

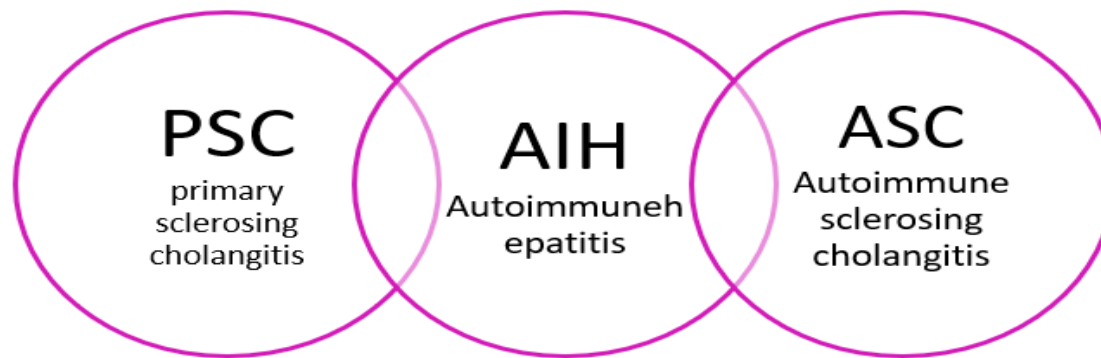
Management of AIH

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Treatment

Definition of Remission/ Relapse

- **Remission** : complete clinical recovery with transaminase levels within normal range (in 60% to 90% of patients) +
 - + 3 more criteria have been added to definition of remission:
 - _ Normalization of IgG levels,
 - _ Negative or very low titer autoantibodies ,
 - _ + Histological resolution of inflammation.
- Histological response lags behind , so the clinical / biochemical / immunological remission does not always reflect histological resolution.
- For clinical purposes remission is considered complete when transaminase and IgG levels are normal , ANA & SMA & antiLKM-1 & antiLC-1 are negative or low titer.

Relapse

- Increase of transaminase levels after remission .
- Relapse occur in about 40% of patients and requiring temporary increase in steroid dose.
- The most common reason of relapse is non-adherence.
- The risk of relapse is much higher if steroids are administered on an alternate day schedule.
- Small daily doses are more effective in maintaining disease control and do not affect final height.

When to treat

- AIH should be suspected in all children with evidence of liver disease after exclusion of infectious and metabolic etiologies.
- Goal of treatment is to reduce or eliminate liver inflammation , induce remission, improve symptoms and prolong life expectancy.
- AIH is exquisitely responsive to immunosuppression and treatment should be initiated promptly to avoid progression of disease.
- Although cirrhosis (in AIH) is present in between 44% and 80% of children at the time at diagnosis, mortality within childhood/adolescence is low and most children remain clinically stable and well on long term treatment.

Non Invasive Assessment of Hepatic Fibrosis By Serum Biomarker panels

- Among 14 serum-based biomarker panels for hepatic fibrosis, the more common use is Fibro Test, the serum AST/platelet ratio index (APRI).
- However, their role in AIH and their relative merit in assessing the progression or reversal of hepatic fibrosis, immediate and long-term prognosis, and treatment outcome remain unknown.

Non Invasive Assessment of Hepatic Fibrosis By Liver Stiffness

(Vibration-Controlled Transient Elastography (or FibroScan))

- (VCTE) or Fibro Scan correlates strongly with the histological stage of fibrosis in ALH, but its accuracy in quantifying fibrosis is impaired within the first 3 months of treatment.
- Liver stiffness estimated by VCTE is affected by both inflammation & fibrosis.
- After 6 months of successful therapy to reduce hepatic inflammation, VCTE can accurately distinguish advanced stages of fibrosis (F3, F4) from less severe stages (F0-F2).
- The cutoff values that best predicted fibrosis stages were 5.8 kPa for $F \geq 2$, 10.5 kPa for $F \geq 3$, and 16 kPa for $F \geq 4$.

Magnetic Resonance Elastography

- Findings of (MRE) correlate strongly with fibrosis stage, and appears to outperform TE for staging hepatic fibrosis .
- Differences in liver stiffness detected by MRE in untreated and treated patients with AIH have not been significant, but suggest that liver stiffness can be influenced by therapy, possibly by reducing liver inflammation or hepatic fibrosis.
- MRE assessment of splenic stiffness can have prognostic value for predicting portal hypertension and esophageal varices.
- *In AIH, the accuracy of MRE for advanced hepatic fibrosis are excellent.*

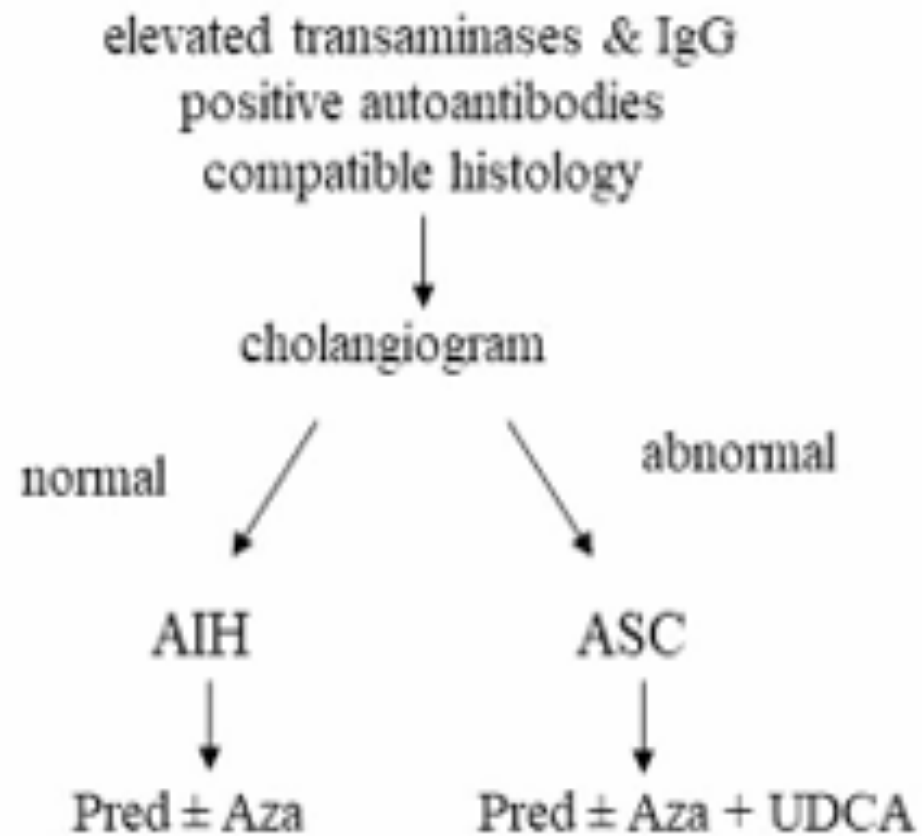
Acoustic radiation force impulse imaging (ARFI)

- The accuracy of ARFI for cirrhosis > 90% , and results have been comparable to VCTE in predicting fibrosis stage ≥ 2 and cirrhosis.
- Splenic stiffness by ARFI has correlated with the grade of esophageal varices, and ARFI may evolve as a method to assess portal hypertension.
- ARFI overestimate hepatic fibrosis in patients with massive hepatic necrosis, cholestasis, severe inflammation, and hepatic congestion.

Guidance Statements

- Serum-based biomarker panels for hepatic fibrosis are unestablished in AIH and should not be used.
- TE can identify advanced fibrosis or cirrhosis in patients with AIH with reasonable accuracy, but it should be deferred for at least 6 months after successful treatment of AIH in order to avoid the confounding effects of hepatic inflammation.

Diagnosis & Management of Pediatric ALD



Pretreatment Evaluation

- The aims of the pretreatment evaluation of patients with AIH are to limit treatment-related complications and ensure an optimal therapeutic response.
- HBsAg, HBS Ab, HBc Ab
- Vaccinations
- Ca, P , 25(OH) vit D
- TB
- UA/UC
- Pretreatment testing of thiopurine methyltransferase (TPMT) activity

Management AIH

- The objectives of first-line therapy are to improve symptoms, control hepatic inflammation, achieve biochemical remission, prevent disease progression, and promote the regression of fibrosis at the lowest risk of drug-induced complication.
- The ideal laboratory response is normalization of serum ALT, AST, and IgG levels.
- *All patients with AIH are candidates for therapy.*

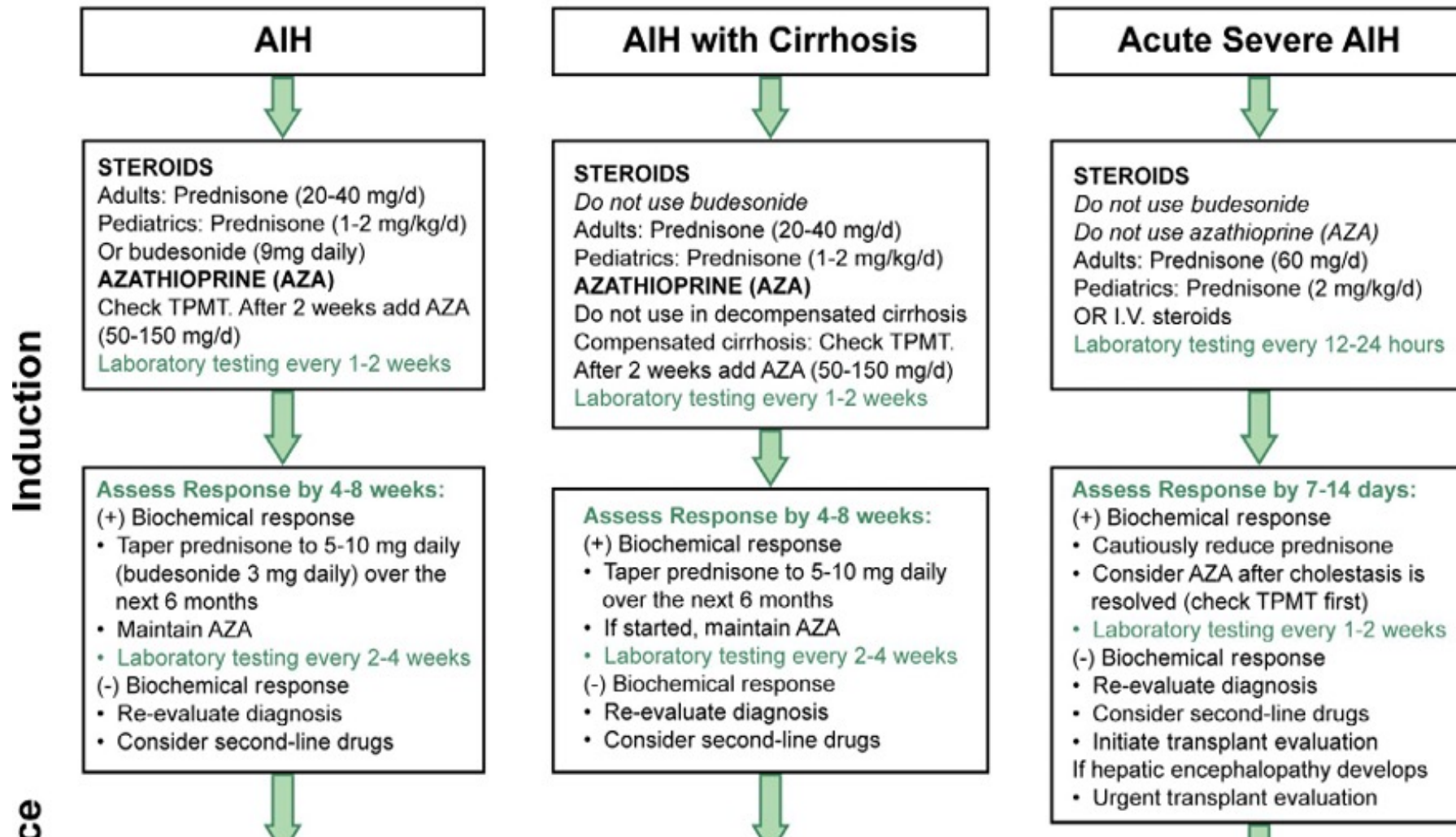
Standard treatment

- Prednisolone (prednisone) 2mg/kg/day (MAX : 60mg)
- It gradually decreased during 4-8 weeks , in parallel to decline of transaminase levels, maintain at dose 2.5 to 5 mg/day.
- In most patients , an 80% decrease of transaminase levels is achieved in the first 2 month, but complete normalization may take several months.
- In the first 6-8 weeks , liver function tests should be checked weekly to allow frequent dose adjustments, avoiding severe steroid side effects.

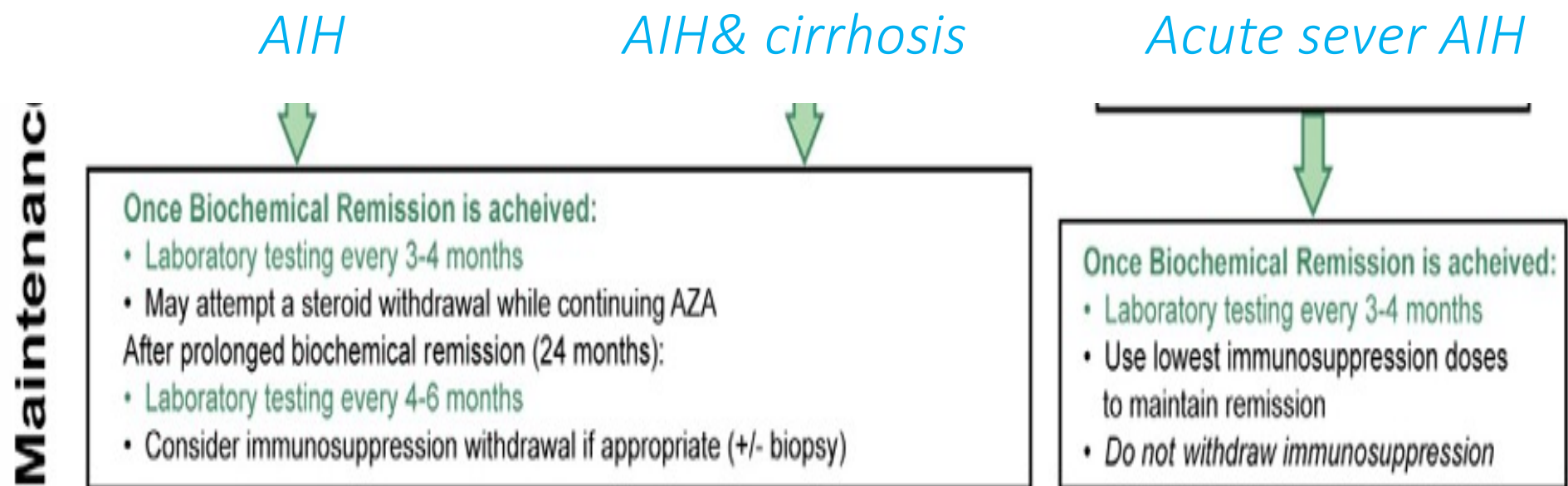
Standard treatment

- Time for AZA addition is different according the protocols.
- In some AZA is added only in the presence of serious side effects, or if transaminase levels stop decreasing on steroid alone.
- Dose start 0.5mg/kg/day , increase in the absence of toxicity to 2-2.5 mg/kg/day.
- In other centers AZA is added at a dose of 0.5 to 2 mg /kg /day after a few weeks of steroid treatment (2 weeks) .

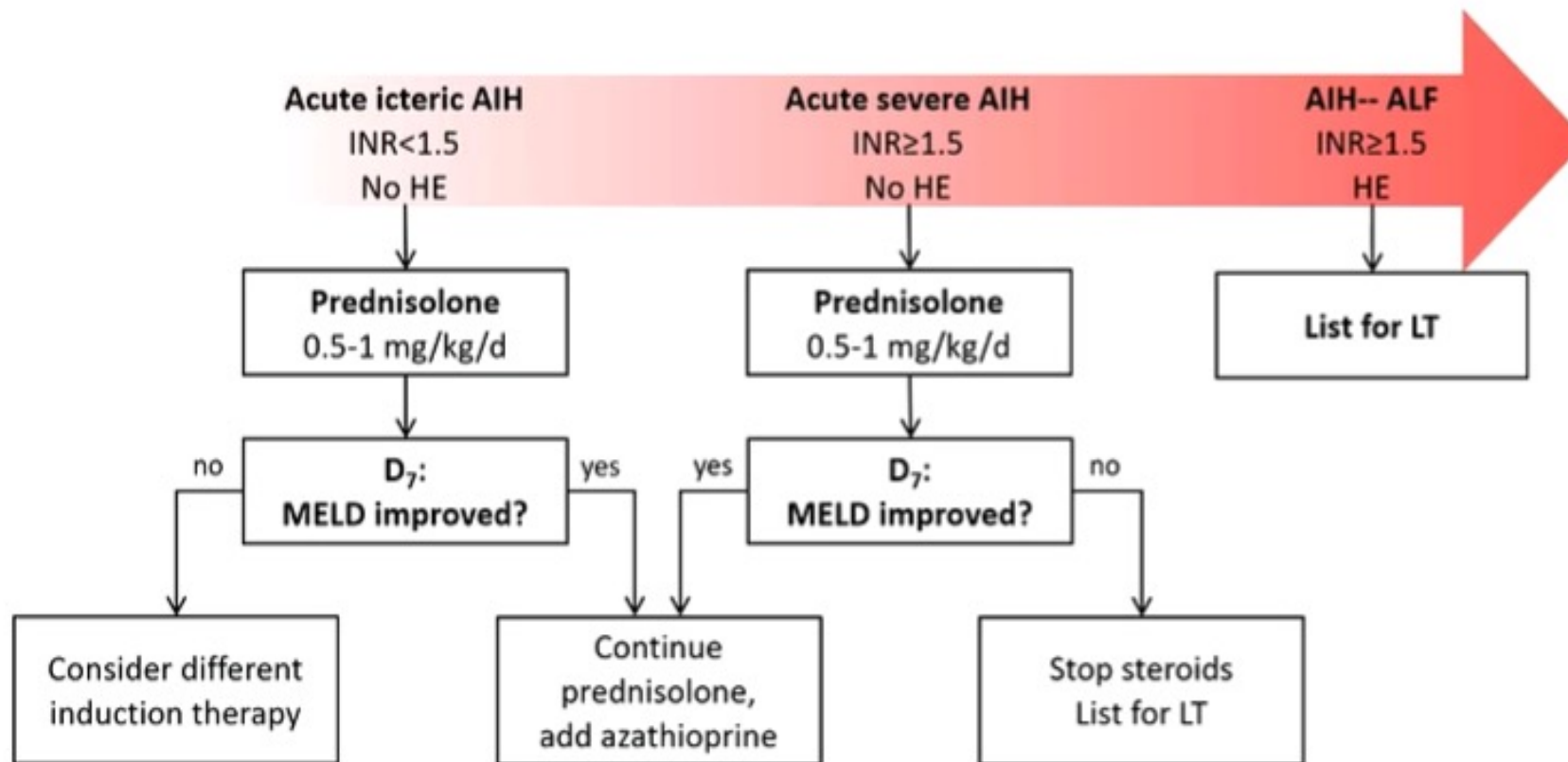
First Line Treatment of AIH



First Line Treatment of AIH



Algorithm for acute presentations of AIH



Pred ± AZA

- ◆ Some centers use combination therapy from the beginning.
- ◆ Caution with this approach , because AZA can be hepatotoxic , particularly in cirrhotic and severely jaundiced patients.
- ◆ *Retrospective analysis of patients treated with of AZA, + Pred from diagnosis reports more side effects and a higher relapse rate , than patients treated with steroid induction followed by AZA only when indicated .*
- ◆ TPMT activity level has been proposed as a predictor of drug metabolism and toxicity .

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AZA

- Measurement of the AZA metabolites, 6-thioguanine (6 TGN) and 6-MMP help in identifying drug toxicity and nonadherence .
- In children with AIH, the 6-TGN level is titrated between 100 and 300 pmol/ 8×10^8 red blood cells (RBCs) to avoid bone marrow toxicity, and the 6-MMP level is kept.
- In a retrospective review, 87% of children with AIH were reported to maintain sustained biochemical remission (normal transaminase levels) in association with low 6-TGN levels .

Remission can be maintained on low-dose AZA monotherapy.

For Induction of Remission

- **Budesonide**, a drug with hepatic first pass clearance of > 90% of oral dose and fewer side effects than Pred (28%/53%) (3 mg thrice daily, reduced to twice daily following remission).
- Do not use budesonide in ALF or decompensated cirrhosis (AASLD).
- Portosystemic shunting in cirrhosis may reduce drug efficacy and promote SSSE by allowing budesonide to bypass the liver.
- In a large study in Europe budesonide + AZA compared with Pred + AZA :

— Remission rates are much poorer than standard treatment, so caution is advisable in using budesonide to induce remission in AIH.

Alternative treatments

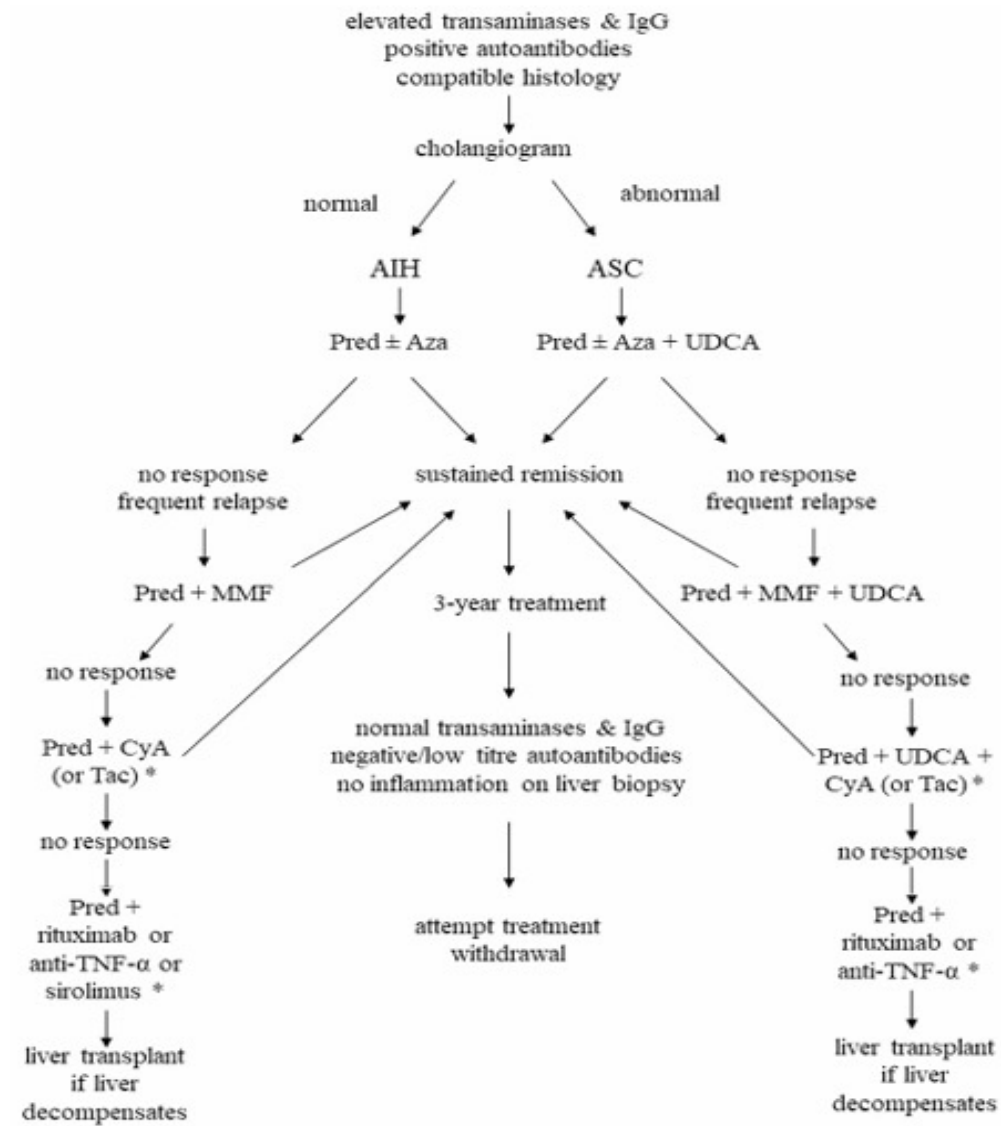
_To induce remission in an attempt to decrease steroid side effects;
to treat refractory patients, those intolerant to standard immunosuppression, often referred to as difficult to treat.

Alternative First Line Regimens

- MMF has been used in place of AZA in combination with prednisolone.
- MMF/prednisone was superior to prednisone/AZA in the normalization of serum ALT, AST, and IgG levels and in the rate of nonresponse.
- First-line treatment with MMF seemed to be at least as effective as AZA when each was combined with prednisone, but data are insufficient to recommend its first-line use.

Calcineurin inhibitors

- Used to a limited extent as first-line agents in AIH.
- Cyclosporine (CsA) has induced biochemical remission in children with AIH with good results during long-term follow-up.
- Trough levels of CsA are typically maintained higher initially (i.e., 150-200 ng/mL) and then tapered to 50-70 ng/mL , providing the disease is in remission.
- Tacrolimus (TAC) reduced serum AST and ALT levels by 70% to 80% after 3 months, but this early promise has not been developed further.
- There are insufficient data to recommend calcineurin inhibitors as front-line agents.



For Refractory cases (second line therapy)

- In patients resistance to standard induction regimen, MMF at dose 20mg/kg twice daily + Pred has been used successfully.
- *MMF should be the first choice for the second line therapy in AIH children refractory to standard treatment.*
- If no response or if intolerance for MMF (head ache, diarrhea, nausea, dizziness, hair loss, and neutropenia) , use of calcineurin inhibitors should be considered.
- Successful use of anti-B lymphocyte monoclonal antibody rituximab in 2 children with refractory AIH .
- It use as rescue treatment , however potential serious infectious side effects .
- TNF- α ??

putative predictors Of treatment Response

- The rapidity of response to treatment is the most important index of outcome, and the serum amino transferase levels should improve within 2 weeks.
- Biochemical remission , within 6 months is associated with a significantly lower frequency of progression to cirrhosis or need for LT .
- *Cholestasis (increased serum alkaline phosphatase or GGT levels) have been associated with incomplete or delayed response and may indicate an alternative diagnosis (e.g., overlap syndrome).*
- *In type 1 ALH, persistent production of SMA in the setting of biochemical remission have been associated with histological features of active liver inflammation.*

When and how to stop treatment :

Attempt withdrawal of treatment only:

- Treat children for at least 2-3 years,
- Transaminase & IgG levels have been normal and autoantibody negative for at least a year.
- A liver biopsy should be repeated before deciding to cessation.
- Do not try near puberty or konkoor !!

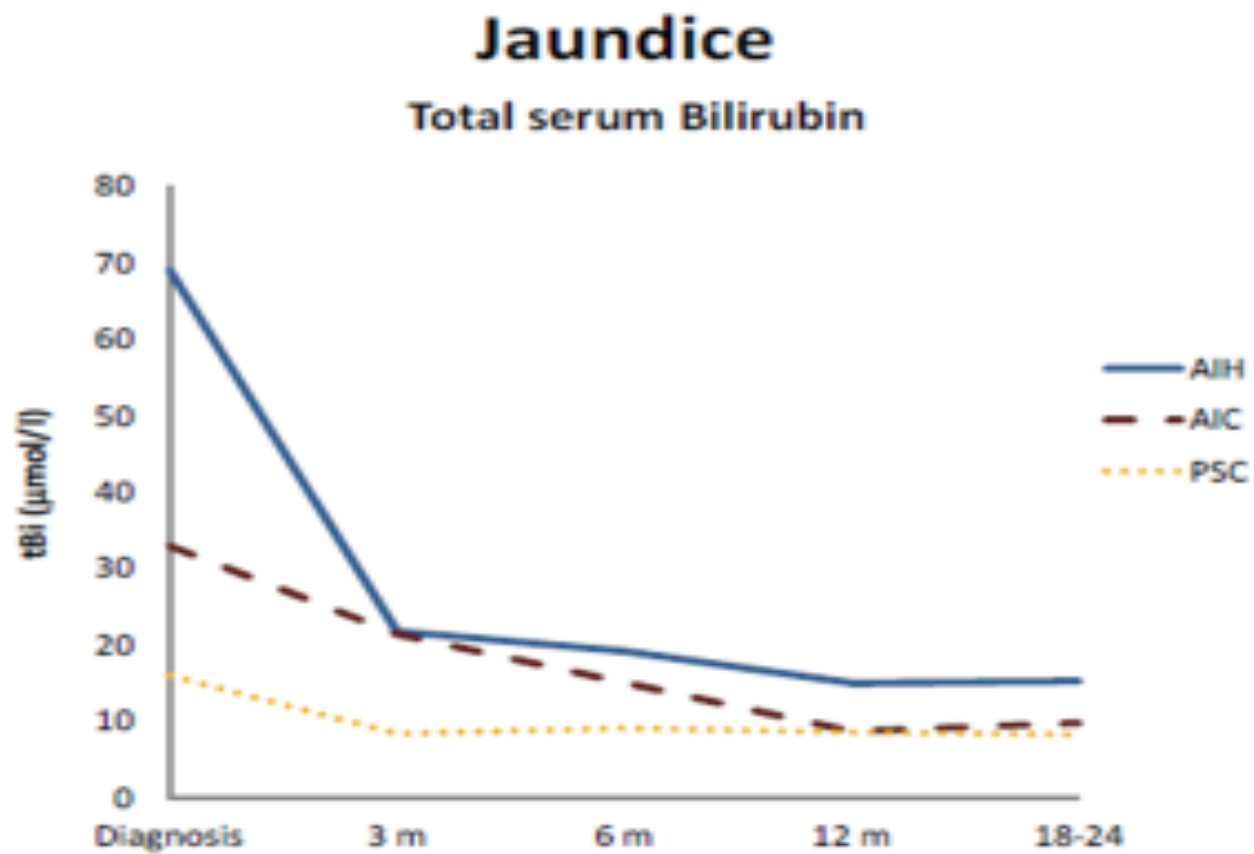
Following this protocol, successful long term complete withdrawal of treatment was possible in 20% of AIH-1, but not in AIH-2..??

- *Failure to suspend immunosuppression successfully was associated to elevated INR, PANCA+, cirrhosis & presence of non hepatic autoimmune disorders.*

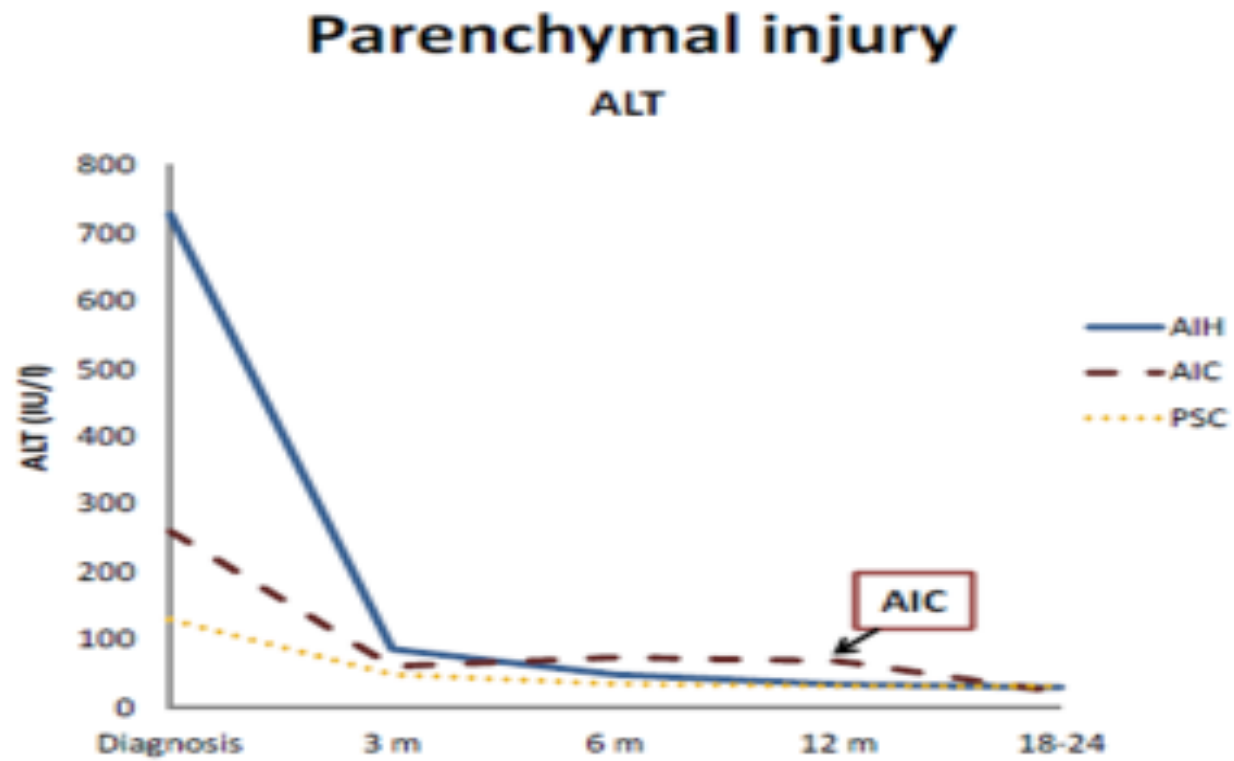
Conditions for stop treatment

Definition of remission	Treatment length	Before attempting treatment withdrawal
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

AILDs Prognosis



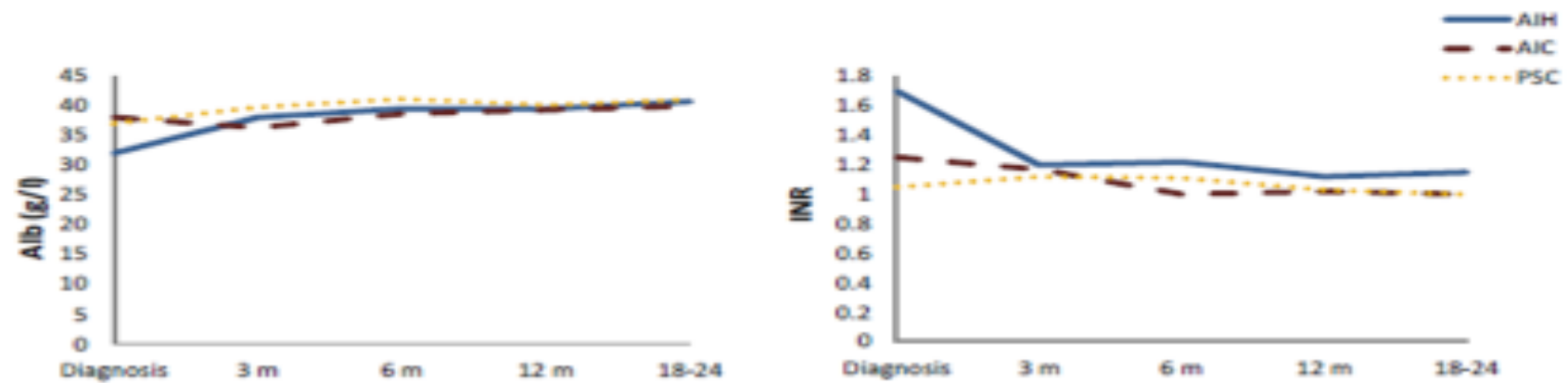
AILDs Prognosis



AILDs

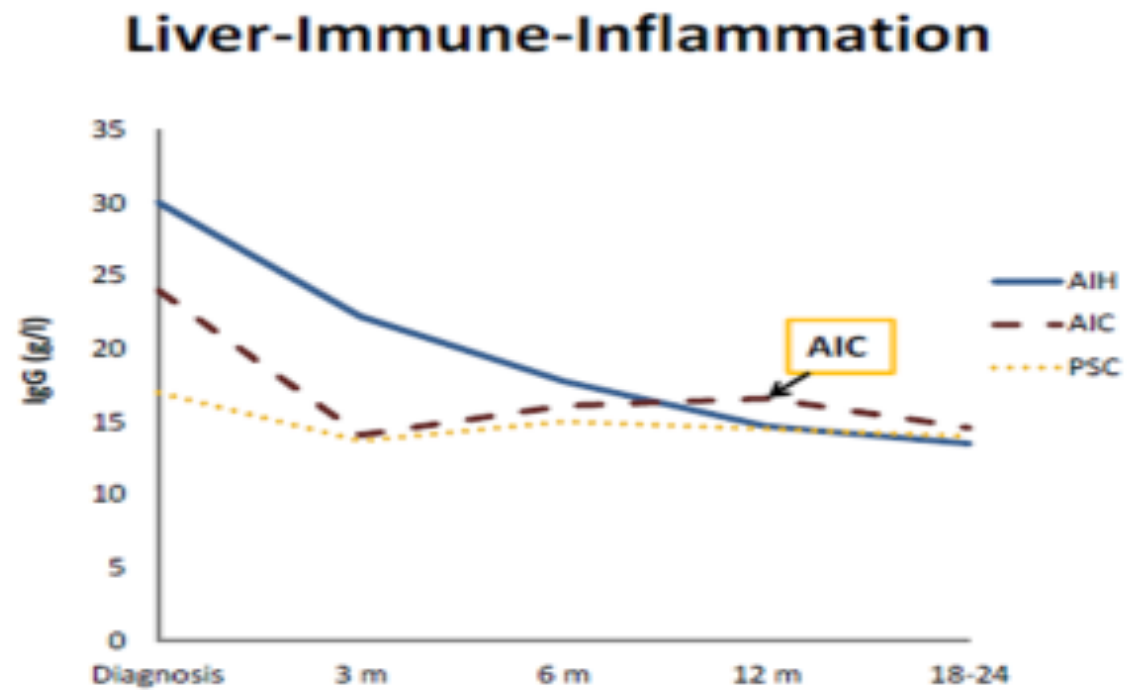
Prognosis

Liver failure



AILDs

Prognosis



Relapse

- Relapse occurs in 60%-80% of children after drug withdrawal.
- Long-term biochemical remission has been possible in 20% of children with type 1 AIH but rarely in children with type 2 AIH.
- Relapse is typically asymptomatic, manifested by mild increases in serum AST or ALT level, and rapidly responsive to retreatment.
- Delayed or failed detection, resulting in increased hepatic fibrosis and clinical deterioration .
- *50% of all relapses occur within the first 3 months after drug withdrawal, and 90% within 28 months .*

Relapse.....

- The principal predisposing factors for relapse are the duration and completeness of inactive disease prior to treatment withdrawal.
- *Other factors :*
 - psychological stress, concurrent autoimmune disease, treatment with multiple agents, increased serum ALT and IgG levels at drug withdrawal, portal plasma cells in the liver tissue pre withdrawal, delayed biochemical remission, and Pred monotherapy.
- Relapse almost invariably respond to retreatment with the original regimen .
- Drug withdrawal are commonly followed by another relapse, and patients should be treated long term after their first relapse (additional 2 years of normal lab tests).
- Cirrhosis develops more commonly in patients with repeated relapses after drug withdrawal and liver-related death or LT is also more common.

Guidance Statements (Relapse)

Drug withdrawal should be considered in patients who have normalized serum AST/ALT and IgG levels for at least 2 years.

- Liver tissue examination prior to drug withdrawal is valuable in excluding unsuspected inflammation and reducing the frequency of relapse, but it is not mandatory in adults.
- Patients must be closely monitored for relapse with regular laboratory assessments during the first 12 months after treatment withdrawal and annually thereafter to cover for lifelong risk.
- Relapse requires prompt reinstitution of the original treatment until biochemical remission and subsequent transition to a long-term maintenance regimen.

Second-Line Treatments

- Second-line therapies have been used to manage treatment failure, incomplete response, and drug intolerance.
- **For treatment failure** : include MMF, calcineurin inhibitors (CsA, TAC),6MP & biologics (rituximab, infliximab).
- **Incomplete response** : an improvement in laboratory findings but without complete normalization of serum AST, ALT, or IgG levels. Incomplete response occurs in ~15% of children.
- Patients unable to normalize liver tests & liver tissue within 36 months have a higher frequency of cirrhosis and need for LT.
- Second-line therapies for incomplete response include MMF& calcineurin inhibitors.
- **Intolerance**: indicates the inability to continue therapy due to side effects . Patients who cannot tolerate AZA will tolerate 6 MP . Other are MMF and TAC.

MMF

- MMF use in intolerant of AZA or in incomplete response or treatment failure with glucocorticoid / AZA.
- *Combination of MMF & Pred was the most widely used second-line treatment.*
- The effectiveness of MMF in induction of biochemical remission in 60%.
- MMF is more effective in patients intolerant of primary therapy than in failure to therapy (62% versus 38%).

Normalization of serum ALT and AST levels by month 6 in patients with treatment failure was achieved in 36% of treated with MMF and 83% with CsA and in 50% with TAC.

- MMF was well tolerated, and adverse events occurred in 35% compared to 78% treated with CsA & 42% treated with TAC.

Calcineurin Inhibitors

TAC in the setting of treatment failure, incomplete response, and AZA intolerance have moderate-to-high efficacy.

TAC has been administered in combination with prednisone, budesonide with serum trough levels ranging from 1 to 10 ng/mL.

Patients with either AZA intolerance or incomplete response, treatment failure documented normalization of serum amino transferases in (94% with AZA intolerance and 57% with incomplete response or treatment failure).

TAC...

- Side effects necessitating decreased dose or cessation of TAC occurred in ~25% .
- The most frequently side effects were neurologic symptoms (tremors, head aches), renal complications(hypertension , renal insufficiency), and hair loss.
- **CsA** may be considered as the second-line therapy of choice for patients with concurrent diabetes when compared to TAC as diabetes can develop as a side effect of TAC.

Cyclosporine A

- Induction of remission obtained with cyclosporine A.
- CsA was used at dose 4mg/kg in 3 doses , increased if necessary every 2-3 days to achieve blood level 250 ± 50 ng/ml for 3 months.
- If clinical and biochemical response in the first months, CsA reduced to achieve a 200 ± 50 ng/ml for 3 months before discontinuing.
- After continue with Pred + AZA

Guide Line Recommendations

- In children who have treatment failure, incomplete response, or drug intolerance to first-line agents, the AASLD suggests the use of MMF or TAC to achieve and maintain biochemical remission .
- Based on a superior ease of use and side-effect profile, the AASLD suggests a trial of MMF over TAC as the initial second-line agent in patients with AIH .

Guidance Statements :Salvage Evolving Therapies

(Antibodies to TNF- α , anti-CD20)

- In children or adults with AIH who have non response to first-line treatment, the accuracy of the original diagnosis and medication adherence should be reevaluated.
- Anti-TNF and anti-CD20 (rituximab) are possible alternative therapies after first-line & second-line regimens have failed, but the data supporting their use are limited.

Long-Term Outcomes

- The overall 10-Y & 20-Y survival rates of treated AIH are 91% & 70%, respectively.
- The 10-year liver-related mortalities in the USA range from 6.2% to 7.5%, and they are similar to those in the UK (9%) .
- Cirrhosis is present in 28%-33% of patients at presentation; and it may develop in 10%-40% of treated patients.
- Cirrhosis has been associated with reduced survival, and LT has been necessary in 21% of steroid-refractory patients.

Prognosis

Liver transplantation

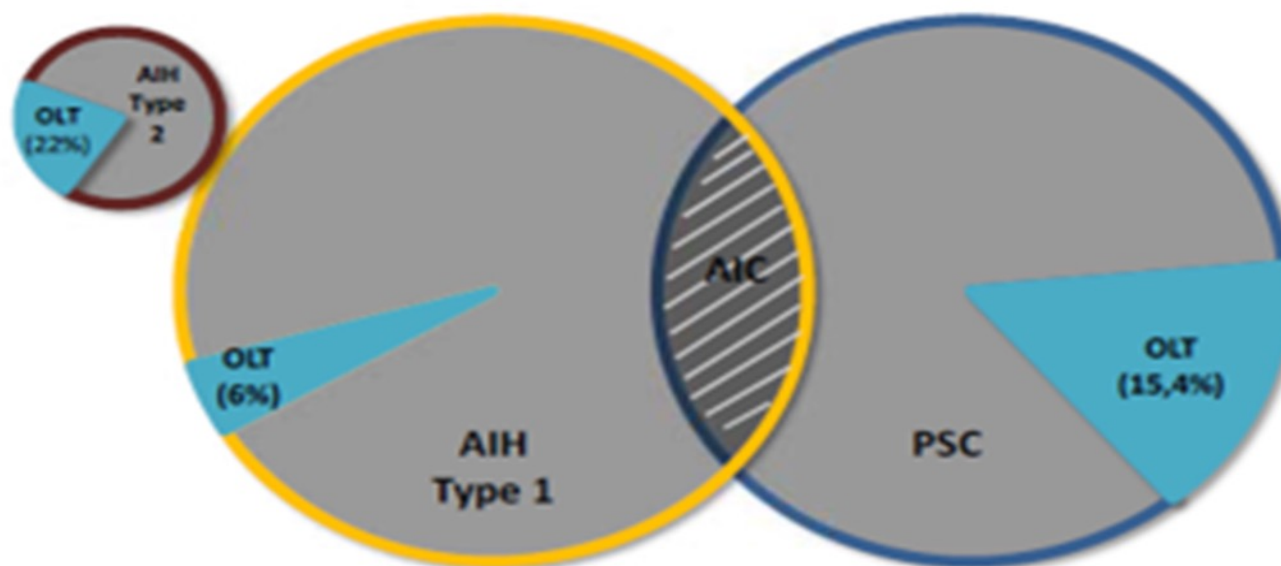




TABLE 2. Definitions of AIH and Its Treatment Outcomes

Condition	Definition
AIH	Characteristic histologic abnormalities (lymphoplasmacytic interface hepatitis), elevated AST, ALT, and total IgG and the presence of one or more characteristic autoantibodies
Inactive cirrhosis	Absence of inflammatory infiltrates in both portal tracts and fibrous bands in cirrhosis
Acute severe AIH	Jaundice, $\text{INR} > 1.5 < 2$, no encephalopathy; no previously recognized liver disease ⁽³⁷⁰⁾
ALF	$\text{INR} \geq 2$; hepatic encephalopathy within 26 weeks of onset of illness; no previously recognized liver disease ^(100,136)
Biochemical remission	Normalization of serum AST, ALT, and IgG* levels
Histological remission	Absence of inflammation in liver tissue after treatment
Treatment failure	Worsening laboratory or histological findings despite compliance with standard therapy
Incomplete response	Improvement of laboratory and histological findings that are insufficient to satisfy criteria for remission
Relapse	Exacerbation of disease activity after induction of remission and drug withdrawal (or nonadherence)
Treatment intolerance	Inability to continue maintenance therapy due to drug-related side effects

*Patients with cirrhosis in biochemical remission may have persistent elevation of IgG.