Autoimmune hepatitis

By

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AUTOIMMUNE HEPATITIS

- It's a chronic **relapsing** hepatitis, associated with a plasma cell hepatic infiltrate, hypergammaglobulinaemia and positive autoantibodies.

- Associated with genetic predisposition and therapeutic response to immunosuppression.
- -Exclusion of drug precipitants and inherited metabolic liver disease in addition to confirmation of negative viral studies is required.

EPIDEMIOLOGY

- patients of all ages, both genders (F:M ratio of about 4:1 for type1 AIH compared to 9:1 for type 2 AIH)
- And all races may develop AIH.
- AIH accounts for 11% to 23% of cases of chronic hepatitis and affects 100,000 to 200,000 persons in the USA.

- AIH accounts for 2.6% of liver transplants in Europe and 5.9%in USA
- The disease has a bimodal peak occurring between the ages of. 10 and 20 and then later in life between the ages of 40 and 50

Pathogenesis

- The prevailing theory for the development of autoimmune hepatitis is thought to be the interplay of genetic predisposition, an environmental trigger (virus, drugs, herbs, immunizations), and failure of the native immune system resulting in chronic inflammation of hepatocytes and subsequent fibrosis of the liver.

- The exact genes and triggers responsible remain undefined, but studies show association of early-onset, severe disease with the HLA-DR3 serotype and late-onset disease with the HLA-DR4 serotype.

Classification

- On the basis of detected autoantibodies, autoimmune hepatitis can be classified into three subtypes
- **Type 1 autoimmune hepatitis. Positive antibodies include:**

❖ Antinuclear antibody (ANA)

❖ Anti-smooth muscle antibody (ASMA) - 65% of people

❖ Anti-actin antibodies

❖ Anti-mitochondrial antibodies - rare except for overlap syndromes with primary biliary cholangitis

❖ Anti-soluble liver antigen/liver pancreas antibody antigen - 20% of people

❖ Anti-double stranded DNA - 30% of people

❖ Atypical perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA)

- **Type 2 autoimmune hepatitis. Positive antibodies include:**

❖ Liver Kidney Microsomal antibody (LKM-1)

❖ Anti-liver cytosol antibody-1 (SLC-1)

- **Autoantibody negative autoimmune hepatitis.**

❖ Lack positive ANA, ASMA, LKM-1, etc. antibody panels but present with clinical features of autoimmune hepatitis that resolve with standard treatment.

- Types of autoimmune hepatitis

	Type 1 AIH	Type 2 AIH
Relative prevalence	> 80%	20% in Europe, 4% in USA
Autoantibodies commonly associated	ANA, SMA	LKM1
Patient demographic	Female: male ratio 4:1	Female: male ratio 9:1
Age of onset	Peak incidence 16-30 y, although 50% are > 30 y	Average 10 y old but seen in adults (Europe)
Other commonly associated autoimmune diseases	Prevalence of 17-48%: thyroid disease, rheumatoid arthritis, ulcerative colitis	Prevalence unclear: Type 1 DM, thyroid disease, vitiligo, pernicious anemia, IgA deficiency
Presentation	Acute onset rare	Frequently presents with cirrhosis in children and more aggressively
Response to treatment	Excellent response	May be more treatment resistant
Progression of disease	25% have cirrhosis at diagnosis; 45% develop cirrhosis	~ 80% develop cirrhosis

Signs and symptoms

- Autoimmune hepatitis may present completely asymptomatic (12–35% of the cases), with signs of chronic liver disease, or acute or even fulminant hepatic failure.
- People usually present with one or more nonspecific, long-lasting symptoms such as fatigue, general ill health, lethargy, weight loss, mild right upper quadrant abdominal pain, malaise, anorexia, itching, nausea, jaundice or joint pain especially affecting the small joints.
- Rarely, rash or unexplained fever may appear. In women, the absence of menstruation (amenorrhoea) is a frequent feature.
- Physical examination may be normal, but it may also reveal signs and symptoms of chronic liver disease.

- Many people have only laboratory abnormalities as their initial presentation, as unexplained increase in transaminases and are diagnosed during an evaluation for other reasons.
- Others have already developed cirrhosis at diagnosis. Of note, alkaline phosphatase and bilirubin are usually normal.

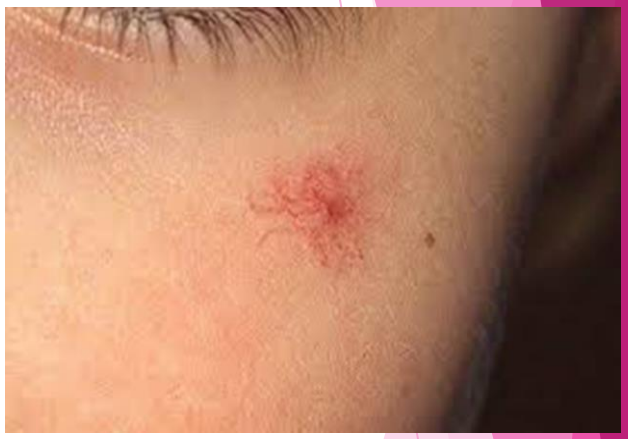
- Autoimmune hepatitis may overlap with other autoimmune conditions, mainly type 1 diabetes mellitus, ulcerative colitis, lupus, celiac disease, vasculitis, and autoimmune thyroiditis

SIGNS AND SYMPTOMS

- Fatigue
- Abdominal discomfort
- Jaundice
- Skin rashes
- Joint pain
- Loss of menstrual
- periods Nausea

PHYSICAL EXAMINATION

- Hepatomegaly (83%)
- Jaundice (69%)
- Splenmegaly (32%)
- Spider angiomata (58%)
- Ascites (20%)
- Encephalopathy (14%)
- Malnutrition (with poor growth in children)



Investigations

Liver biochemistry

- The serum aminotransferases are high, with lesser elevations in the ALP and bilirubin.
- The serum γ-globulins are high: frequently twice normal,particularly the IgG. The biochemical pattern is similar in both types.

Hematology

- A mild normochromic normocytic anaemia with thrombocytopenia

and leucopenia is present, even before portal hypertension and splenomegaly. The PT is often high

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Autoantibodies

- antinuclear antibody (ANA) : positive in 75% of type 1 autoimmne hepatitis
- Anti smooth muscle antibody (ASMA) : positive in 90% of type 1 autoimmne hepatitis .

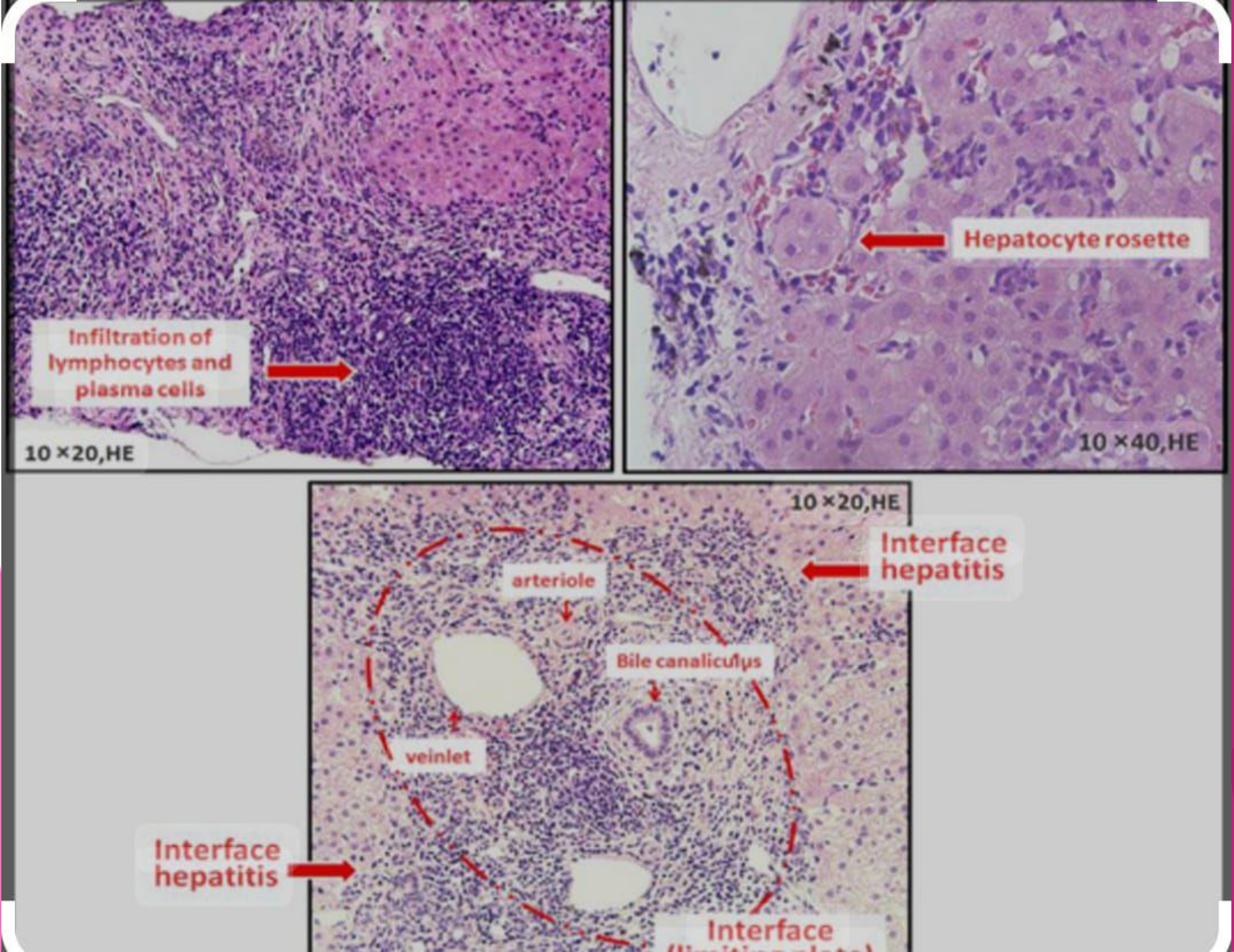
- Anti liver kidney microsomal (LKM) :diagnostic for type 2 autoimmune hepatitis .

MICROSCOPIC (HISTOLOGIC) DESCRIPTION

- Liver biopsy. clinicians perform a liver biopsy to confirm the diagnosis and to determine the degree and type of liver damage .

- Typical liver histology for autoimmune hepatitis = each of the following features had to be present namely, interface hepatitis, lymphocytic/lymphoplasmacytic infiltrates in portal tracts and extending into the lobule, emperipolesis , and hepatic rosette formation.

- Atypical = showing signs of another diagnosis, like steatohepatitis


Infiltration of lymphocytes and plasma cells
10 ×20,HE
Hepatocyte rosette
10 ×40,HE
10 ×20,HE
Interface hepatitis
arteriole
Bile canaliculus
veinlet
Interface hepatitis
Interface

Diagnostic scoring

- The Internal Autoimmune Hepatitis Group developed a standardized scoring system for clinical diagnosis .
- A simplified scoring system for clinical use incorporates titers of autoantibodies, total IgG levels, liver histology, and the exclusion of viral hepatitis for diagnostic scoring

Criteria for the diagnosis of A.I.H., on which the 1999 (IAIHG) diagnostic score was based

Definite AIH	Probable AIH
Normal α-1AT phenotype	Partial α-1AT deficiency
Normal ceruloplasmin level	Non-diagnostic ceruloplasmin/copper levels
Normal iron and ferritin levels	Non-diagnostic iron and/or ferritin changes
No active hepatitis A,B,C infection	No active hepatitis A,B,C infection
Daily alcohol <25 g/day	Daily alcohol <50 g/day
No recent hepatotoxic drugs	No recent hepatotoxic drugs
Predominant AST/ALT abnormality	Predominant AST/ALT abnormality
γ-globulins or IgG level >1.5 times the upper normal limit	Hypergammaglobulinemia of any degree
ANA, SMA anti-LKM1 >1:80, in adults and >1:20 in children	ANA, SMA, anti-LKM1 >1:40 in adults
AMA negative	Other autoantibodies
Liver histology	Liver histology
Interface hepatitis moderate to severe	Interface hepatitis moderate to severe
No biliary lesions, granulomas or prominent changes suggestive of another disease	No biliary lesions, granulomas or prominent changes suggestive of another disease

Simplified diagnostic criteria of the International A.I.H. group (2008) .

Feature/parameter Discriminator Score

Feature/parameter	Discriminator	Score
ANA or SMA+	≥1:40	+1*
ANA or SMA+	≥1:80	+2*
or LKM+	≥1:40	+2*
or SLA/LP+	Any titer	+2*
IgG or γ-globulins level	>upper limit of normal >1.1x upper limit	+1 +2
Liver histology (evidence of hepatitis is a necessary condition)	Compatible with AIH Typical of AIH Atypical	+1 +2 0
Absence of viral hepatitis	No Yes	0 +2

- Definite autoimmune hepatitis: ≥ 7
- Probable autoimmune hepatitis: ≥ 6

Goals of treatment

1. Improvement of liver inflammation(histological response)
2. Improvement of liver chemistries(biochemical response)
3. Improvement of symptoms(clinical response)
4. Prevention of disease progression (eg, to cirrhosis)
5. Minimization of risks of immunosuppressive therapy

Indication of treatment

Table 2. Indications for Treatment of Autoimmune Hepatitis in Adults (Open Table in a new window)

Absolute Indications	Relative Indications
Serum aspartate transaminase (AST) ≥10-fold the upper limit of normal (ULN)	Symptoms (eg, fatigue, arthralgia, jaundice)
Serum AST ≥5-fold the ULN and gamma-globulin level ≥2-fold the ULN	Serum AST and/or gamma-globulin less than absolute criteria
Bridging necrosis or multiacinar necrosis on histologic examination	Interface hepatitis

- Adults can initiate treatment with **prednisone** 20-40 mg/day.
- Children can initiate treatment with prednisone 1-2 mg/kg/day.
- As an alternative, both adults and children can initiate treatment with **budesonide** 9 mg per day. Budesonide treatment has the potential advantage of reducing steroid-specific side effects.
- **Budesonide should be avoided**, due to concerns that the portosystemic shunting of cirrhosis might permit budesonide to bypass the liver, thereby reducing drug efficacy
- **Azathioprine** (at a dose of 50-150 mg/day) can be initiated after2 weeks, provided that TPMT testing has ruled out a complete deficiency of TPMT activity.

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- Lboratory tests should be followed every 1-2 weeks.
- Respaonse to treatment should be assessed at 4-8 weeks.
- For patients with a biochemical response, prednisone can be tapered to 5-10 mg daily (and budesonide to 3 mg daily) over the next 6 months.
- Treatment with azathioprine should be maintained.

- For patients without a biochemical response, either the diagnosis of autoimmune hepatitis should be reconsidered second-line drugs (eg, mycophenolate mofetil or tacrolimus) can be employed

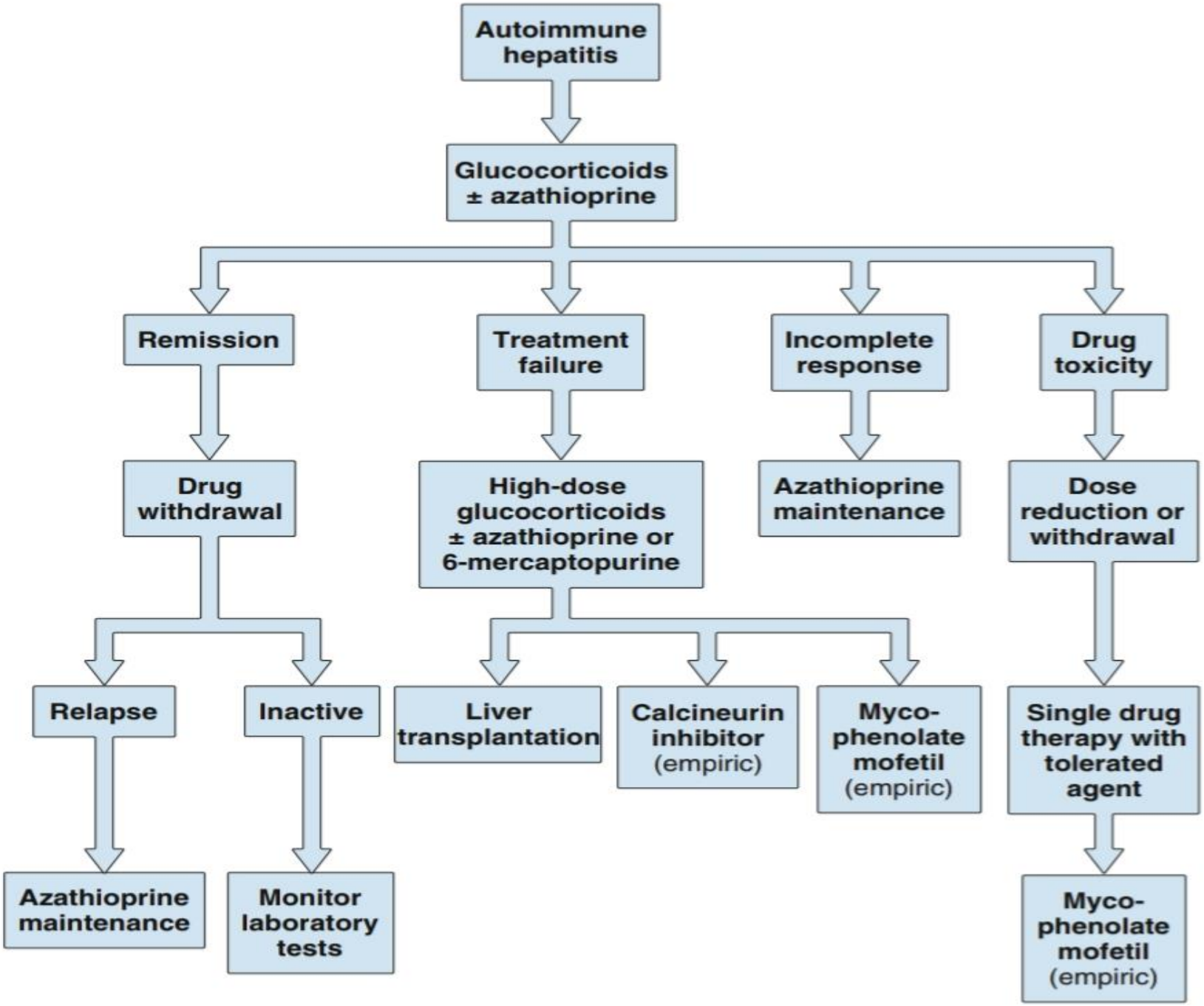
- If patients achieve a prolonged biochemical remission (eg, 24 months)perhaps after doing of a second liver biopsy immunosuppression withdrawal may be attempted.

- Liver transplant evaluation should be initiated when autoimmune hepatitis doesn't respond to drug treatmeant or in cases of advanced liver disease.

Treatment Endpoints

Patients may achieve 1 of 4 treatment end points, as follows :

- 1-Remission
- 2-Treatment failure
- 3-Incomplete response
- 4-Drug toxicity


Autoimmune hepatitis
Glucocorticoids ± azathioprine
Remission
Treatment failure
Incomplete response
Drug toxicity
Drug withdrawal
High-dose glucocorticoids ± azathioprine or 6-mercaptopurine
Azathioprine maintenance
Dose reduction or withdrawal
Relapse
Inactive
Liver transplantation
Calcineurin inhibitor (empiric)
Myco-phenolate mofetil (empiric)
Single drug therapy with tolerated agent
Azathioprine maintenance
Monitor laboratory tests
Myco-phenolate mofetil (empiric)


Thank
You