?



Patients with <50% decrease of serum transaminases within 4 weeks after initiation of treatment (non-responders) are compared with patients with a ≥50% decrease of serum transaminases within 4 weeks (responders) (log-rank *p* <0.001)

Pape S et al. *J Hepatol*. 2022 Apr;76(4):841-849.

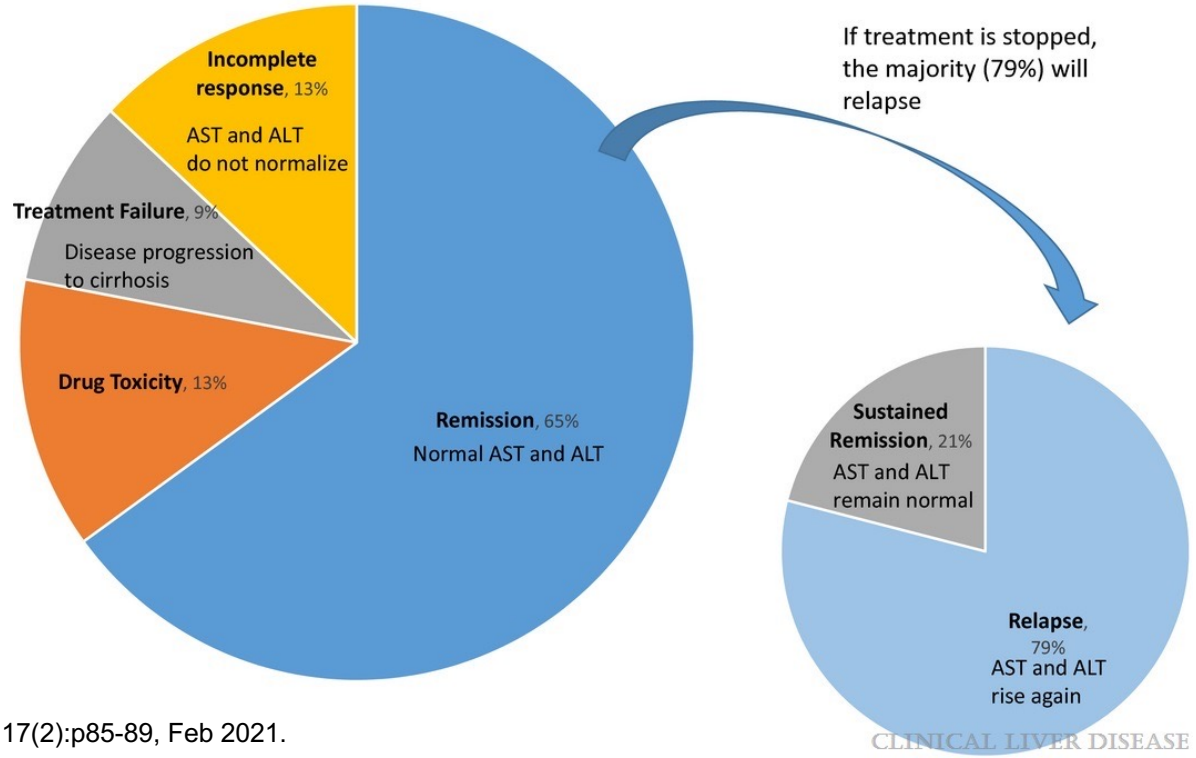
Normalization of AST, ALT, IgG Are Important in AIH



Cumulative transplant-free survival estimates according to whether normalization of transaminases or serum IgG achieved

Gerussi A et al. *Dig Liver Dis*. 2020 Jul;52(7):761-767.

Response to Treatment



Volk M et al. *Clin Liv Dis.* 17(2):p85-89, Feb 2021.

Second Maintenance Line Therapy for AIH

Medication	Dose	Major side effects
Mycophenolic acid (MMF)	500-1500 mg BID	Responds to prednisone Cannot tolerate AZA **Teratogenic** GI symptoms (diarrhea), leukopenia
Tacrolimus	1-5mg PO BID (trough ~5)	Hypertension, renal insufficiency, hyperglycemia, neuropathy
Budesonide	3mg PO TID	Initial therapy + AZA to induce remission Decrease side effects Cannot use in cirrhosis

Manns MP et al. *J Hepatol*. 2015 Apr;62(1 Suppl):S100-11; EASL Clinical Practice Guidelines: Autoimmune Hepatitis. 2015.

Back to the Patient in Our Case Presentation

Started prednisone 40mg daily (taper lasted 10 months)

Transplant evaluation initiated and listed for acute severe AIH

INR and TB normalized but AST 132 and ALT 223, IgG 1050 (prior 3180) – MMF added

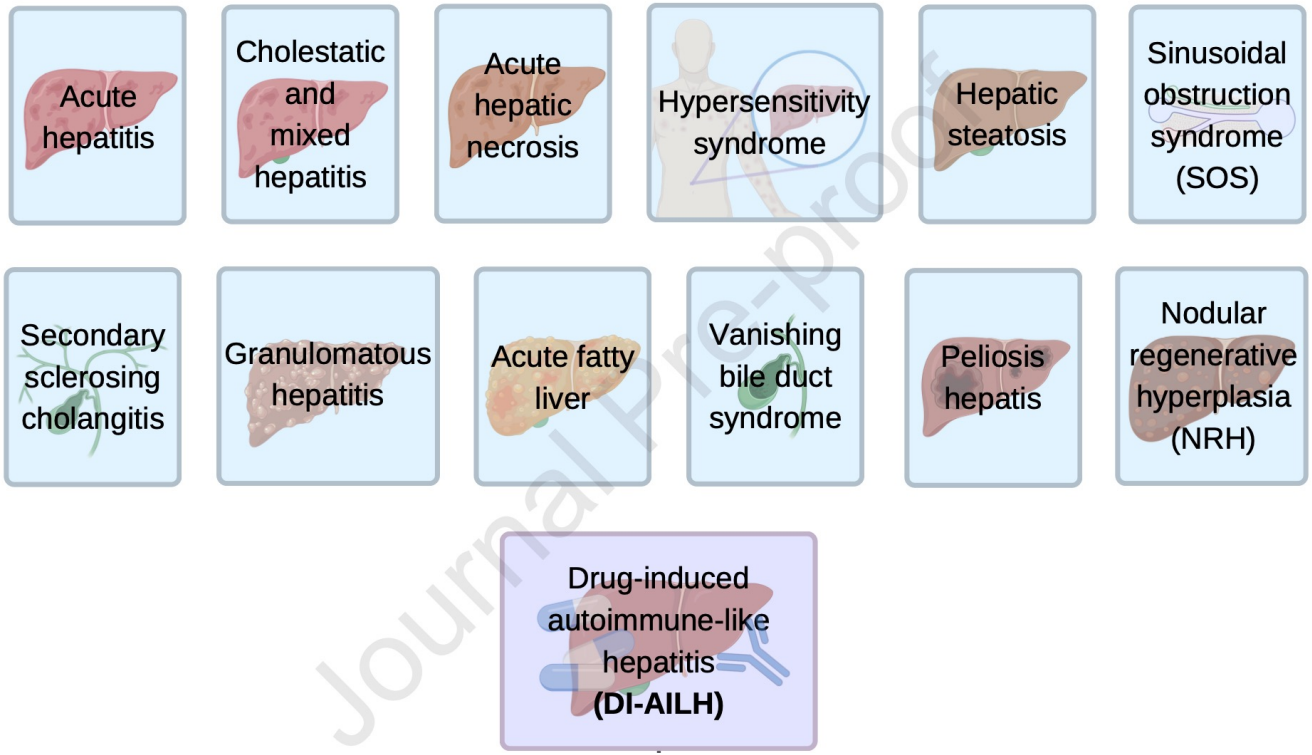
Liver elastography (FibroScan) at 6 months showed 11 kPa = stage 3 fibrosis

FibroScan (kPa)	Fibrosis stage
5.8	F≥2
10.5	F≥3
16	F ≥ 4

Mack CL et al. *Hepatology* 72(2):p671-722, August 2020; Hartl J et al. *J Hepatol.* 2016;65:769-775

But, Is This Drug Induced Autoimmune Like Hepatitis?

What Is DI-ALH? A Unique Subtype of Drug Induced Liver Injury



Andrade RJ et al. *J Hepatol*. 2023 Sep;79(3):853-866.

What Is DI-ALH? Be Familiar With the Usual Suspects

Drugs and herbal supplements associated with DI-ALH
Infliximab
Methyldopa
Hydralazine
Minocycline
Nitrofurantoin
Interferon α and β
Imatinib
Adalimumab
Diclofenac
Khat
Tinospora cordifola

Andrade RJ et al. *J Hepatol*. 2023 Sep;79(3):853-866.

AIH Versus DI-ALH: How Do You Tell Them Apart?

Laboratory and histological features of DI-ALH are similar to those of AIH

DI-ALH usually manifests within 3 months of drug exposure

Majority of DI-ALH cases present with an acute hepatocellular pattern of injury without hypersensitivity features (e.g. eosinophilia, fever, rash)

Biopsy is helpful

Advanced fibrosis, which is observed only in AIH, is the main microscopic finding that may help discriminate between the two conditions

Andrade RJ et al. *J Hepatol*. 2023 Sep;79(3):853-866.

AIH Versus DI-ALH: Treatment and Treatment Response

Differentiating the two is difficult but important as patients with DI-ALH rarely require long term immunosuppression

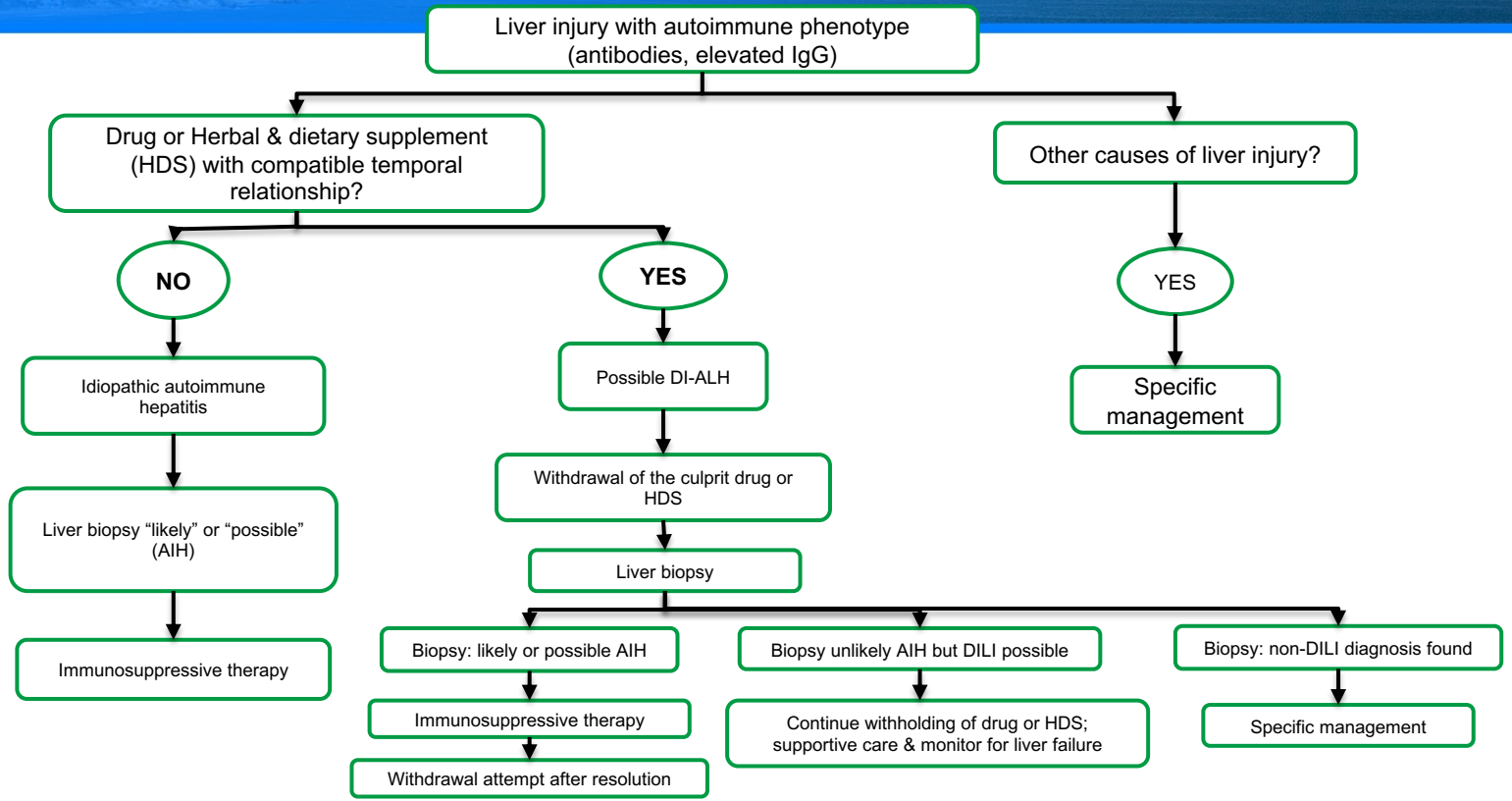
After withdrawal of the causal agent, the liver injury resolves either spontaneously (within 6 months) or with corticosteroids

Recovery time is reported to be longer for DI-ALH than for DILI

But, the response to immunosuppressive treatment was found to be faster in DI-ALH patients than for AIH patients (2 months vs 16.8 months)

Andrade RJ et al. *J Hepatol*. 2023 Sep;79(3):853-866.

Algorithm to Approach Suspected DI-ALH



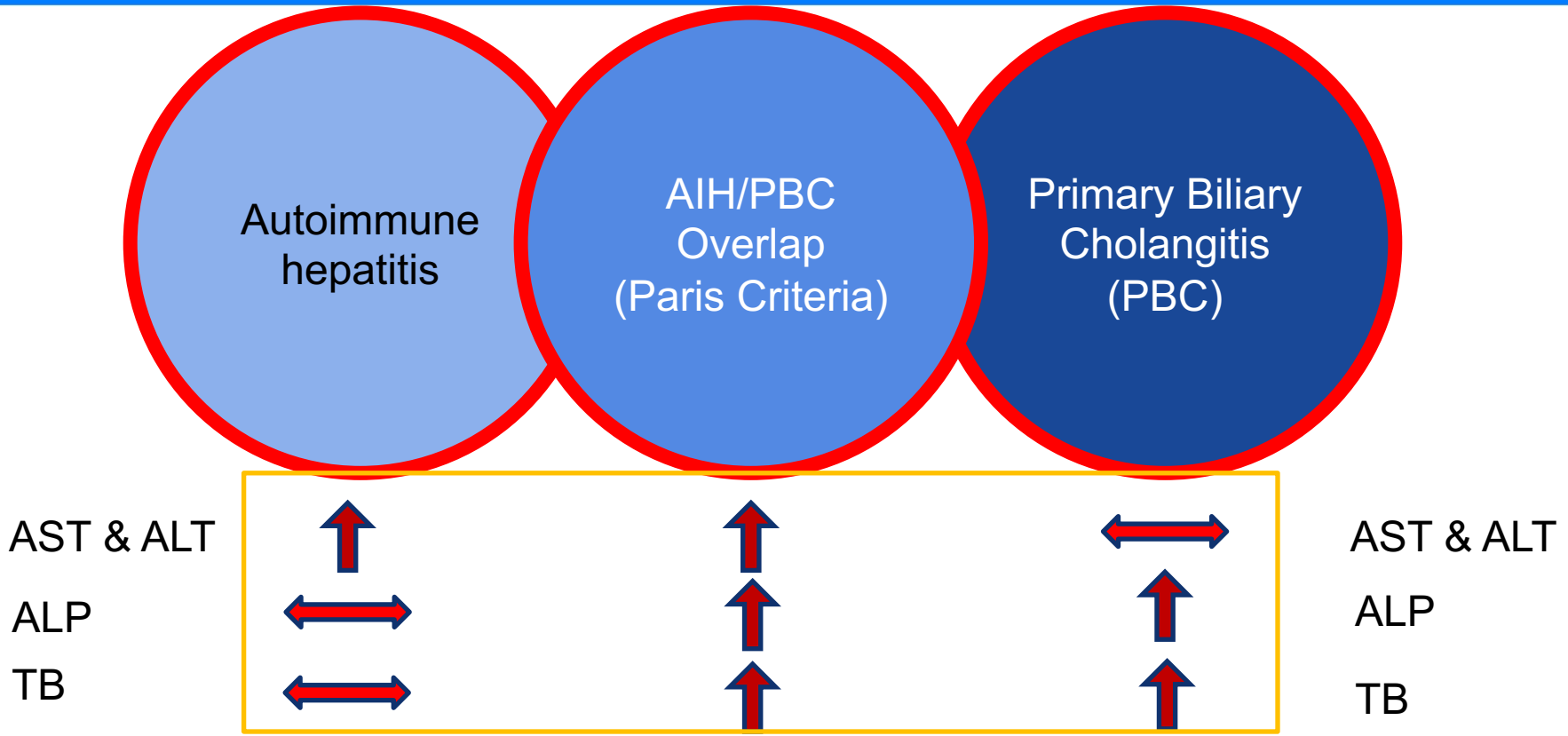
Andrade RJ et al. *J Hepatol*. 2023 Sep;79(3):853-866.

Conclusion

- AIH has a heterogeneous clinical presentation
- Budesonide and AZA OR prednisone and AZA are recommended first-line AIH treatments (without cirrhosis, acute severe hepatitis, or ALF)
- MMF or tacrolimus can be used as second-line treatment for those who failed to respond to first-line therapy
- Data shows that treatment goals for AIH should be normalization of liver tests
- Laboratory and histological features of DI-ALH are similar to those of AIH
- Advanced fibrosis, which is observed only in AIH, is the main microscopic finding that may help discriminate between the two conditions
- Treatment response (including time to response) is helpful


Thank You

Overlap Autoimmune Hepatitis



Overlap of AIH With Primary Biliary Cholangitis

Simultaneous AIH in patient with AMA-positive PBC

Overlap is NOT:

- PBC patients with +ANA
- PBC patients with mild degree of interface hepatitis

Clinical presentations include:

- Simultaneous AIH in patients with AMA+ PBC
- PBC followed by AIH, or AIH followed by PBC

Lindor KD et al. *Hepatology*. 2019 Jan;69(1):394-419.

Consecutive PBC/AIH

- AMA+ PBC, responds to UDCA, presents with clinical features of AIH
- AMA+ may disappear
- Liver biopsy more consistent with AIH (consider liver biopsy if ALT>5x ULN)
- Treat with immunosuppressive therapy
- 0.5% - 2.5% of PBC patients develop subsequent AIH
- Treatment should be targeted at the predominant histological injury pattern

Gossard AA et al. *Liver Int*. 2007;27(8):1086; Efe C et al. *Eur J Gastroenterol Hepatol*. 2014;26(5):532-7