Autoimmune Hepatitis

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Objective

- Epidemiology
- Pathogenesis
- Clinical Features
- Diagnosis
- Treatment
- Overlap syndromes

Epidemiology

- Norway/Sweden incidence is 1-2 per 100,000 persons/year
- Similar incidence is assumed for Caucasian N. Americans
- 100,000-200,000 affected in the US
- AIH accounts for 5.9% of liver transplantations by NIH data
- Frequency of AIH among chronic liver disease patients in N. America is 11-23%
- Women > Men 3.6:1

Pathogenesis

- No definite answer…but multiple theories
- Environmental agent triggers a T-cell mediated cascade of events directed at liver antigens in someone genetically predisposed to the disease
- Possible triggers include:
  - Viruses: measles, hepatitis, CMV and EBV
  - Drugs: oxyphenisatin, methyldopa, nitrofurantoin, infliximab, Hep A vaccine, propylthiouracil, diclofenac, interferon, pemoline, minocycline, atorvastatin and herbals such as black cohosh and dai-saiko-to

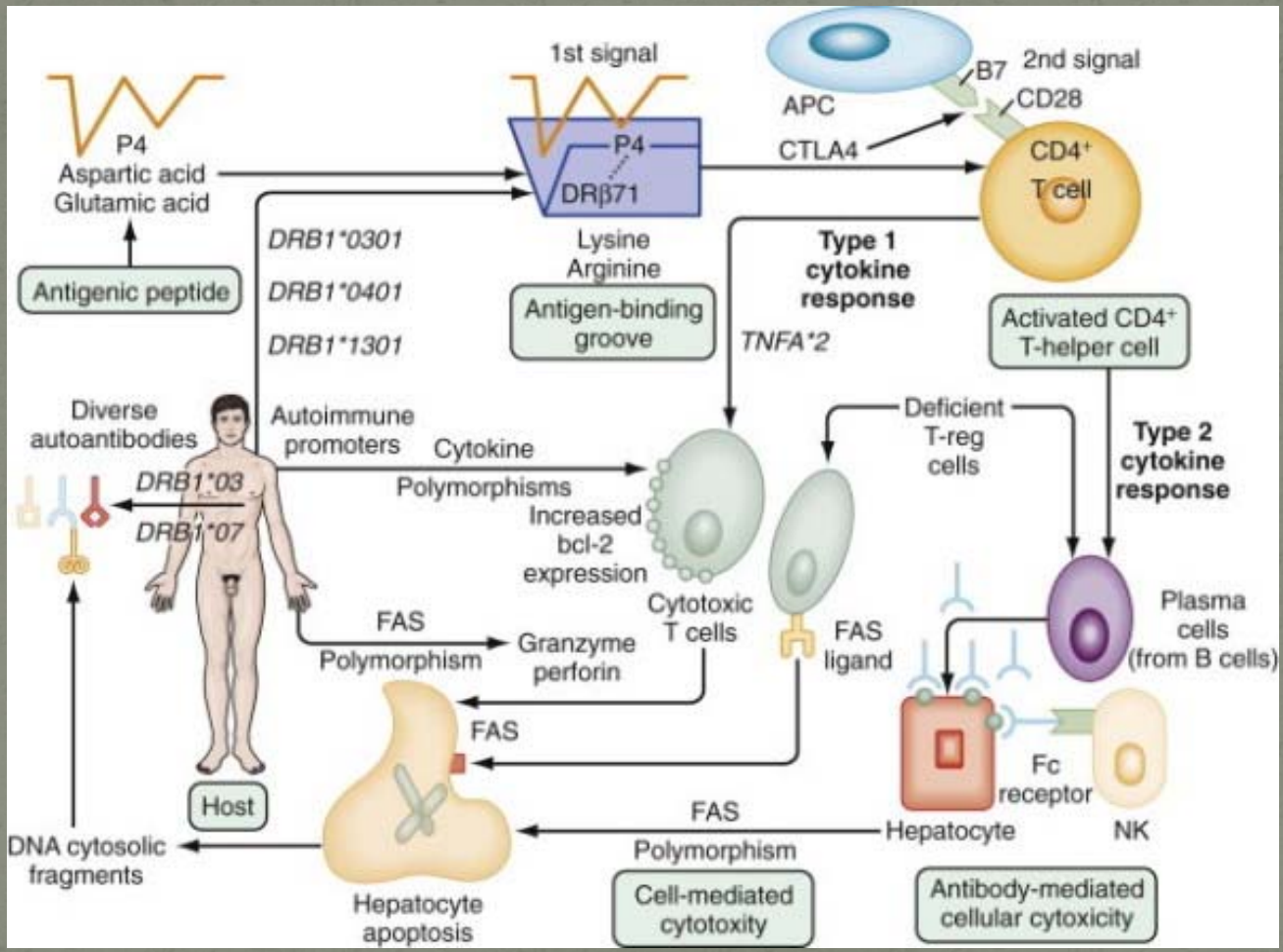
Pathogenesis

- Susceptibility in N. Americans (white) and N. Europeans DRB1*0301 and DRB*0401
- Different ethnic groups have different susceptibility alleles
  - *1501 protective in N. Americans and N. Europeans
  - DRB1*0404 and *0405: Mexican, Japanese, mainland Chinese and Argentine
  - *1301: Argentine children and Brazilian
    - Associated with protracted Hep A virus infection

Pathogenesis

- Increased type 1 cytokines leading to increased cytotoxic T cell induced liver injury
- Decreased counter-regulatory cytokines leading to T regulatory cell failure
- Inflammation then lead to fibrogenesis by transformation of stellate cells into myofibroblasts by TGFβ
- All of the above are why glucocorticoids work…more on that later

Pathogenesis



Clinical Features

- >70% of cases are women, 50% younger than 40
- 40% may present with acute onset while 25-34% present with asymptomatic liver test abnormalities
- 20-25% will present after age 60 with a greater degree of fibrosis, and higher rate of ascites and cirrhosis
- Can present with acute liver failure although less common

Clinical Features

Manifestations vary by ethnicity:

- Alaskan – acute icteric
- Aboriginal N. American, African, Asian and Arab – cholestatic and advanced disease
- Japanese – mild
- Somali – severe and rapidly progressive
- African Americans – cirrhosis in up to 85% (vs 38% in white Americans)

Clinical Features

Most common symptoms:

- Fatigue 88%
- Jaundice 77%
- Abdominal discomfort 48%
- Mild pruritus 36%
- Asymptomatic 25-34%
- Anorexia 30%
- Myalgias 30%

Clinical Features

Most common physical exam findings:

- Hepatomegaly 78%
- Jaundice 69%
- Spider angiomata 58%
- Other immune diseases <38%
  - Thyroiditis, RA, UC, Vitiligo and Sjogrens
- Splenomegaly >32%
- None <25%
- Ascites 20%

Clinical Features

Most common laboratory abnormalities:

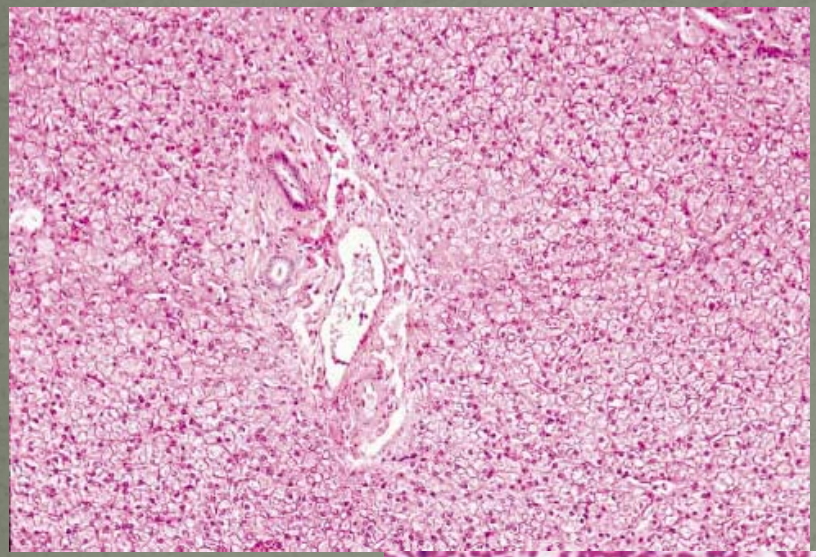
- Elevated AST 100%
- Hypergammaglobulinemia 92%
- Increased IgG 91%
- Hyperbilirubinemia 83%
- Alkaline phosphatase >2 x normal 33%

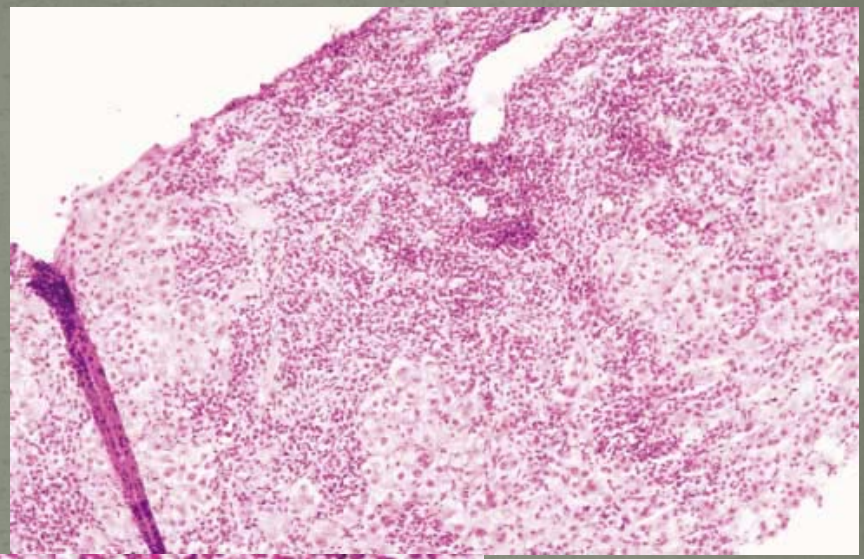
Clinical Features

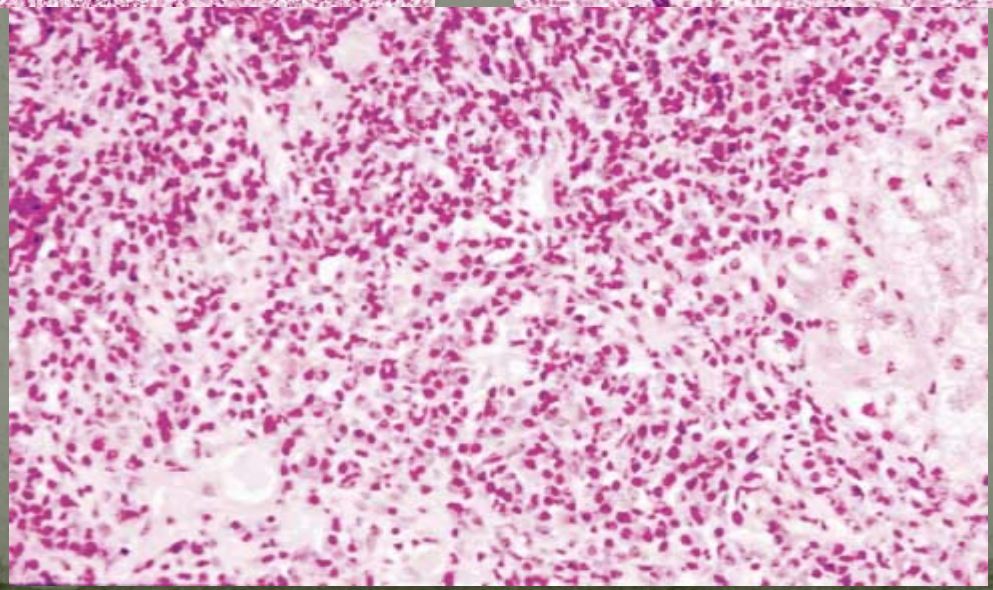
Histology:

- Mononuclear cell infiltrate invading the limiting plate
- Piecemeal necrosis or interface hepatitis that progresses to lobular hepatitis
- +/- plasma cell predominance
- Biliary tree usually spared
- Fibrosis commonly present

Clinical Features







Clinical Features

- Autoantibodies:
  - Anti-smooth muscle antibody (ASMA)
  - Anti-liver kidney microsomal (LKM1)
  - Anti-liver cytosol type 1 (LC1)
  - Anti-nuclear antibody (ANA)
  - Anti-LKM3
  - Anti-actin
  - Anti-soluble liver antigen (SLA)
  - Anti-asialoglycoprotein (ASGPR)
  - Antibody to histone and double stranded DNA (dsDNA)
  - Anti-chromatin
  - Perinuclear antinuclear neutrophil cytoplasmic antibody (pANCA)

Classifications

- Type 1:
  - 80% of all AIH cases, 25% cirrhotic at presentation
  - ANA and/or SMA
  - Less commonly: pANCA, actin, ASGPR, chromatin, SLA
  - Associated auto-immune diseases: Thyroidits, Graves and UC
  - Abrupt onset 40%

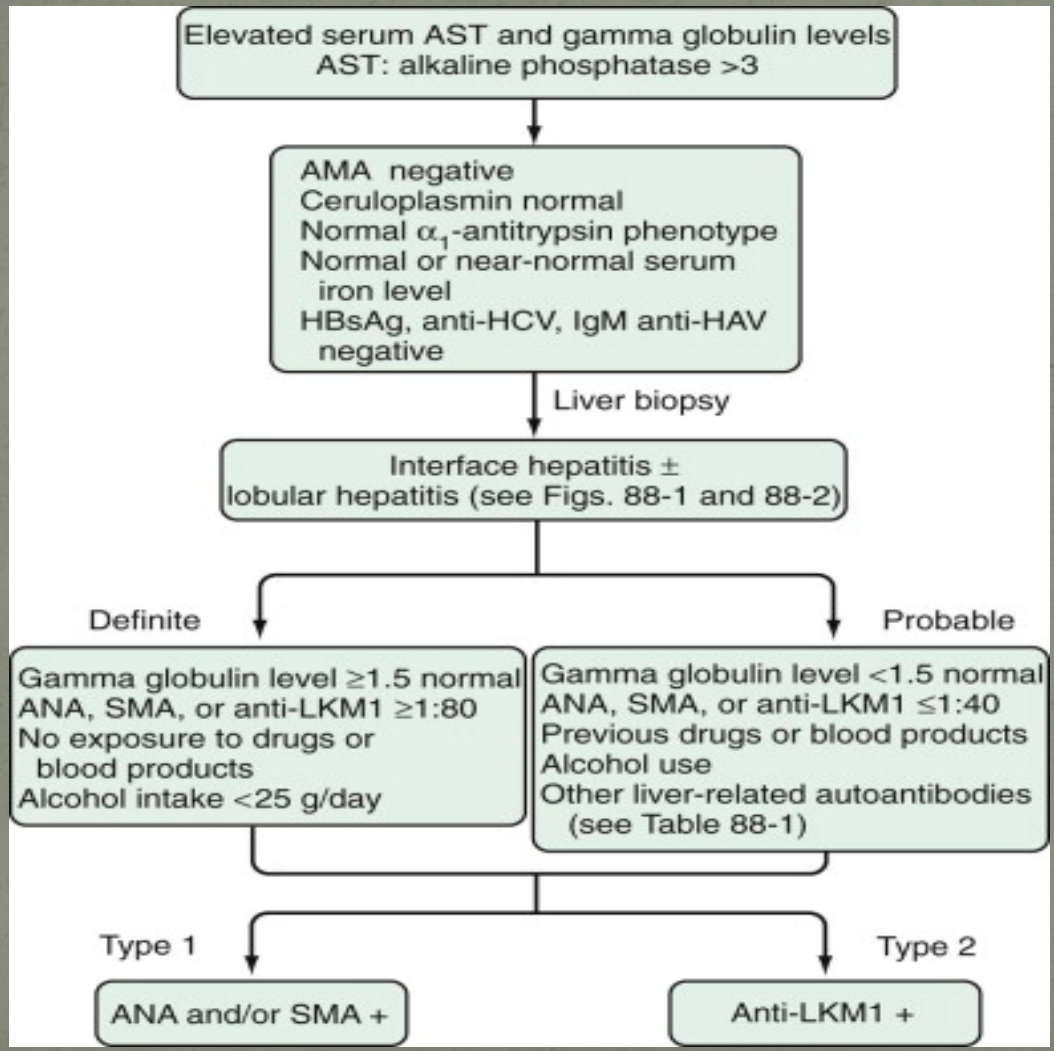
Classifications

- Type 2:
  - Anti-LKM1
  - Less commonly: LC1 and SLA
  - Children are primarily affected however 20% are adults in Germany and France, 4% in the US
  - Target auto-antigen CYP2D6
  - Associated auto-immune disease: Thyroiditis, Vitiligo, DM type 1 and APCED

Simplified Scoring System

CATEGORY	VARIABLE	SCORE
Autoantibodies		
Antinuclear antibodies or smooth muscle antibodies	1:40	+1
	≥1:80	+2
Antibodies to liver-kidney microsome type 1	≥1:40	+2
Antibodies to soluble liver antigen	Positive	+2
Immunoglobulin Level		
Immunoglobulin G	>Upper limit of normal	+1
	>1.1 times upper limit of normal	+2
Histologic Findings		
Morphologic features	Compatible with autoimmune hepatitis	+1
	Typical of autoimmune hepatitis	+2
Viral Disease		
Absence of viral hepatitis	No viral markers	+2
Pretreatment Aggregate Score		
Definite diagnosis		≥7
Probable diagnosis		6

Diagnostic Algorithm




OHIO
OHIO
-10
-20
-30
-40
50
40-
30
20-
10-

Treatment

Indications for Treatment

	Absolute	Relative	None
Clinical	Incapacitating symptoms	Symptoms (Fatigue, Arthralgia, Jaundice, Abdominal Pain)	Asymptomatic
Laboratory	AST ≥ 10 fold ULN AST ≥ 5 fold ULN and HG ≥ 2 fold ULN	AST or HG less than absolute criteria	Normal or near normal AST and γ Globulins
Histology	Bridging necrosis or Multiacinar necrosis on Histology	Interface hepatitis	Inactive cirrhosis or mild portal hepatitis

Treatment Regimen

Combination therapy		Monotherapy
Prednisone (mg/day)	Azathioprine (mg/day)	Prednisone (mg/day)
30mg × 1 week	50mg	60mg × 1 week
20mg × 1 week	50mg	40mg × 1 week
15mg × 2 weeks	50mg	30mg × 2 weeks
10mg maintenance dose	50mg	20mg maintenance dose

Reasons for preference

Postmenopausal	Cytopenia
Osteoporosis	TPMT deficiency
Brittle DM	Pregnancy
Obesity	Malignancy
Acne	Short course <6mos
Emotional lability	
HTN	

Treatment End Points

- Remission:
  - 90% see improvement in labs within 2 weeks
  - Rarely occurs in less than 12 months and probability of remission decreases after 24 months
  - Histological improvement lags behind labs by 3-8 months
  - Average treatment duration 18-24 months
- Incomplete response - 13% of patients after 36 months
- Failure of therapy:
  - ~9% of patients
  - 70% will improve within 24 months, only 20% will achieve remission
- Drug toxicity – affects 13% of patients

Treatment

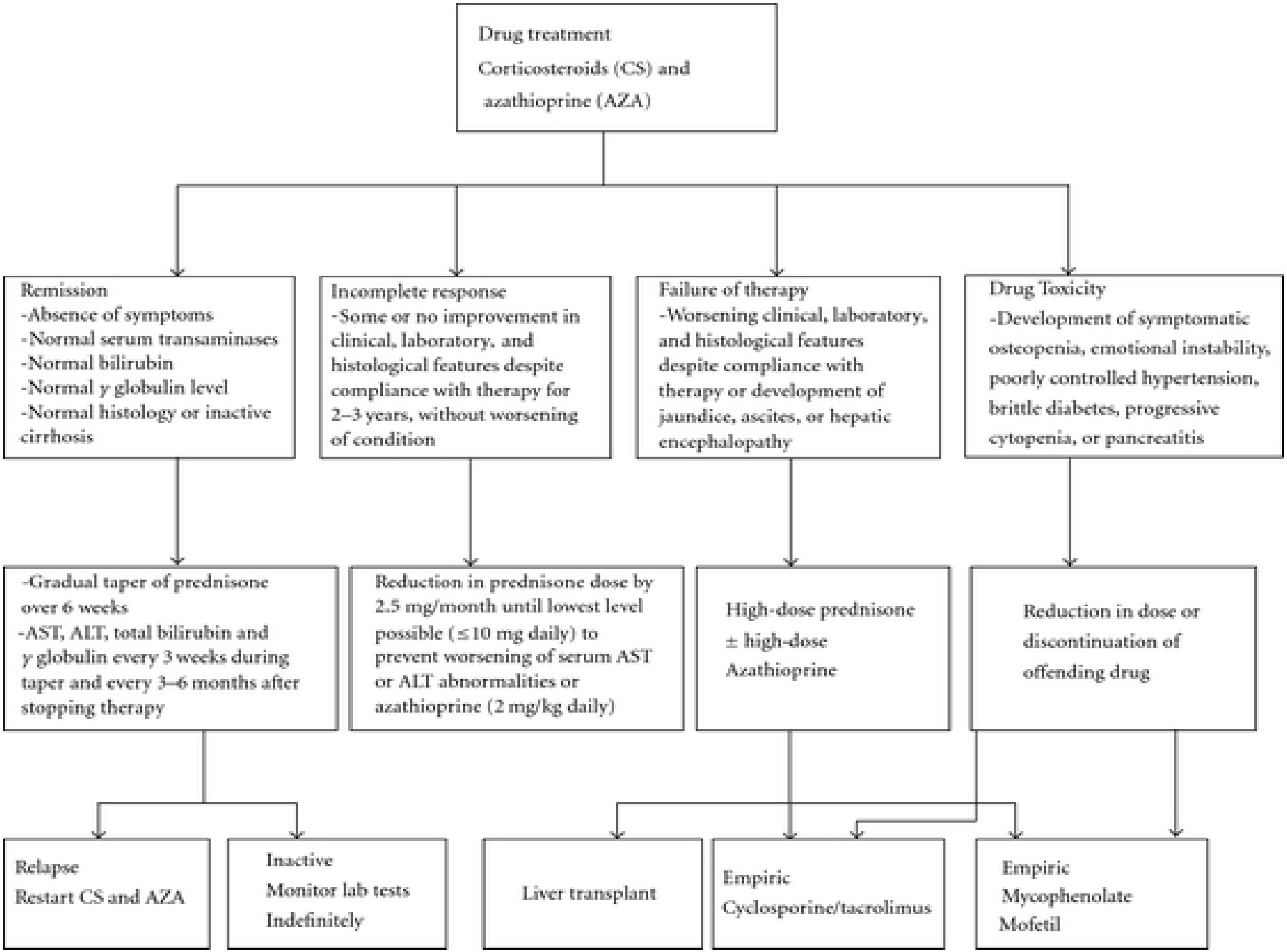
- 21% of patients achieve sustained long-term remission
- Should not attempt treatment withdrawal in the first 24 months
- Repeat liver biopsy prior to initiation of treatment withdrawal: 55% will have interface hepatitis despite normal laboratories (60% vs 90% relapse rates)
- Relapse occurs in 50% within 6 months and most will experience within the first 3 years
- Despite relapse 28% can still achieve long-term remission
- The more flares the more risk for progression to cirrhosis

Treatment Advances

- TPMT assays – has not been predictive of patients who will have AZA drug toxicity
  - Obtain assay in those with pre-treatment cytopenia or patients on higher than conventional doses >50mg/day
  - Calcineurin inhibitors – have been used as salvage therapy in children
  - Cyclosporine
  - Tacrolimus – has shown early promise for patients unresponsive to conventional treatment
- Mycophenolate – not better first line than AZA (1 study)
- Budesonide – 90% metabolized on first pass through the liver
  - Recent study comparing budesonide to prednisone showed budesonide to be superior although remission took longer
  - Dosing 3mg TID

Liver Transplant

- For patients intolerant or refractory to therapy
- Associated with DRB*0301
- Indicated in acute liver failure, decompensated cirrhosis, MELD >15 and HCC
- 80-90% survival at 5 years; 75% at 10 years
- Recurrence rate as high as 30-42%
- Combination prednisone and calcineurin inhibitor is the most common immunosuppressive regimen following transplant
- *De novo* AIH found in 6-10% of non-AIH transplant patients, responds to standard AIH treatments


Drug treatment
Corticosteroids (CS) and azathioprine (AZA)
Remission
-Absence of symptoms
-Normal serum transaminases
-Normal bilirubin
-Normal γ globulin level
-Normal histology or inactive cirrhosis
Incomplete response
-Some or no improvement in clinical, laboratory, and histological features despite compliance with therapy for 2–3 years, without worsening of condition
Failure of therapy
-Worsening clinical, laboratory, and histological features despite compliance with therapy or development of jaundice, ascites, or hepatic encephalopathy
Drug Toxicity
-Development of symptomatic osteopenia, emotional instability, poorly controlled hypertension, brittle diabetes, progressive cytopenia, or pancreatitis
-Gradual taper of prednisone over 6 weeks
-AST, ALT, total bilirubin and γ globulin every 3 weeks during taper and every 3–6 months after stopping therapy
Reduction in prednisone dose by 2.5 mg/month until lowest level possible (≤10 mg daily) to prevent worsening of serum AST or ALT abnormalities or azathioprine (2 mg/kg daily)
High-dose prednisone ± high-dose Azathioprine
Reduction in dose or discontinuation of offending drug
Relapse
Restart CS and AZA
Inactive
Monitor lab tests
Indefinitely
Liver transplant
Empiric
Cyclosporine/tacrolimus
Empiric
Mycophenolate Mofetil

HCC

- 4% of patients with type 1 AIH
- 10 year probability is 2.9%
- Increased risk: male, portal HTN, immunosuppressive therapy >3 years and cirrhosis > 10 years
- Recommend U/S every 6 months for those with above risks

Overlap Syndromes

Variant with PBC

- Features of AIH and AMA+ (usually low titer)
- Histologic features of cholangitis and cholestasis
- 18% of AIH will have AMA+ intermittently throughout the disease therefore histologic changes needed to diagnose
- Response to treatment depends primarily on predominant component
  - Prednisone if Alk phos < 2 x normal
  - Prednisone and Urso if Alk phos > 2 x normal, GGT > 5 x normal and/or florid duct lesions

Variant with PSC

- Cholangiography in AIH:
  - Cholangitis by histology
  - Cholestatic lab abnormalities
  - IBD
  - Failure to respond to glucocorticoids
- May have normal cholangiography constituting small duct disease
- Prednisone + Urso (13-15mg/kg daily)
  - Treatment is typically ineffective

Variant with Cholestatic Features

- 8% of AIH patients have bile duct injury or cholestasis with –AMA and normal cholangiography
- These represent AMA-negative PBC, small-duct PSC or autoimmune cholangitis
- Destruction of bile ducts may be seen in class AIH due to severe inflammatory activity therefore this entity may simply represent classic AIH

Autoantibody Negative AIH

- 13% satisfy criteria for AIH but are antibody negative
- Commonly HLA-B8, DR3 and A1-B8-DR3
- Respond well to glucocorticoids
- Assays for atypical antibodies such as pANCA, SLA, anti-endomysial and TTG may yield positive results
- Some patients will have waxing and waning antibody positivity throughout the course of the disease and if checked later may be positive for conventional antibodies

References

Czaja A. Difficult treatment decisions in autoimmune hepatitis. World J Gastroenterol 2010;16(8):934-947.

Czaja A and Bayraktar Y. Non-classical phenotypes of autoimmune hepatitis and advances in diagnosis and treatment. World J Gastroenterol 2009;15(19):2314-2328

Krawitt E. Autoimmune hepatitis. N Engl J Med 2006;354:54-66.

Manns MP, Czaja A, et al. Diagnosis and management of autoimmune hepatitis. Hepatology 2010;51(6):2193-2213.

Mayo MJ. Management of autoimmune hepatitis. Current Opinion in Gastroenterology 2011;27:224-230.

Vergani D and Mieli-Vergani G. Pharmacological management of autoimmune hepatitis. Expert Opin Pharmacother. 2011;12(4);607-613

Zeniya M. Autoimmune hepatitis: a review of current diagnosis and treatment. Hepatitis Research and Treatment 2011.