The fun and easy way to play
thousands of free Apps on your iPod Touch and iPhone!

Autoimmune Hepatitis

FOR DUMMIES®

A Reference for the Rest of Us!®

FREE eTips at dummies.com®

By

Thomas Frazier

Objective

- "What we need to know about AIH"
  - Diagnosis
  - Treatment
  - Difficulties in both
  - Liver transplantation concerns

AASLD Guidelines: Hepatology. 2010 Jun;51(6):2193-213.

Presentation of AIH

- Insidious with nonspecific complaints
- ALF
- Cirrhosis
- Asymptomatic: ~40%
  - 70% with go on to develop symptoms
- ♀>>>>>>♂
- Other autoimmune diseases (e.g. Hashimoto's thyroiditis, RA, and Celiac sprue)

Diagnosis

- Histology
- clinical and laboratory findings
- abnormal levels of serum globulins
- Autoantibodies
- Exclusion of other etiologies
- Multiple Scoring Systems

Serologic Markers

CONVENTIONAL ANTIBODIES

- AIH Type I
  - Antinuclear ab (ANA)
  - smooth muscle ab (SMA)
- AIH Type II
  - liver/kidney microsome type 1 ab (anti-LKM1)
  - liver cytosol type 1 ab (anti-LC1)

UNCONVENTIONAL ANTIBODIES

- atypical perinuclear antineutrophil cytoplasmic antibody (atypical pANCA)
- soluble liver antigen (anti-SLA)

AIH Subtypes

- Type 1 AIH = ANA, SMA or both
  - 80% of AIH cases
  - Seventy percent of patients are female
  - Fifty percent of patients are older than 30 years
  - At the time of diagnosis cirrhosis is present in 25% of patients
  - Anti-SLA may identify patients with severe AIH who are prone to relapse after corticosteroid withdrawal
- Type 2 AIH = anti-LKM1 and/or anti-LC1 and/or anti-LKM-3.
  - Europe, children, young women. Even more subtypes

Simplified criteria for the diagnosis of autoimmune hepatitis.

variable	cutoff	points
ANA or SMA	≥ 1:40	1
ANA or SMA or	≥ 1:80	2
LKM or	≥ 1:40	
SLA	Positive	
IgG	› Upper limit of normal	1
	› 1.10 times	2
Histology	Compatible	1
	Typical	2
Absence of viral hepatitis	yes	2

* Addition of points achieved for all autoantibodies (maximum, 2 points).

≥ 7: definite AIH (68% Sens./99% Spec.)

≥6: probable AIH (90% Sens./77% Spec.)

Hepatology. 2008 Jul;48(1):169-76.

Diagnostic Challenges

- Overlap syndromes: next lecture!
- Even w/o biliary features AMA + in ~ 5%
- Other Diseases (e.g. hcv + anti-LKM)
- Drugs (e.g. herbs, vaccinations, minocycline, diclofenac, infliximab, propylthiouracil, atorvastatin, nitrofurantoin, methyl dopa, and isoniazid)
- AIH + IBD: 44% have features of PSC

  *All children, patients with IBD + AIH, and those with AIH that do not respond to treatment should get MRCP

Table 2. Diagnostic Scoring System for Atypical Autoimmune Hepatitis in Adults

Category	Factor	Score	Category	Factor	Score
Gender	Female	+2	Concurrent immune disease	Any nonhepatic disease of an immune nature	+2
Alk Phos:AST (or ALT) ratio	>3	−2	Other autoantibodies*	Anti-SLA/LP, actin, LC1, pANCA	+2
	<1.5	+2			
γ-globulin or IgG	>2.0	+3	Histologic features	Interface hepatitis	+3
(times above upper limit of normal)	1.5-2.0	+2		Plasma cells	+1
	1.0-1.5	+1		Rosettes	+1
	<1.0	0		None of above	−5
				Biliary changes†	−3
				Atypical features‡	−3
ANA, SMA, or anti-LKM1 titers	>1:80	+3	HLA	DR3 or DR4	+1
	1:80	+2			
	1:40	+1			
	<1:40	0			
AMA	Positive	−4	Treatment response	Remission alone	+2
				Remission with relapse	+3
Viral markers of active infection	Positive	−3			
	Negative	+3			
Hepatotoxic drugs	Yes	−4	Pretreatment score		>15
	No	+1	Definite diagnosis		10-15
			Probable diagnosis		
Alcohol	<25 g/d	+2	Posttreatment score		>17
	>60 g/d	−2	Definite diagnosis		12-17
			Probable diagnosis		

Abbreviations: Alk phos, serum alkaline phosphatase level; AST, serum aspartate aminotransferase level; ALT, serum alanine aminotransferase level; IgG, serum immunoglobulin G level; AMA, antimitochondrial antibodies; HLA, human leukocyte antigen.

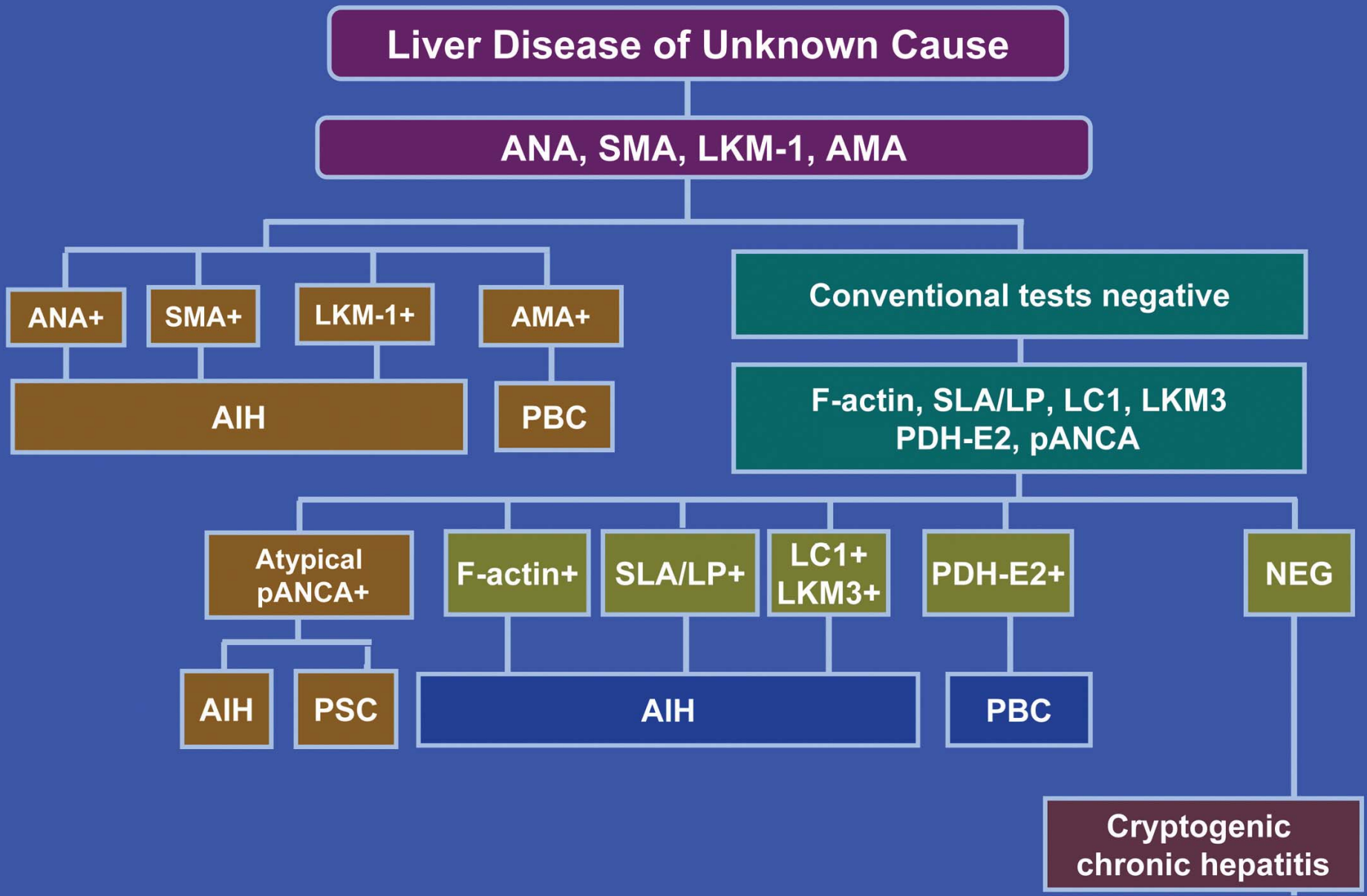
*Unconventional or generally unavailable antibodies associated with liver disease include perinuclear anti-neutrophil cytoplasmic antibodies (pANCA) and antibodies to actin, soluble liver antigen/liver pancreas (anti-SLA/LP), asialoglycoprotein receptor (ASGPR), and liver cytosol type 1 (LC1).

†Includes destructive cholangitis, nondestructive cholangitis, or ductopenia.

‡Includes steatosis, iron overload consistent with genetic hemochromatosis, alcohol-induced hepatitis, viral features (ground-glass hepatocytes), or inclusions (cytomegalovirus, herpes simplex).

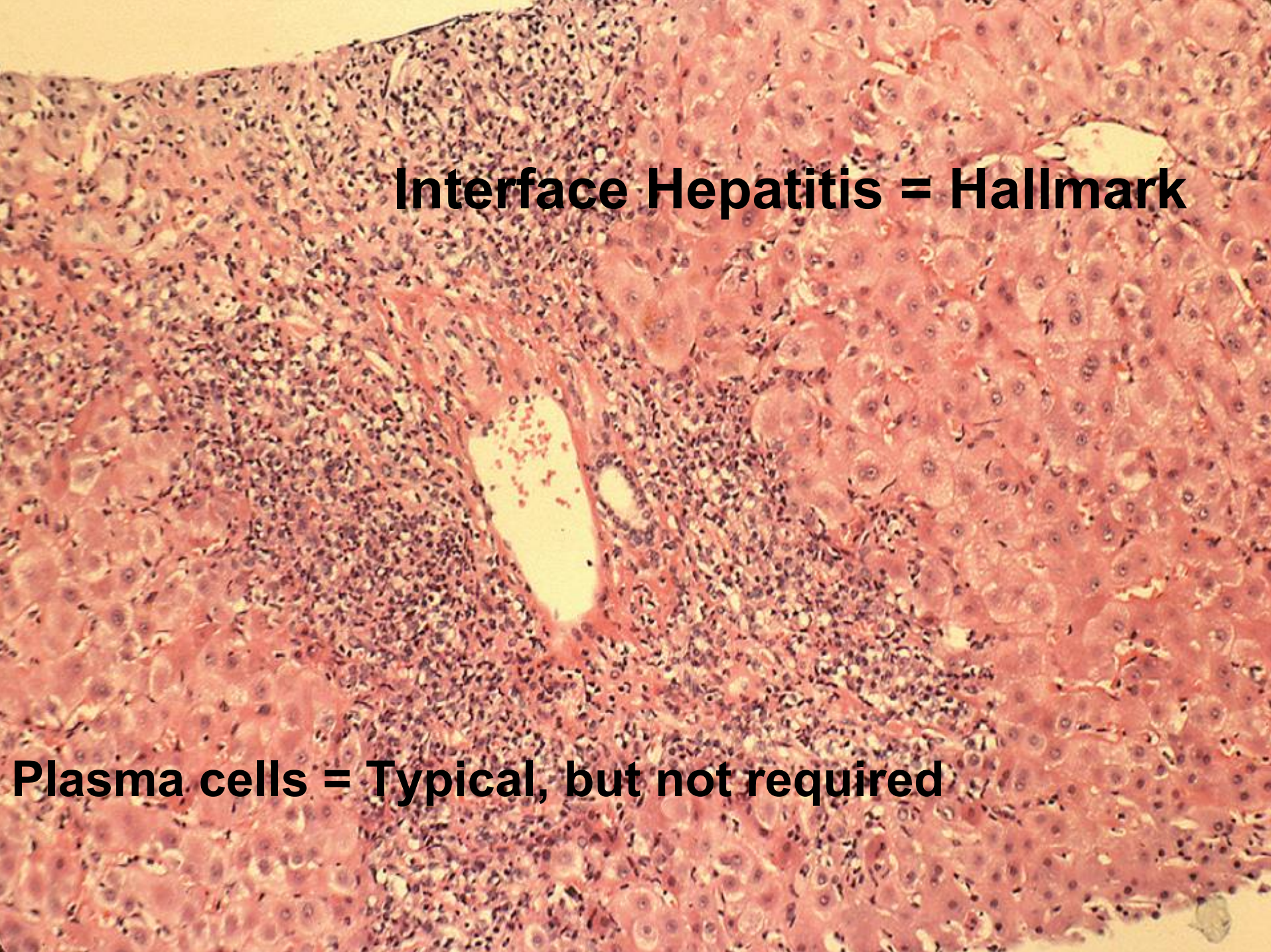
Based on recommendations of the International Autoimmune Hepatitis Group (J Hepatol 1999;31:929-938).

Hepatology. 2010 Jun;51(6):2193-213.



Hepatology. 2010 Jun;51(6):2193-213.


"I Ate Too Much Cheese" Poop
Pissed Off At My Girlfriend
Swallowed Her Tennis Bracelet "Poop
"White Castle Sliders" Poop
"It's Time For A Colonoscopy" Poop
"Thank God I'm Regular" Poop
"Cousin Cornelius" Poop


Interface Hepatitis = Hallmark
Plasma cells = Typical, but not required

Indications for Treatment

Absolute	Relative	None
Serum AST ≥10 fold ULN	Symp…atigue, arthralgia jau…	Asymptomatic with normal
Serum AST ≥ 5 fold ULN and γ globulin level ≥ 2 fold ULN		
Bridging necrosis or multiacinar necrosis on histological examination	Inte…	
Incapacitating symptoms	Osteopeni…emotional instability, hy…pertension, diabetes, or cytopenia	Contraindication to steroids or imuran

82 % are cirrhotic within 5 yrs with a mortality of 45%

Hepatology. 2010 Jun;51(6):2193-213.

Treatment of AIH

- Two treatment regimens are equally effective in severe AIH
  - Prednisone alone (60 mg daily)
  - Prednisone (starting with 30 mg daily and tapering down to 10 mg daily within 4 weeks) in combination with azathioprine (50 mg daily)
- Tapering Prednisone
  - @ 20 mg daily onward, reduction should be done by 5 mg every week until 10 mg/day are achieved and even further reduction by 2.5 mg/week have been considered up to 5 mg daily.

Treatment of AIH

- The combo regimen
  - ↓ occurrence of corticosteroid-related side effects than the higher dose prednisone regimen (10% versus 44%),
  - preferred treatment

Indications for Prednisone alone therapy

- severe cytopenia
- those undergoing a short treatment trial (duration of therapy <6 months)
- individuals who are pregnant or contemplating pregnancy
- patients with some active malignancies
- individuals with known complete thiopurine methyltransferase deficiency

Remission/End points

- The maintenance regimen is continued until resolution of the disease, treatment failure, or drug-intolerance
- Ideal Endpoint
  - Normal labs
  - Normal liver biopsy
  - The average duration of treatment is 18-24 months
  - 87% of patients who achieve long-term remission have normal labs prior to the termination of therapy

Pre-treatment Termination Biopsy

- Interface hepatitis is found in 55% of patients with normal AST and γ-globulin levels during therapy, and these individuals typically relapse after cessation of treatment

Termination of Therapy

- Termination of therapy should be considered after at least 2-year treatment, when liver function tests and immunoglobulin levels have been repeatedly normal
- Gradual, well-monitored dose reduction over a 6-week period of close surveillance
- Watch for adrenal insufficiency!

Treatment Failure/Incomplete Response

- Treatment Failure
  - 9% of patients
  - Treat with Prednisone 60mg or Prednisone 30mg + AZA 150mg
  - Most improve but histological remission is achieved in only 20%
- Incomplete Response
  - Failure to achieve remission @ 36 month
  - 13%
  - Maintained on lowest dose of steroid possible or imuran alone (2mg/kg)

Relapse

- ~ 80% of those in remission
- ↑ in the serum AST level > three-fold the ULN and/or increase in the serum ɣ-globulin level > 2 g/dL
- the number of relapse episodes correlates with disease progression and an adverse clinical outcome

Relapse

- 1st Relapse: rx with combo therapy and taper to monotherapy with AZA (2mg/kg) or Prednisone (10mg daily)
- Withdrawal only after remission + 24 months of therapy in the setting of risk/benefit discussion

Alternative Therapies

- Budesonide (3mg tid)
- Cyclosporine
- Tacrolimus
- 6-mercaptopurine
- Methotrexate
- Cyclophosphamide
- Mycophenolate mofetil (1gm bid)

LT and AIH

- 5-year and 10-year patient survivals of ~ 75%.
- prednisone and calcineurin inhibitor (tacrolimus more frequently than cyclosporine) is the most common immunosuppression regimen after LT
- mycophenolate (2 g daily) is added when this is ineffective
- Recurrent AIH in transplant allografts occurs in approximately 30% of patients

HCC and AIH

- Hepatocellular carcinoma occurs in 4% of patients with type 1 AIH, and the 10-year probability of developing this neoplasm is 2.9%.
- Q6 month u/s recommended for AIH cirrhotics

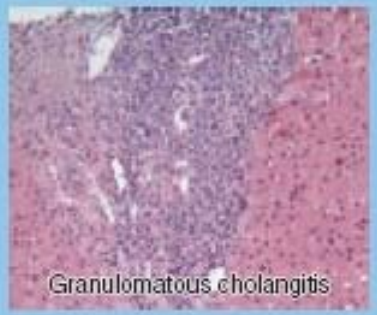
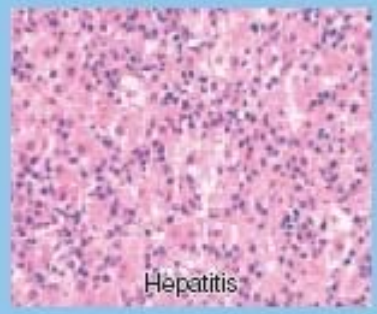
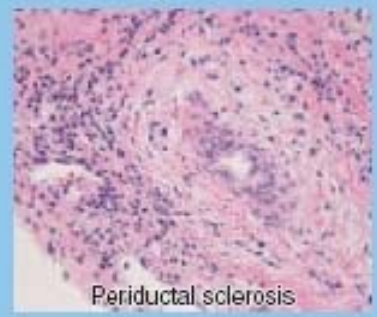
Pregnancy and AIH

- Postpartum exacerbation of AIH must be anticipated
  - resume standard therapy 2 weeks prior to anticipated delivery
  - closely monitor serum AST or ALT levels at 3-week intervals for at least 3 months after delivery

Bonus Question

- AIH + multiple endocrine organ failure, mucocutaneous candidiasis, and ectodermal dystrophy.
- autoimmune polyendocrinopathy candidiasis-ectodermal dystrophy (APECED)

Questions?

	Primary biliary cirrhosis	Autoimmune hepatitis	Primary sclerosing cholangitis	IgG4 associated autoimmune pancreatitis/ sclerosing cholangitis
Examples of presentation	Asymptomatic cholestasis, fatigue/ pruritus	Asymptomatic transaminitis, jaundice, arthralgia	Asymptomatic cholangitis, abdominal pain	Diabetes, jaundice, pancreatic mass, fleeting cholangiopathy
Specific investigations	Anti-mitochondrial antibodies (M2 fraction); liver biopsy showing active granulomatous duct lesions	Raised globulins; autoantibodies (ANA/SMA/LKM); liver biopsy showing interface hepatitis and lymphoplasmacytic infiltrate	Cholangiography; liver biopsy showing periductal sclerosis	Elevated IgG4 levels; pancreatic imaging changes; cholangiopathy; retroperitoneal fibrosis
Typical histological or radiological appearance	 Granulomatous cholangitis	 Hepatitis	 Periductal sclerosis	 Sclerosing cholangitis
Untreated natural history	Stable disease in some; progressive portal hypertension and/or chronic liver failure	Mild disease in some; liver failure (acute or chronic with portal hypertension)	Cholangitis; portal hypertension; biliary cirrhosis, portal hypertension and liver failure	Relapsing and remitting course; chronic pancreatitis; secondary biliary cirrhosis
Specific medical intervention	Ursodeo xycholic acid 13–15mg/kg/d	Prednisone (20–40 mg/d) and azathioprine (1–2 mg/kg/d)		Prednisone (20–40 mg/d) largely successful with optimal treatment to be defined