

# Autoimmune Hepatitis: When First Line Therapy Does Not Work

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# Autoimmune Hepatitis (AIH)

## Definition:

- Syndrome of progressive hepatitis characterized by loss of tolerance to hepatic autoantigens that results in:
  - Hepatocellular necroinflammation
  - Autoantibodies: non-organ, non-species-specific
  - Hypergammaglobulinemia and/or  $\square$  IgG
  - Non-pathognomic histopathology
  - Responsiveness to immunosuppressive medications

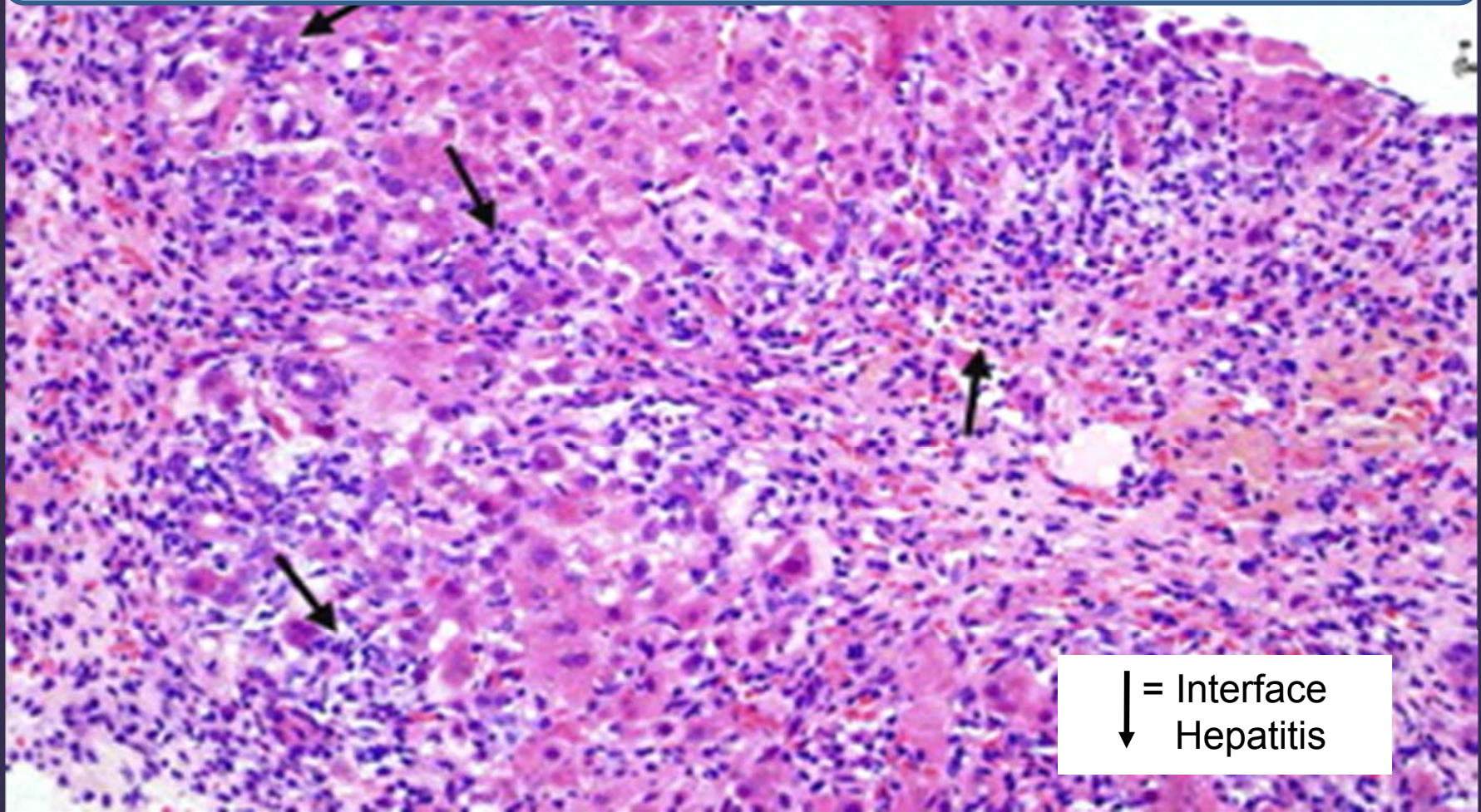
# Autoimmune Hepatitis

## Classification Based on Autoantibodies

Types	1 (95-97%)	2 (3-5%)
AutoAbs	ANA &/or SMA (f-actin ELISA)	LKM1
	SLA/LP pANCA LC-1 ASGPR	SLA/LP LKM3

# Autoimmune Hepatitis: Diagnosis Requires a Liver Biopsy

Characteristic Feature Interface Hepatitis



↓ = Interface  
Hepatitis

# Autoimmune Hepatitis

## Revised Scoring System of the International Autoimmune Hepatitis Group\*

Gender	Female	+2	HLA	DR3 or DR4	+1
AP:AST (or ALT) ratio	>3 <1.5	-2 +2	Immune disease	Thyroiditis, colitis, others	+2
γ-globulin or IgG level above normal	>2.0 1.5-2.0 1.0-1.5 <1.0	+3 +2 +1 0	Other markers	Anti-SLA, actin, LC1, pANCA	+2
ANA, SMA, or anti-LKM1 titers	>1:80 1:80 1:40 <1:40	+3 +2 +1 0	Histological features	Interface hepatitis Plasmacytic Rosettes None of above Biliary changes Other features	+3 +1 +1 -5 -3 -3
AMA	Positive	-4	Treatment response	Complete Relapse	+2 +3
Viral markers	Positive Negative	-3 +3			
Drugs	Yes No	-4 +1	<p><b>Pretreatment aggregate score:</b>  <b>Definite diagnosis &gt;15</b>  <b>Probable diagnosis 10-15</b></p> <p><b>Post-treatment aggregate score:</b>  <b>Definite diagnosis &gt;17</b>  <b>Probable diagnosis 12-17</b></p>		
Alcohol	<25 g/day >60 g/day	+2 -2			

\*A

# Differential Diagnostic Dilemmas

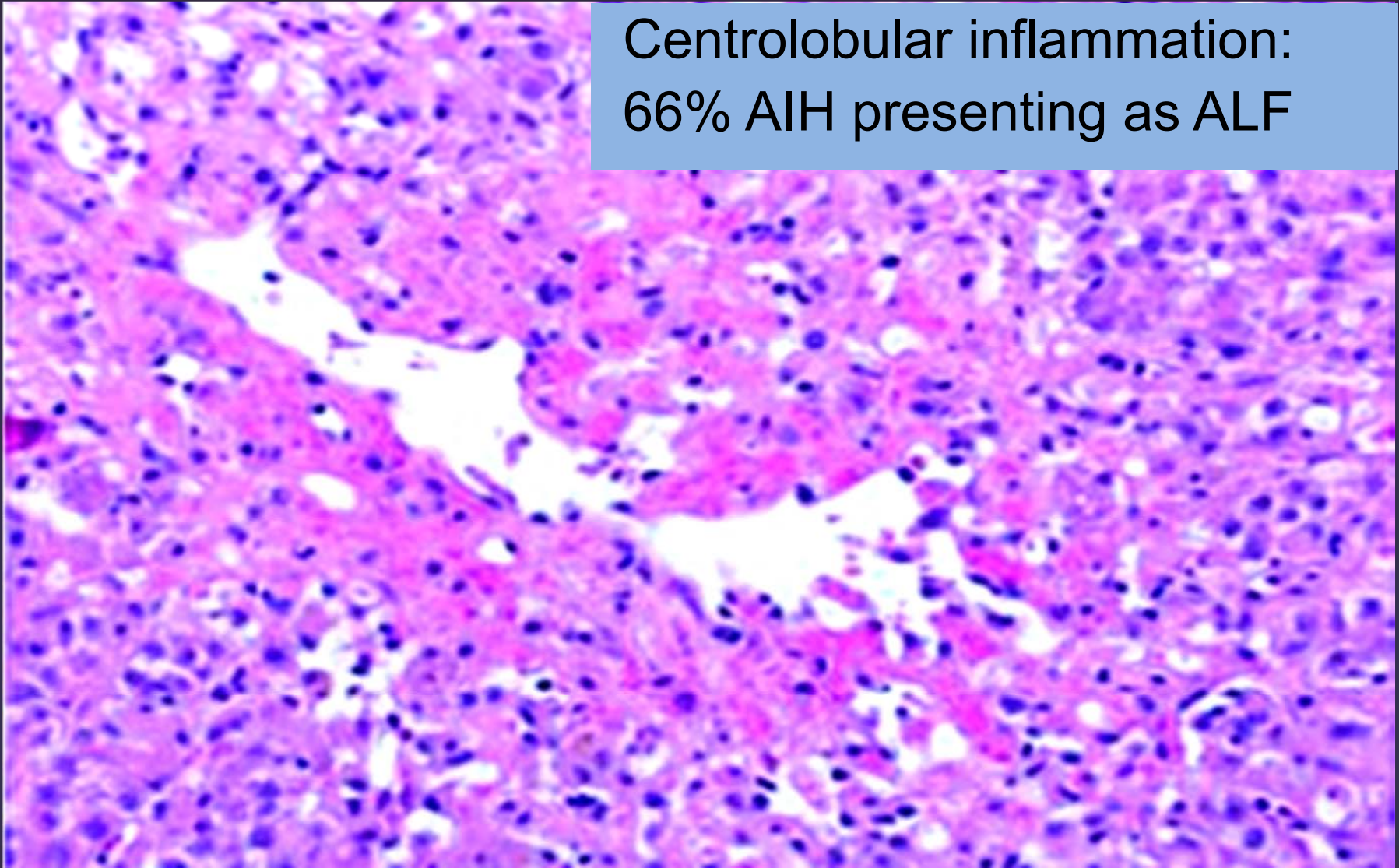
## Autoantibodies Observed in Other Diseases

Disease	ANA/SMA	LKM1	LKM2	LKM3	SLA/LP
Acute Hepatitis	80% +	-	-	-	-
Chronic HCV	20-25%+	0-88%	-	-	-
HBV-HDV	-	-	-	13%	-
Alcoholic Hepatitis	75%+	-	-	-	-
Wilson Disease	Common*	-	-	-	-

\*Acute phase reaction □ normalizes ceruloplasmin concentration!!  
 Test [Cu]: 24 hour urine (>100 □g) & hepatic (250 □g/g dry wt)

# Autoimmune Hepatitis Requires a Biopsy

## Centlobular Inflammation without Interface Hepatitis



Centrolobular inflammation:  
66% AIH presenting as ALF

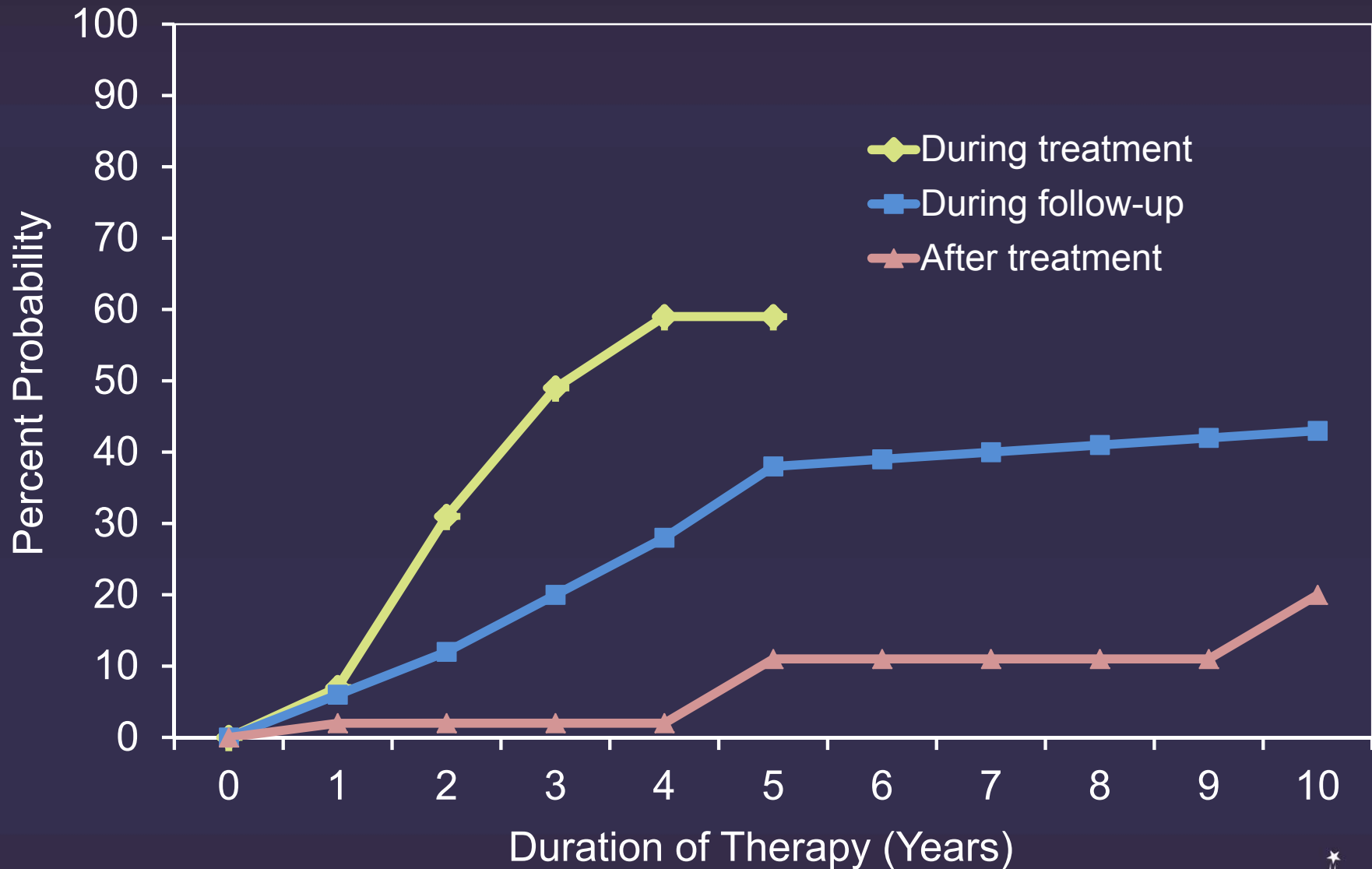
# 2002 AIH Treatment Goals

## Definition of “Remission”

- Reduce mortality, symptoms
- Reduce AST and ALT to 1.5-2 X ULN
- Histology:
  - Confine inflammation to portal tracts
  - Eliminate interface hepatitis
  - Slow progression to cirrhosis
- Minimize immunosuppression to maintain “remission”
- Minimize serious adverse events



# Probability of Cirrhosis During Steroid Therapy



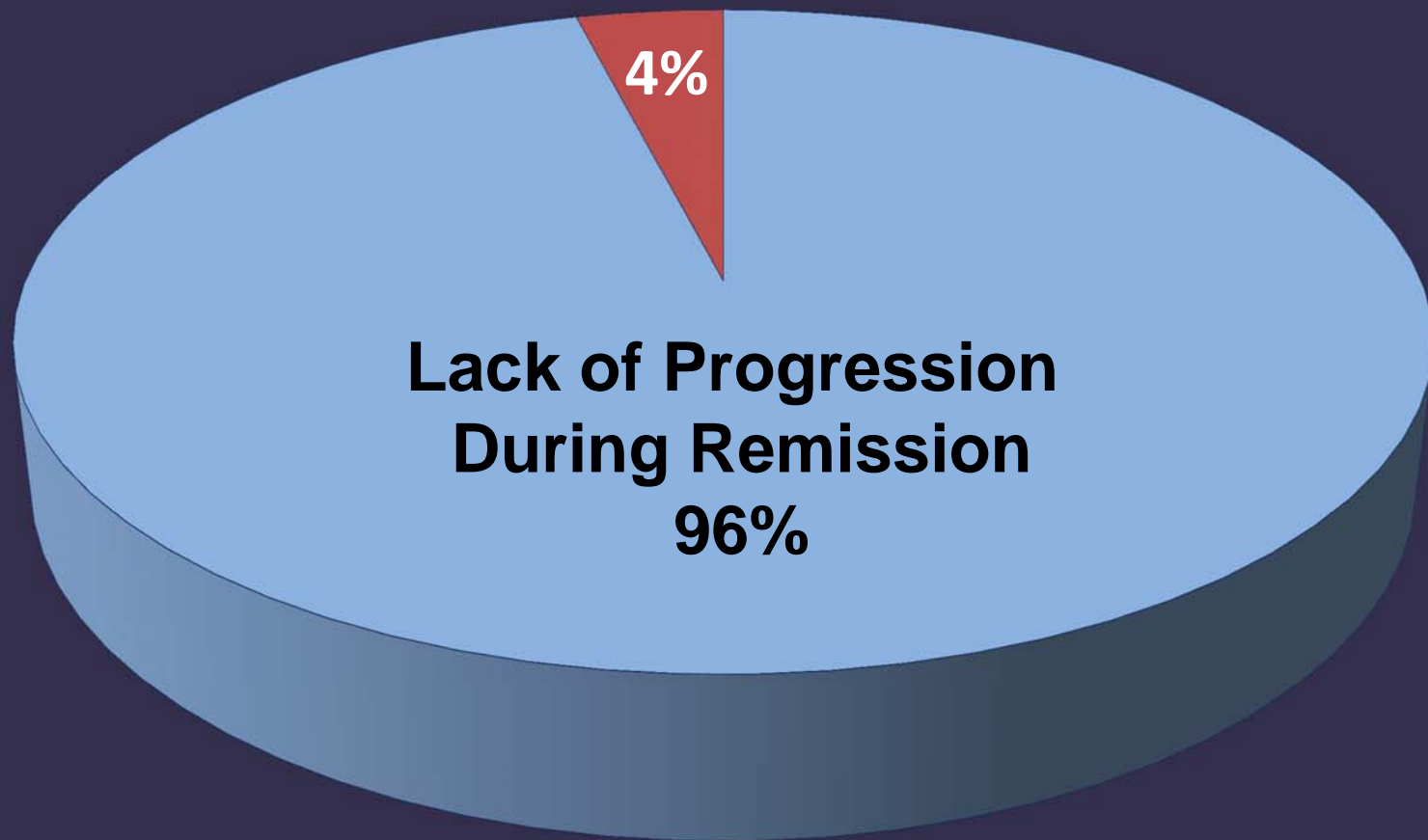
# 2010 AIH Treatment Goals

## New Concept of “Remission”

- Prevent progression and OLT
- Relieve symptoms
- Normalize ALT
  - <19 U/L for women
  - <30 U/L for men
- Histology:
  - Eliminate portal lymphoplasmacytic inflammation
  - Eliminate interface hepatitis
  - Prevent progression to cirrhosis
- Use combinations of immunosuppressive drugs to
  - Inhibit immunopathogenetic mechanisms at multiple sites
  - Minimize adverse events

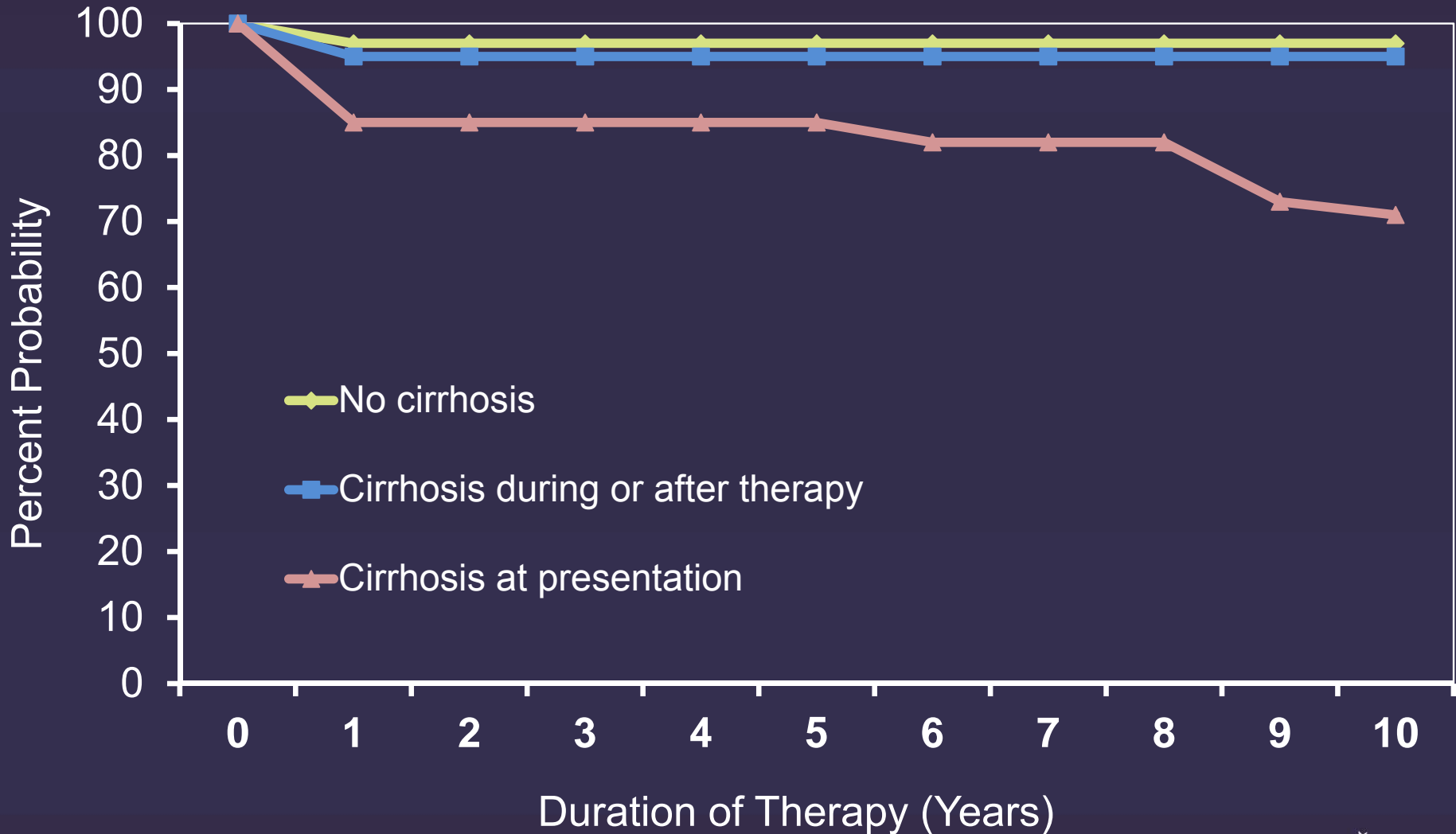
# Autoimmune Hepatitis

Frequency of Progression After “Remission”  
Using Definition in 2010 AASLD Guideline



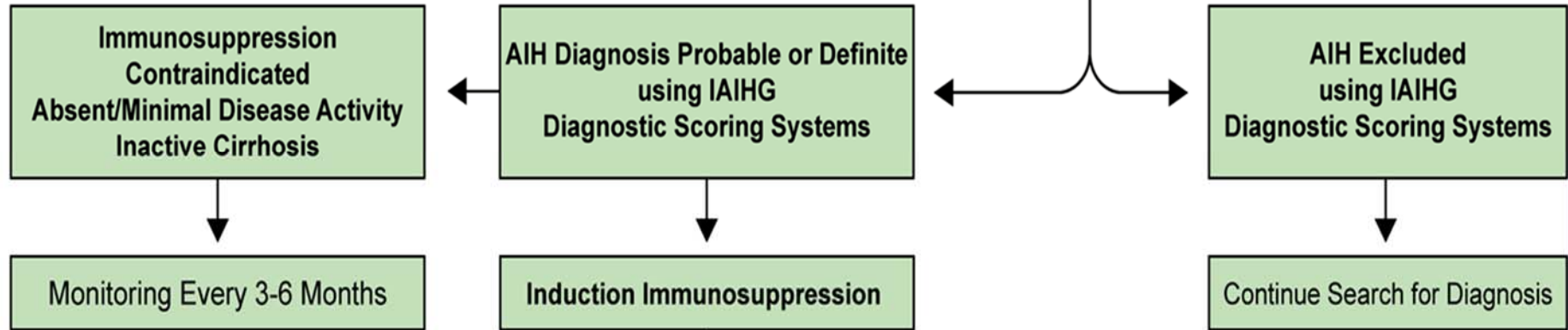
# Autoimmune Hepatitis

## Probability of Survival During Steroid Therapy



# Autoimmune Hepatitis

## Options for Immunosuppression



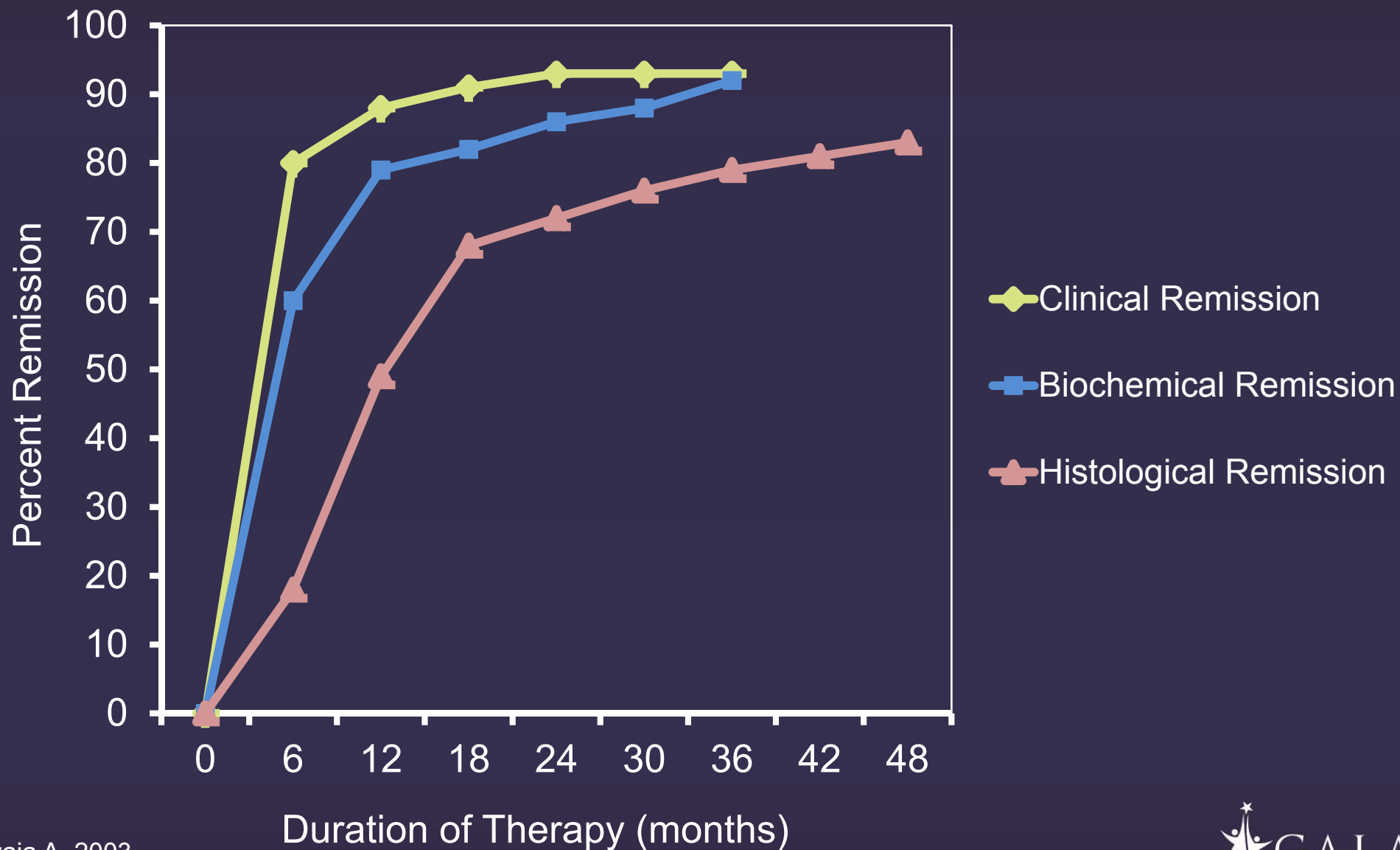
Budesonide + Azathioprine	
3 mg TID	1-2 mg/kg/d
Non-Cirrhotic Patients Only!	

Monotherapy Prednisone (mg/d)	
	Prednisone (mg/d)
Wk 1	60
Wk 2	40
Wk 3	30
Wk 4	30
Maintenance	20 and below

Combination Prednisone+Azathioprine (mg/d)			
	Prednisone (mg/d)	Azathioprine	
		USA (mg/d)	EU (mg/kg/d)
Wk 1	30	50	1-2
Wk 2	20	50	1-2
Wk 3	15	50	1-2
Wk 4	15	50	1-2
Maintenance	10	50	1-2

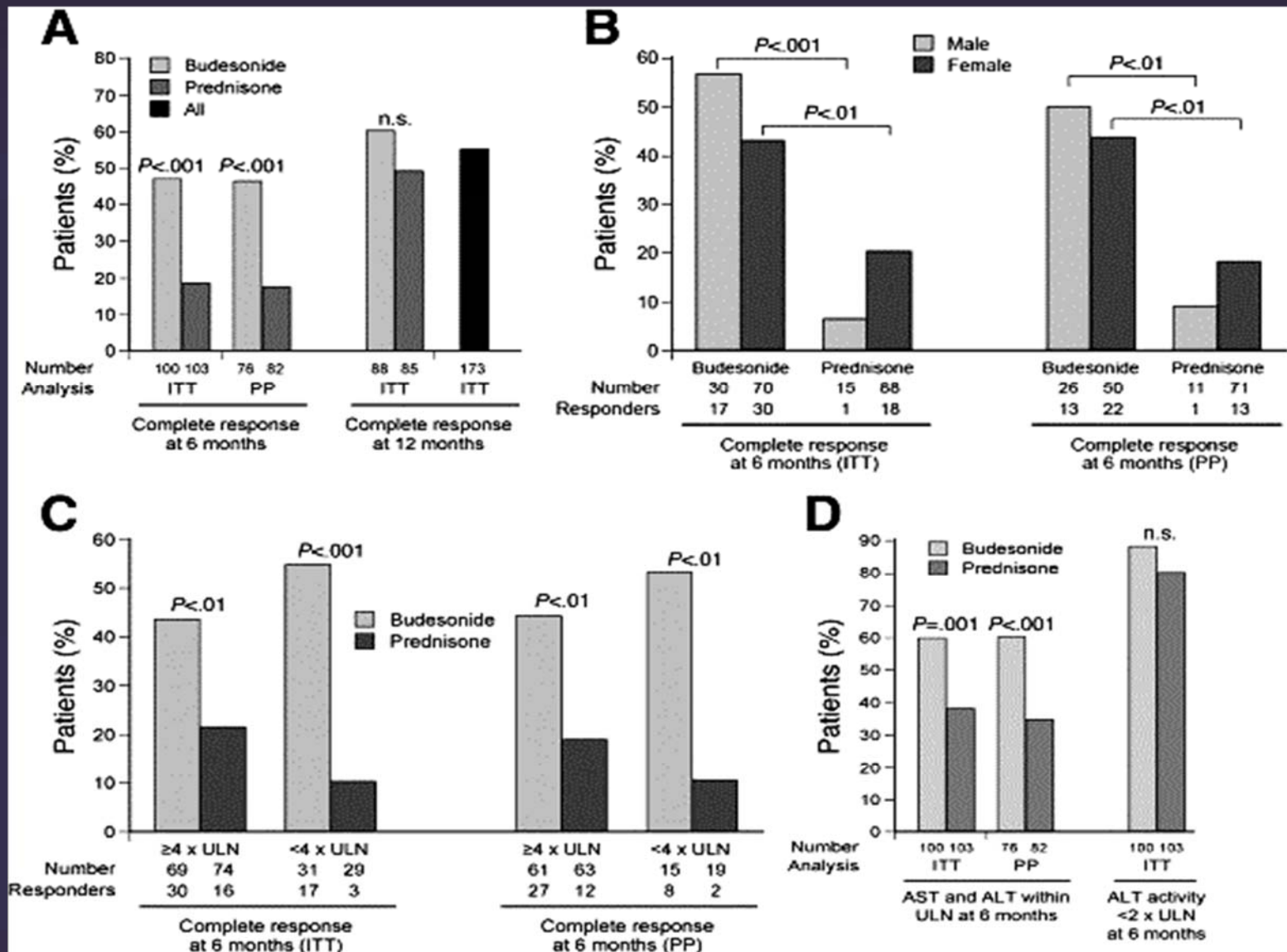
# Autoimmune Hepatitis

## Clinical, Biochemical and Histological Remission During Steroid Therapy



# Autoimmune Hepatitis

Prospective, Double-Blind, Randomized, Controlled Trial  
Budesonide + Aza vs Prednisone + Aza



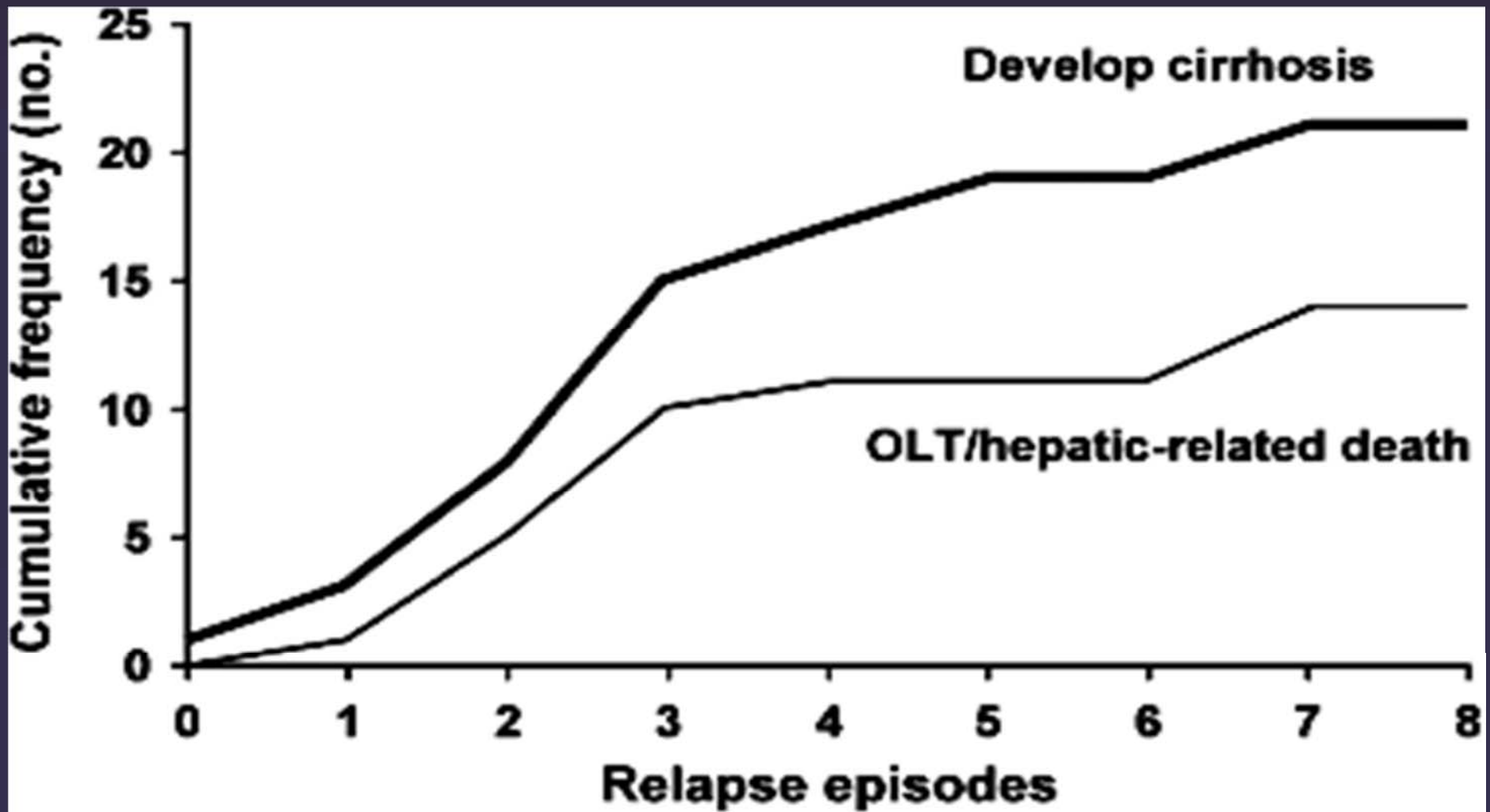
# Autoimmune Hepatitis in Pregnancy

- Fertility due to secondary amenorrhea
- Treatment not contraindicated
- Prednisone alone safe
- Safety of prednisone + azathioprine less clear
- Risk to fetus
  - Prematurity (30%)
  - Low birth rate (35%)
  - C-section (26%)
- Risk of flare post-partum
- Complications of PVHTN due to expanded blood volume, intensified hyperdynamic circulation



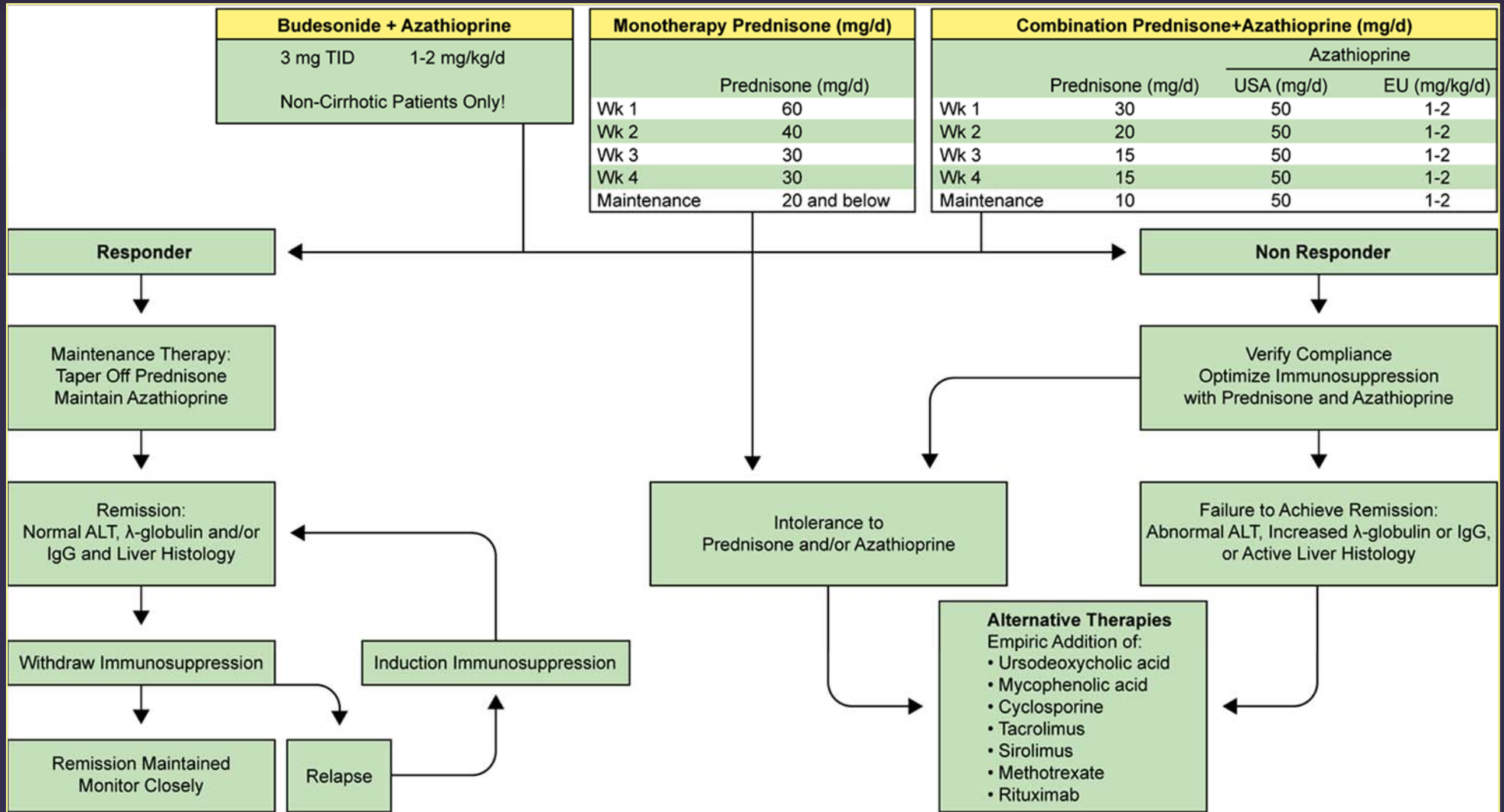
# Autoimmune Hepatitis

Relapse of AIH After Withdrawal of Therapy  
Increased Probability of Cirrhosis and Need for OLT



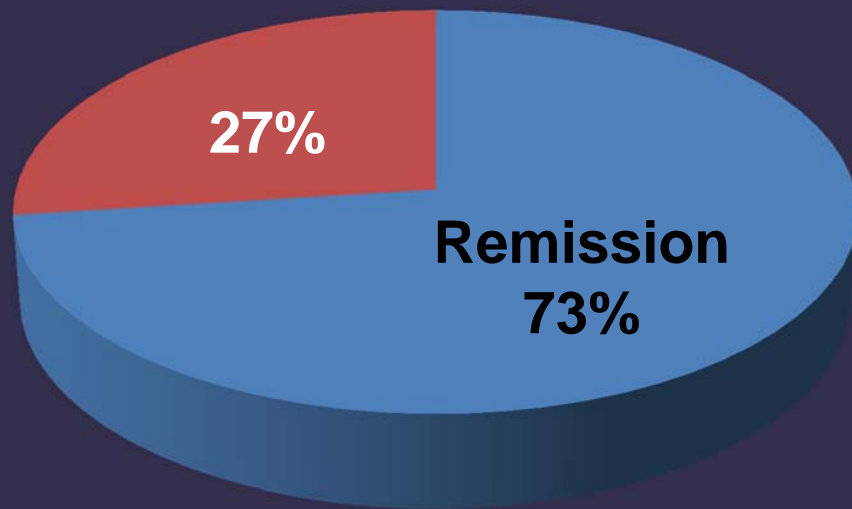
# Autoimmune Hepatitis

## Alternative Immunosuppression to Achieve Remission

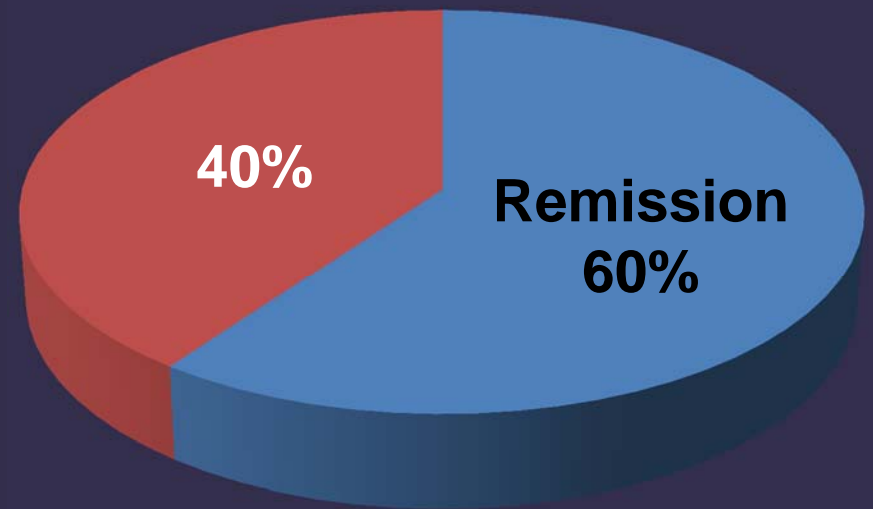


# Autoimmune Hepatitis

Estimated Frequency of “Remission” Using  
2002 vs. 2010 AASLD Guidelines’ Definitions



2002 AIH  
Practice Guideline



2010 AIH  
Practice Guideline

Corticosteroids  
 Ursodeoxycholic acid  
 IVIG, HuOKT3, ALG, ATG  
 Hu-Max-CD4, Efalizumab,  
 Enlimomab

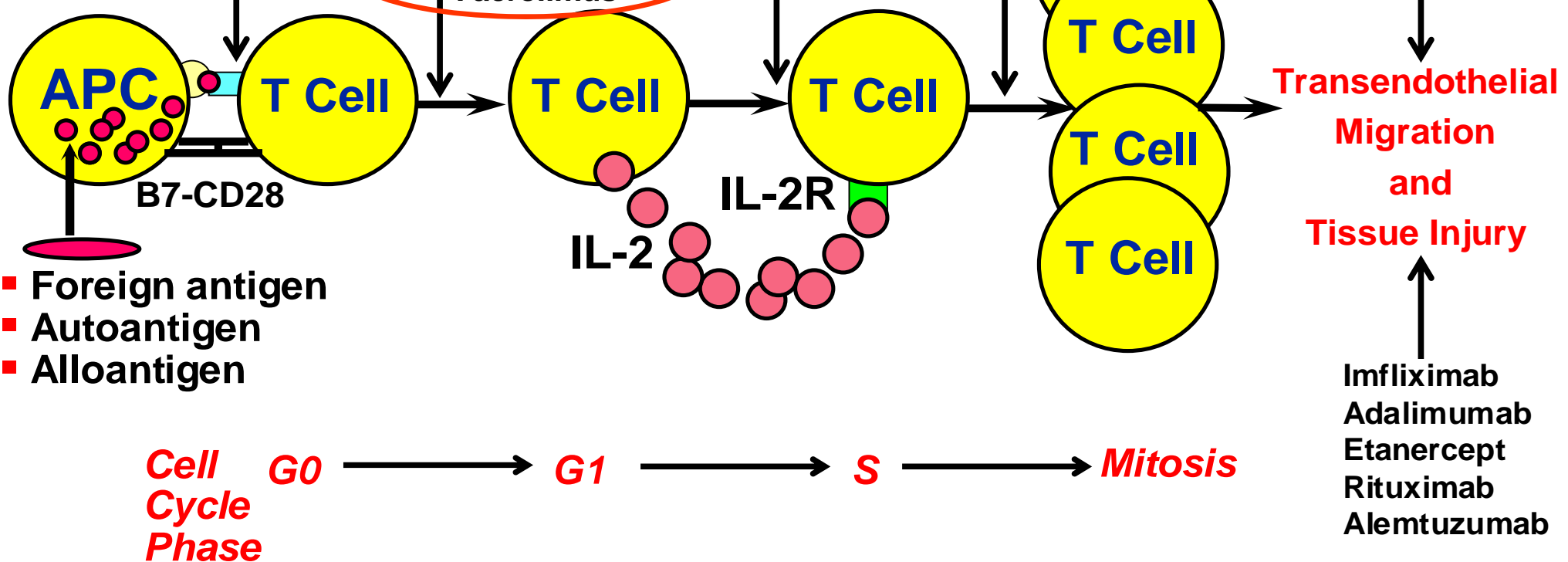
Azathioprine, 6-MP, 6TP  
 Mycophenolate mofetil  
 Leflunomide  
 FK778  
 IVIG, HuOKT3, ALG, ATG  
 Alemtuzumab

Leflunomide  
 Eralizumab  
 Enlimomab  
 FTY720  
 Natalizumab  
 IVIG  
 Chemokine inhibitors

Abetacept, Belatacept,  
 Alefacept, Anti-CD154 (hu5C8)  
 Anti-CD137, Anti-CD4  
 Alemtuzumab

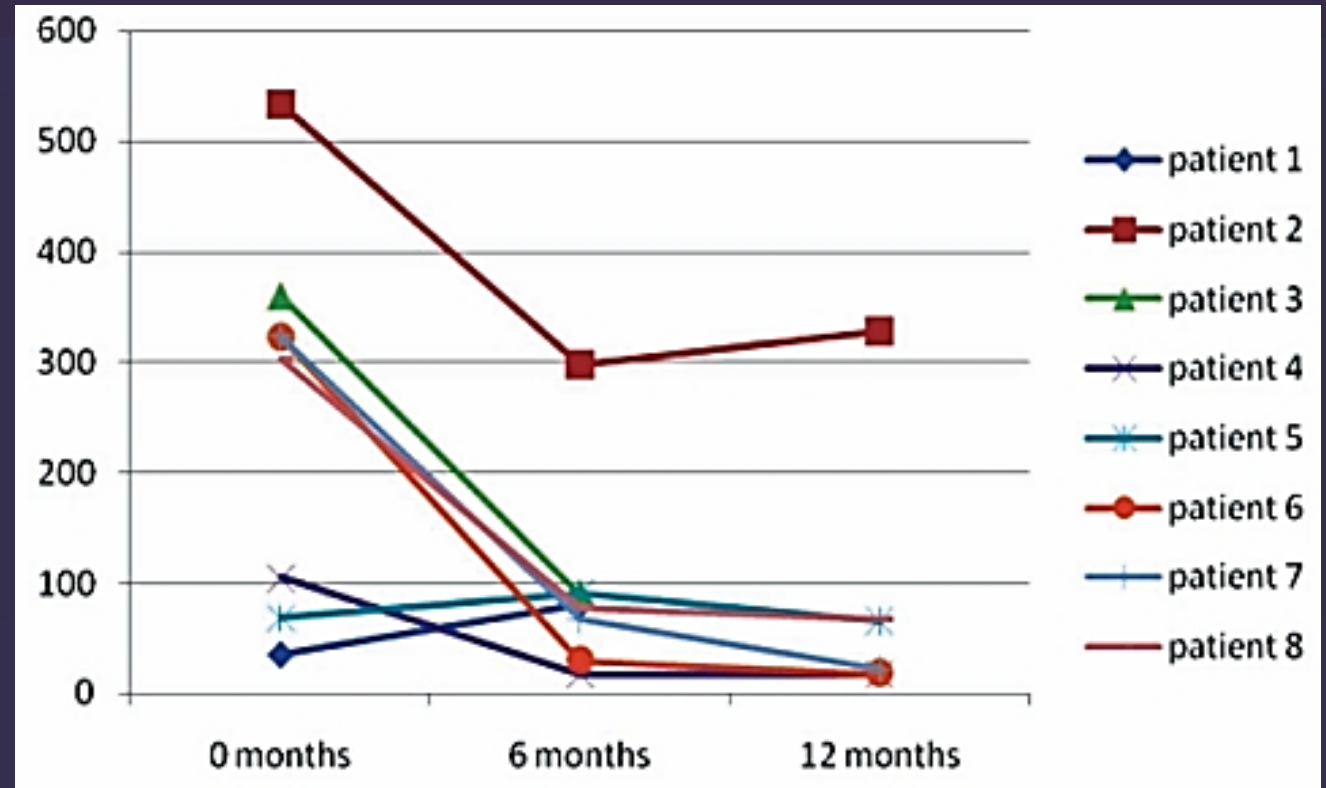
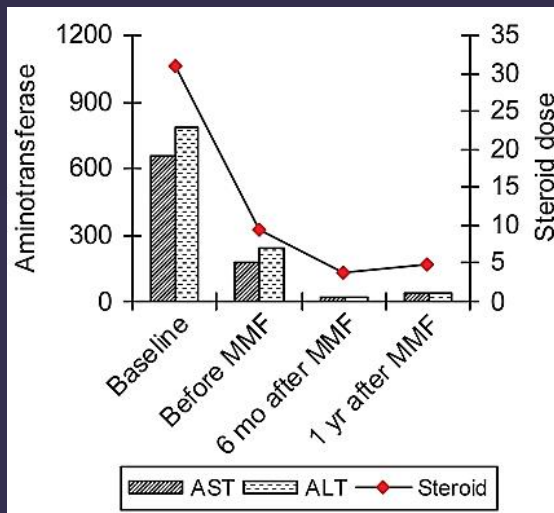
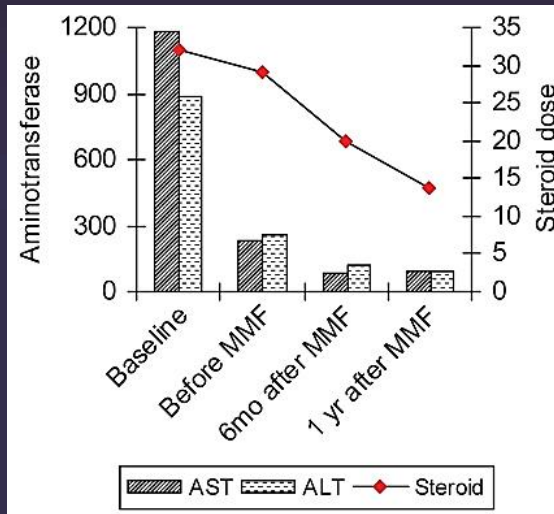
Sirolimus  
 Basiliximab  
 Daclizumab

Cyclosporine  
 Tacrolimus

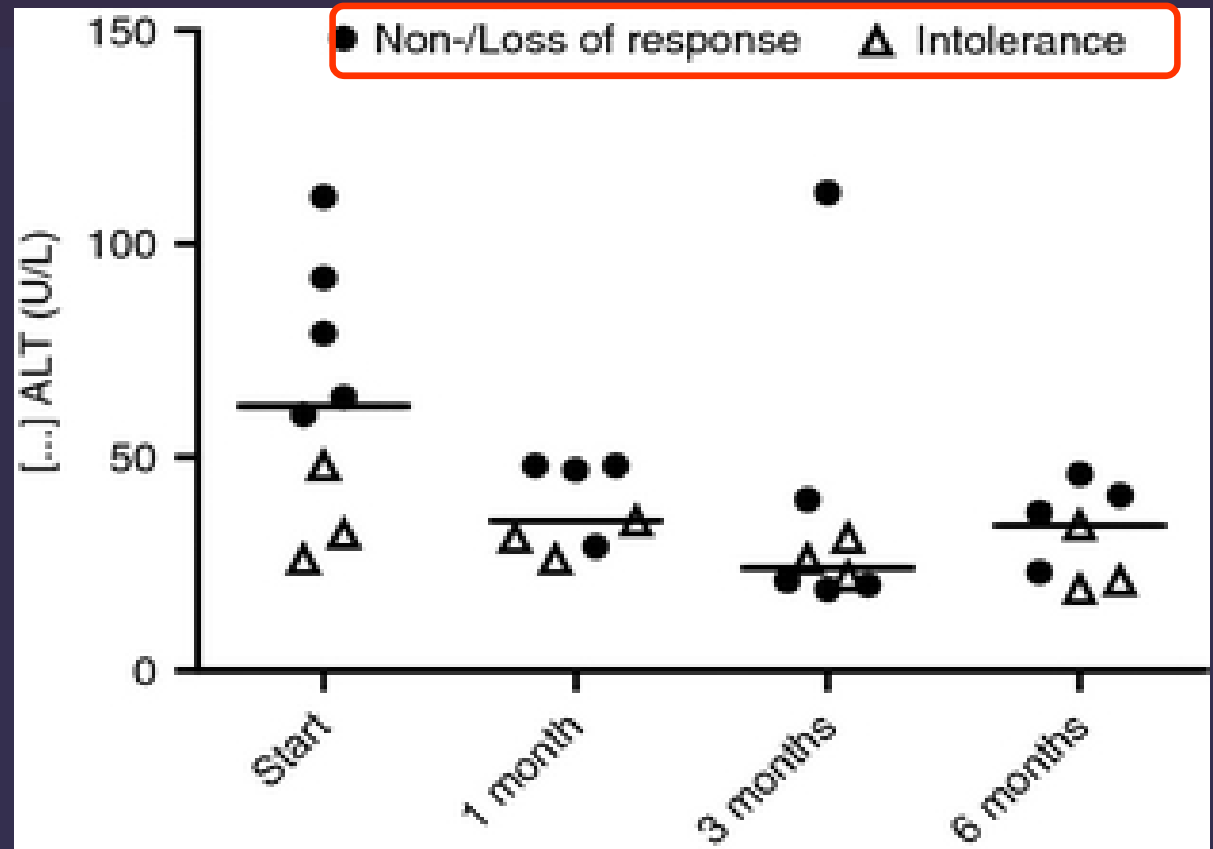
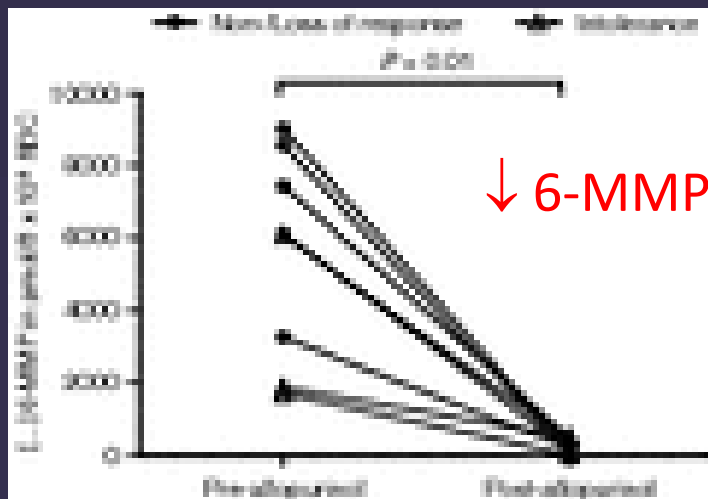
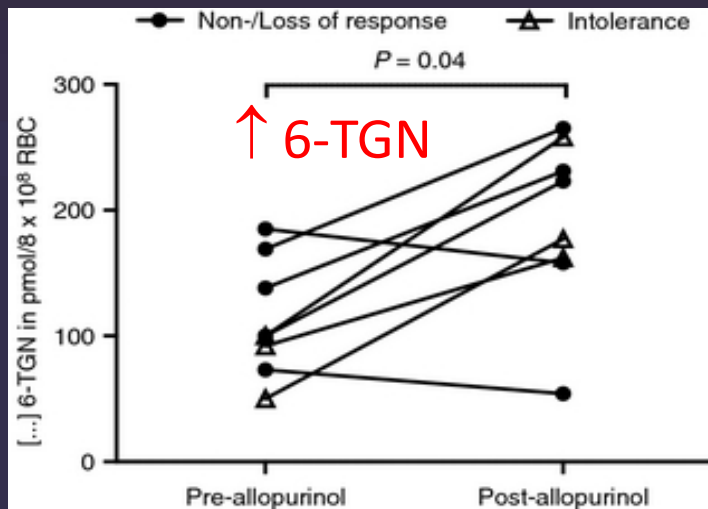


Vierling JM & Flores P: *Clin Liver Dis* 2002; 6: 537-62  
 Vierling JM: *Semin Liv Dis* 2005; 25: 347-63  
 Vierling JM: *Liver Immunology 2nd Ed*, 2007

# Mycophenolate Mofetil Treatment in AIH Patients Refractory or Intolerant to Conventional Therapy



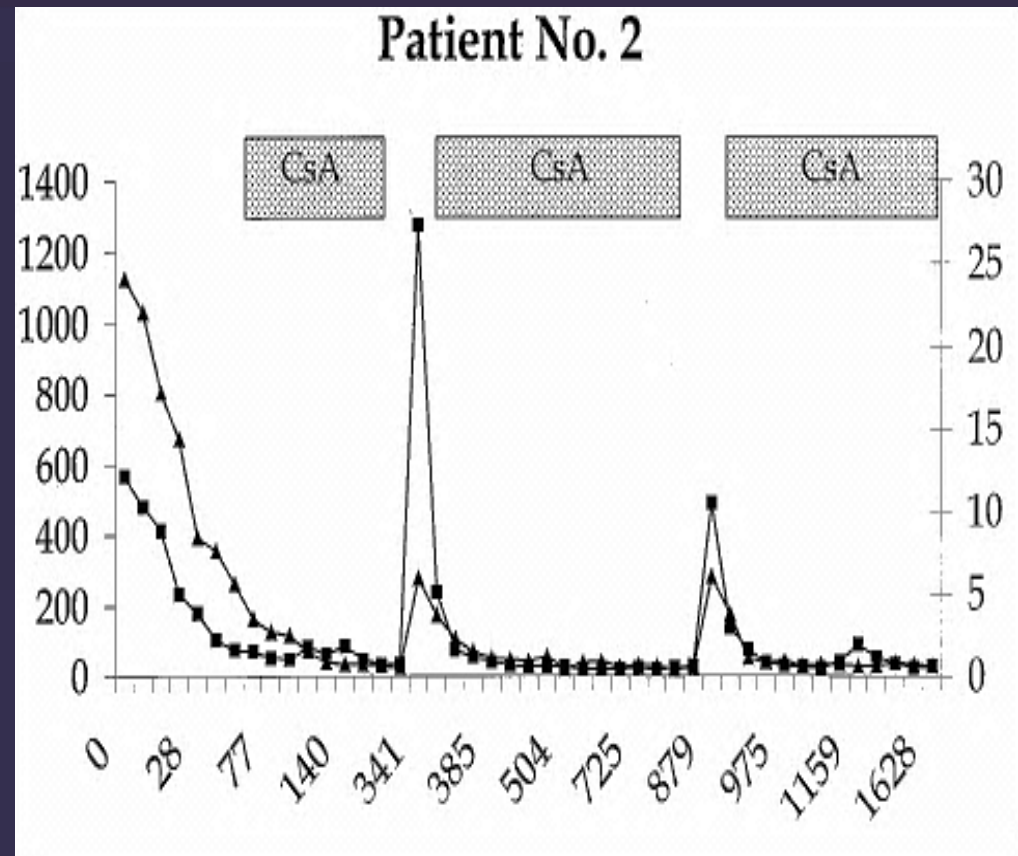
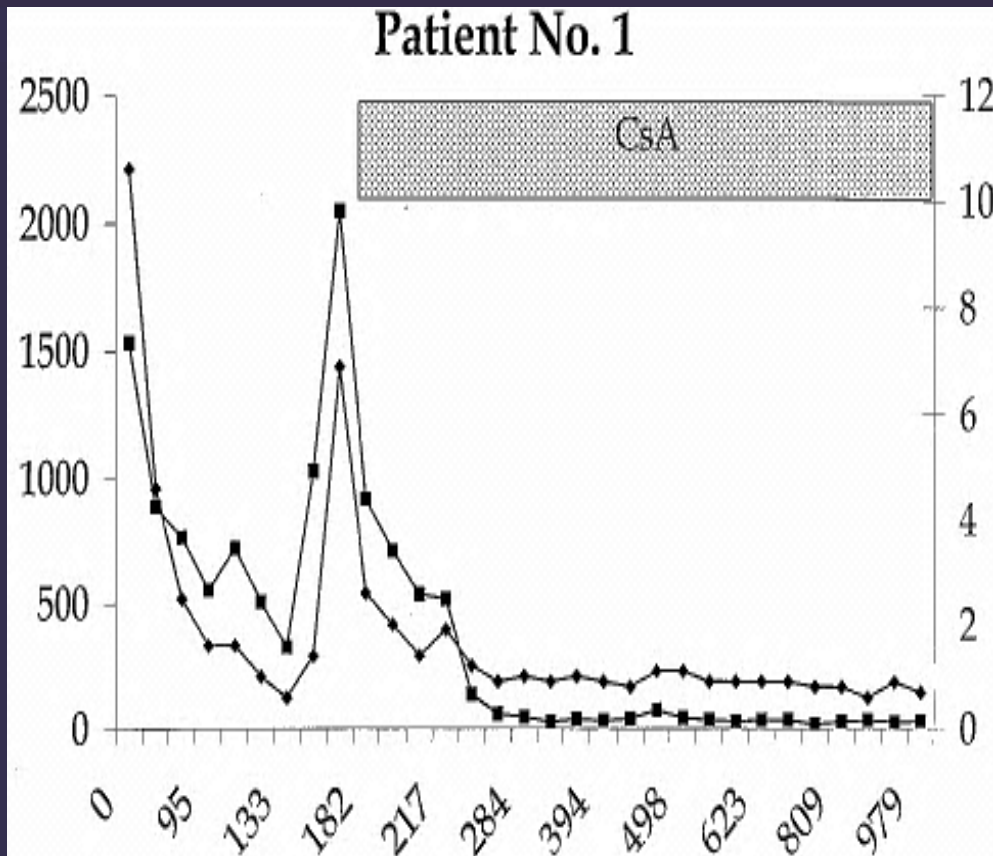
# Allopurinol to Optimize Thiopurine Metabolites in AIH



# Cyclosporine

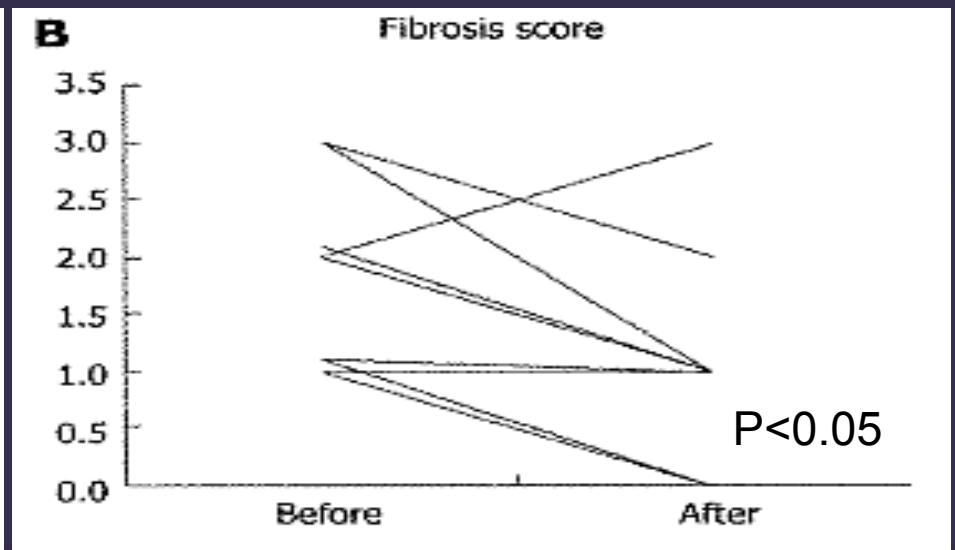
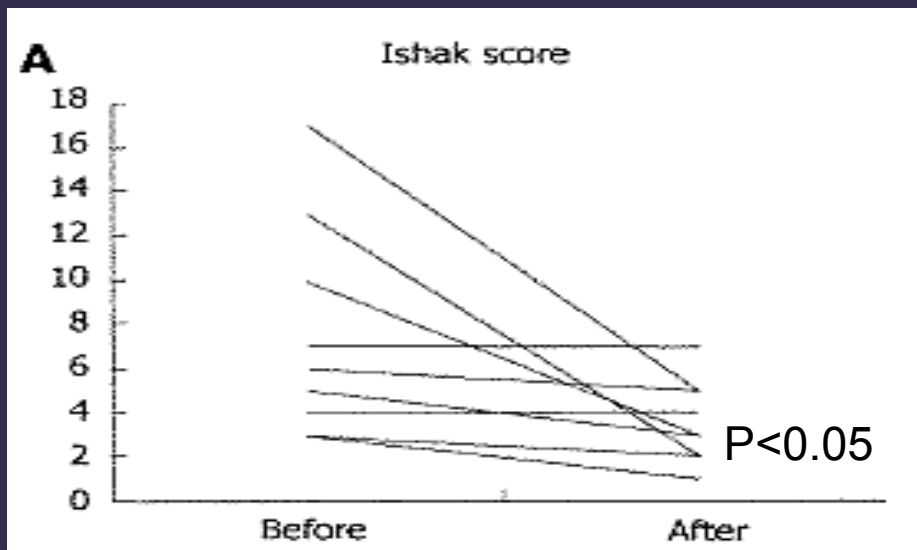
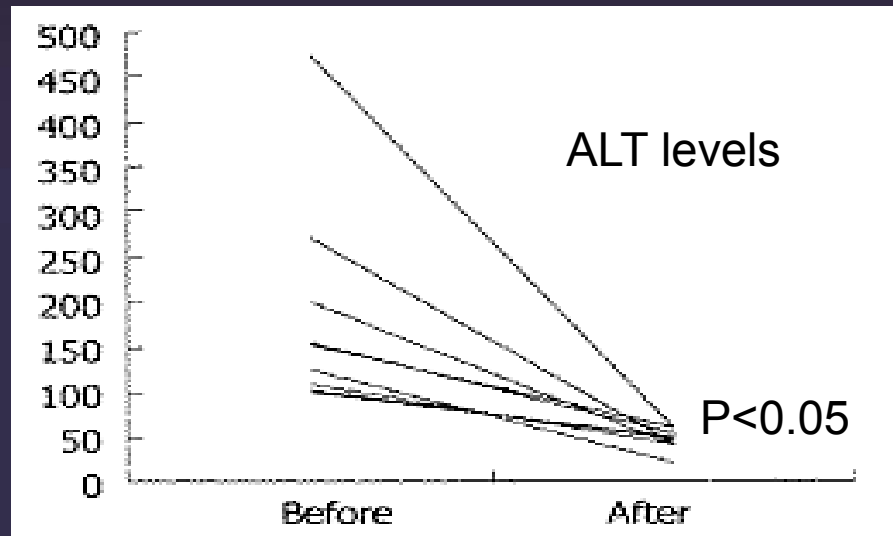
N	Regimen	Response	Comments
15 patients	3 groups 2 CsA alone. 1 with steroids/AZA	100% remission	3 relapses – responded to CsA dose adjustment
32 patients	CsA 6 months AZA/Pred 1 month CsA stopped	100% remission	No relapses
19 patients	CsA 2-5mg/kg/d	Of the patients who continued therapy – 100% response	
6 patients	CsA 3 mg/kg/d	5 of 6	
6 patients	CsA 2-4 mg/kg/d	4 of 5	

# Cyclosporine

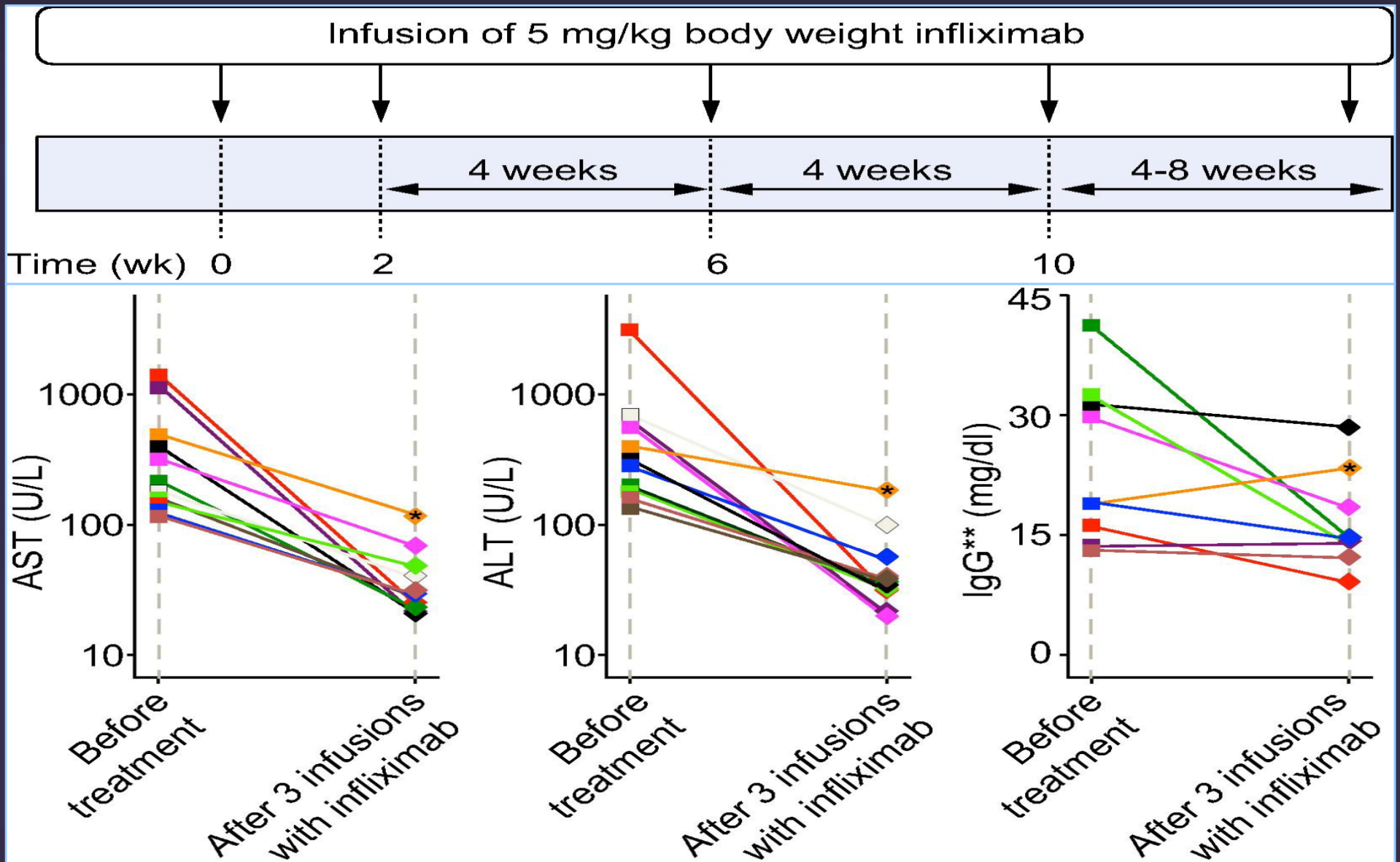




# Tacrolimus



# Infliximab Rescue



# Autoimmune Liver Diseases

## Excellent Survivals Post-OLT UNOS Database

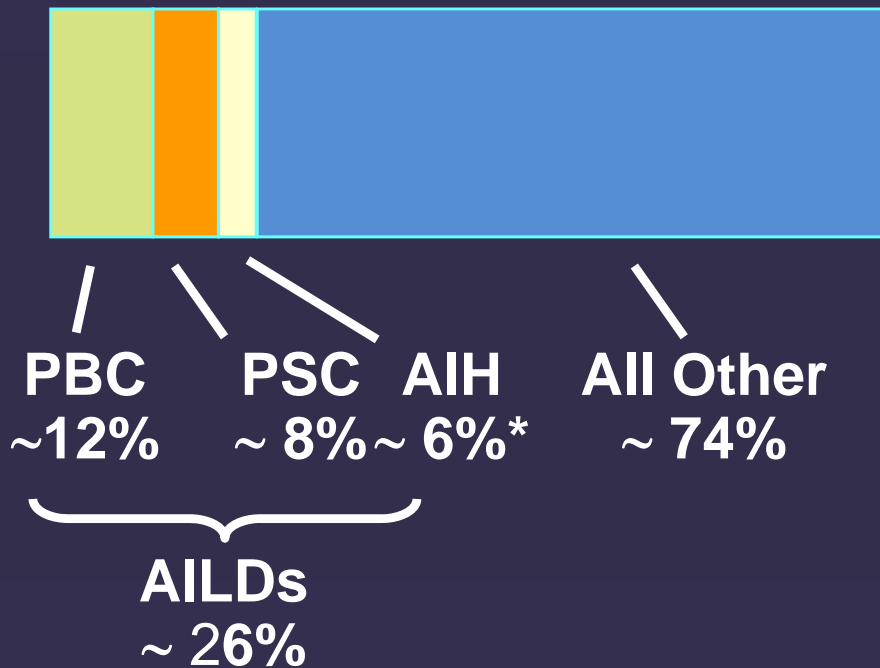
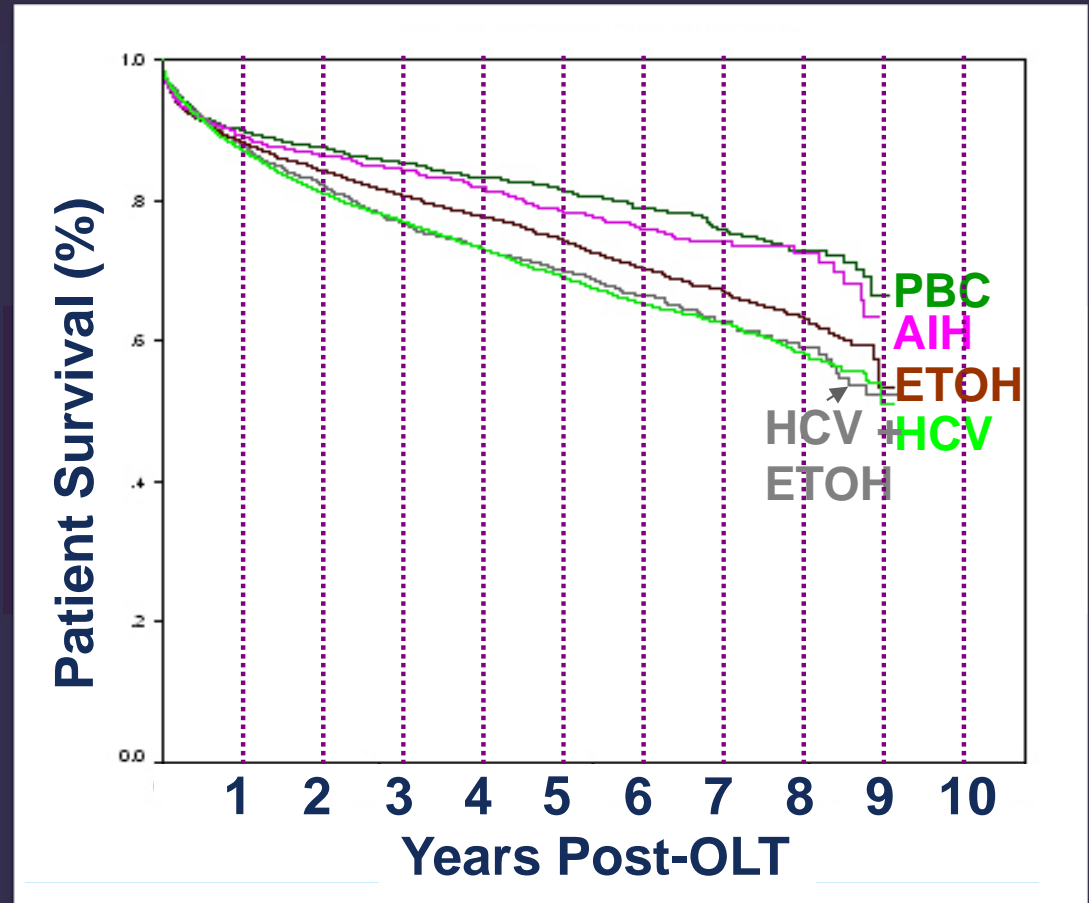
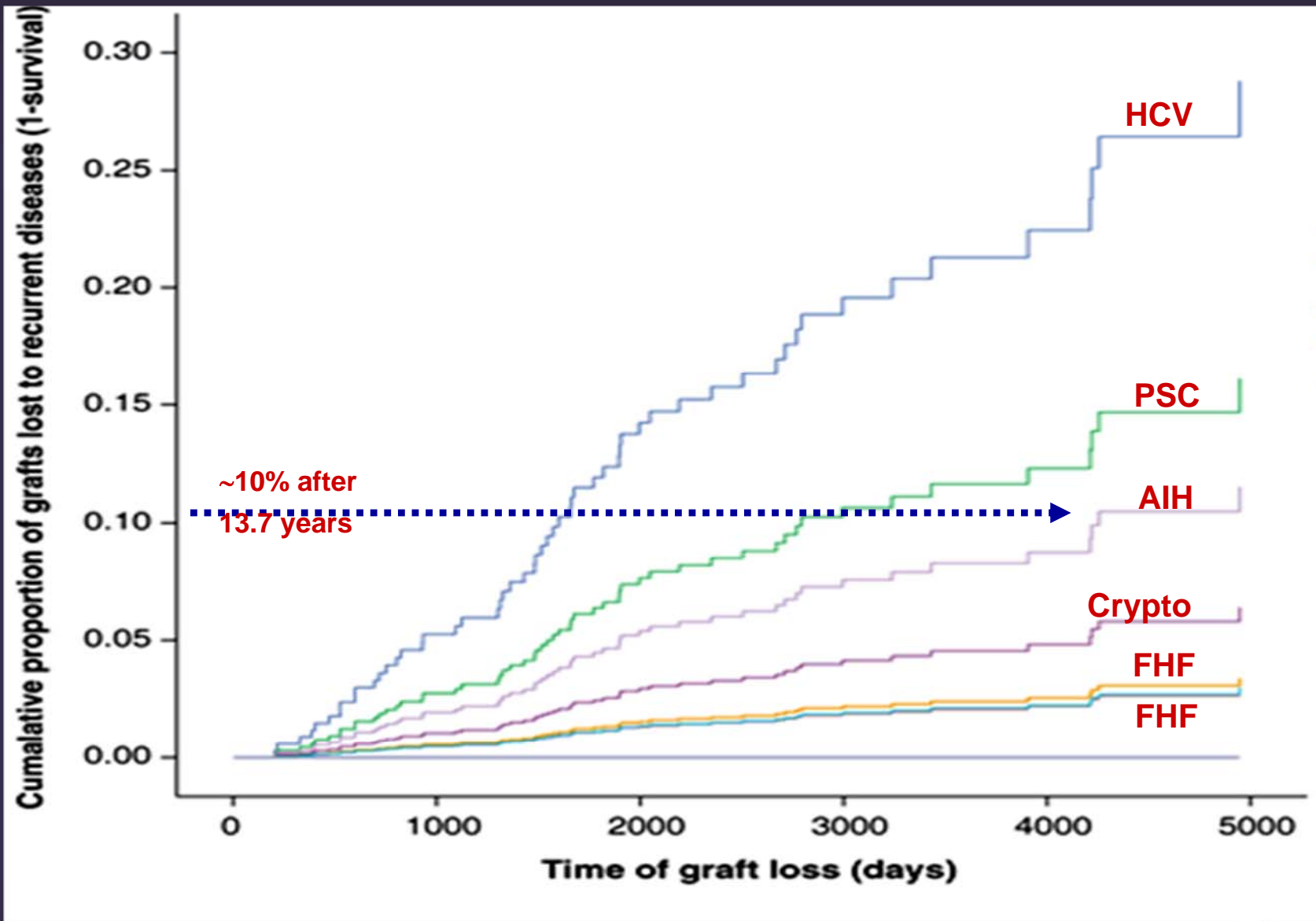


Figure 1. Post-OLT Patient Survival



# Allograft Loss After OLT

## Impact of Recurrent Diseases



# Autoimmune Hepatitis Practical Summary

- Diagnosis of AIH based on inclusion AND exclusion of diseases mimicking biochemical, serological and histopathological features of AIH
  - Wilson disease
  - DILI
  - HCV infection without a positive anti-HCV
- Diagnosis aided by response to 4 week course of induction steroid monotherapy
- If AIH confirmed,
  - Convert to budesonide if non-cirrhotic
  - Add azathioprine: if intolerant to azathioprine, consider 6-MP or MMF
  - If generation of 6-TG inadequate, consider allopurinol
- If remission not achievable with steroids and azathioprine:
  - Switching azathioprine to mycophenolic acid futile
  - Alternative therapy with cyclosporine, tacrolimus, sirolimus, anti-TNF $\alpha$  agents
  - Role of ursodexoycholic acid unclear
- If remission achieved, continue maintenance therapy indefinitely