INTRODUCTION & DEFINITION

Autoimmune Hepatitis (AIH) is generally considered un-resolving inflammation of liver of unknown cause. Pathologic mechanism postulates environmental triggers, failure of immune tolerance mechanisms, genetic pre-disposition collaborate to induce T-Cell mediated immune attack upon liver antigen leading to progressive necroinflammatory and fibrotic process in the liver (Figure 1).

Onset is frequently insidious with non-specific symptoms such as fatigue, jaundice, nausea, abdominal pain and arthralgias, but clinical spectrum is wide ranging from asymptomatic presentation to an acute severe disease. Diagnosis is based on histologic abnormalities, characteristic clinical and laboratory findings, abnormal level of globulin and the presence of one or more characteristic auto antibodies.

It is one of the important causes of chronic liver disease and diagnosed after exclusion of other causes like chronic viral hepatitis, Wilson’s disease, drug induced liver disease, NAFLD (Non alcoholic fatty liver disease), PBC (Primary biliary cirrhosis) and PSC (Primary sclerosing cholangitis).

DIAGNOSIS

The diagnostic criteria for AIH and diagnostic scoring system were co-defined by an international panel in 1993 and revised in 1999.

The clinical criteria for the diagnosis are sufficient to make or exclude definite or probable AIH in the majority of patients:

DEFINITIVE DIAGNOSIS OF AIH:

Require exclusion of other similar diseases, lab findings which indicate substantial immuno reactivity and on histology interface hepatitis.

PROBABLE DIAGNOSIS:

It is justified when findings are compatible with AIH but insufficient for definitive diagnosis. Patients who lack conventional autoantibody but who are seropositive for investigational markers e.g., Antibodies to ASGRP, SLA, actin or LC1, are classified as probable diagnosis.

Diagnosis requires predominant elevation of serum aminotrans- ferase level, exclusion of other similar disorders (e.g., Wilson’s disease, drug induced hepatitis and viral hepatitis), ANA (antinuclear antibody), SMA (smooth muscle antibody), anti-LKM1 (antibodies to liver kidney microsome type 1)

SCORING CRITERIA:

The original scoring system proposed by International Autoimmune Hepatitis group accommodates the diverse manifestation of AIH and render an aggregate score that reflects the net strength of the diagnosis before and after glucocorticoid treatment (Table 1).

A simplified scoring system has been developed to ease clinical application. The original scoring system has greater sensitivity for diagnosis than simplified system (100% vs. 95%) but the simplified system has greater specificity (90% vs. 73%) and predictability (92% vs. 82%).
Diagostic algorithm for AIH:

- Elevated serum AST and gamma globulin levels
  - AST: alkaline phosphatase >3

- Liver biopsy

- Definite
  - AMA negative
  - Ceruloplasmin normal
  - Normal α1-antitrypsin phenotype
  - Normal or near-normal serum iron
  - HBsAg, anti-HCV, IgM anti-HAV negative
  - Gamma globulin level ≥1.5 normal
  - ANA, SMA, or anti-LKM1 ≥ 1:80
  - No exposure to drugs or blood products
  - Alcohol intake < 25 g/day

- Probable
  - Gamma globulin level < 1.5 normal
  - ANA, SMA, or anti-LKM1 ≤ 1:40
  - Previous drugs or blood products
  - Alcohol use
  - Other liver-related auto antibodies

- Type 1
  - ANA and/or SMA+

- Type 2
  - Anti-LKM1 +

Fig. 1: Diagnostic algorithm for AIH
Autoimmune Hepatitis - Better Understanding

CD4+ helper T-Cell is the principle effector cell and its activation is the initial step in the pathogenic pathway.

Classification- Two types of AIH with distinct serologic profile have been identified (Table 2):

Type I- Autoimmune Hepatitis- Type I AIH is characterized by SMA, ANA or both. Antibodies to action have greater specificity but less sensitivity. A typical P-ANCA is found as many as 90% in type I AIH.

Type II- Autoimmune Hepatitis- Type II AIH is characterized by the expression of Anti- LKM1. Most affected person is children between ages of 2 to 14 yrs.

Variant forms

Patients who have atypical features of AIH currently lack an official designation and confident treatment strategy (Table 3). Auto-antibody negative pts are similar in age, female predominant, frequency of concurrent immunology diseases, histologic features and laboratory findings of classic AIH. They are similar frequency of HLA-B8, HLA-DR3 and HLA-A1 –B8 –DR3 and respond to glucocorticoid treatment.

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VARIANT FORMS

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AUTOANTIBODY- NEGATIVE AUTOIMMUNE HEPATITIS

Thirteen percent of adult with chronic hepatitis of undermined cause satisfy international criteria for diagnosis of AIH but lack of the characteristic auto-antibodies. These pts commonly designated as cryptogenic chronic hepatitis.

Auto-antibody negative pts are similar in age, female predominant, frequency of concurrent immunology diseases, histologic features and laboratory findings of classic AIH. They are similar frequency of HLA-B8, HLA-DR3 and HLA-A1 –B8 –DR3 and respond to glucocorticoid treatment.
About 8% of white North American adult with classic AIH have concurrent HCV infection and 52% pts of chronic hepatitis 'C' have auto-antibodies concurrent immune disease or both. It is important to identify to one or other group because interferon therapy can enhance immune manifestations of persons with AIH and concurrent HCV infection and immunosuppressive treatment can increase serum viral level with chronic hepatitis 'C'.

Clinical features of AIH - The clinical features of AIH frequently reflect the inflammatory activity of the liver disease or complication of cirrhosis (Table 4).

## TREATMENT OF AIH (TABLE 5)

### A. Absolute indication of treatment

Three randomized, controlled trails have demonstrated that pts with serum AST level at least 10-fold of upper limit of normal (ULN) or more than 5-fold of ULN is associated with serum y-globulin level more than 2-fold ULN have high mortality (60% at 6 months), if untreated.

Further histological findings of bridging necrosis or multilobular necrosis at presentation progress to cirrhosis is 82% in untreated pts and are associated with 5 yr mortality of 45%.

These laboratory & histologic findings at presentation are absolute indication n of corticosteroid treatment.

### B. Uncertain indications

In pts who have no or only mild symptoms and with mild lab & histologic findings & prospective & randomized controlled treatment trails not performed, their indication for treatment remains uncertain & highly individualized. Asymptomatic individuals with inactive cirrhosis may have an excellent immediate survival without corticosteroid treatment. There is no definite guideline to identify the safe population who require no therapy. Spontaneous resolution is possible in some asymptomatic pts with mild disease but these pts improve less commonly and more slowly than treated pts. Since mild autoimmune hepatitis can progress and a rapid & complete response to a normal end point can be anticipated, corticosteroid therapy is favored in asymptomatic mild disease, especially in young who can tolerate the medication satisfactorily.

Corticosteroid therapy is effective only in pts with clinical, laboratory or histological features of active liver inflammation (Table 6).

Pts with inactive or burned out cirrhosis cannot benefit from therapy and increased risk of drug-induced side effects.

Pts with brittle diabetes, vertebral compression, psychosis or severe osteoporosis must be critically analyzed for treatment benefit before corticosteroid administration.

## TREATMENT INDICATION IN CHILDREN

Treatments of children are similar to those of adults (Table 7).
Autoimmune Hepatitis - Better Understanding

**Table 5: Indications for Treatment in Autoimmune Hepatitis**

<table>
<thead>
<tr>
<th>Findings</th>
<th>Absolute Findings</th>
<th>Relative Findings</th>
<th>None Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td>Incapacitating symptoms</td>
<td>Mild or no symptoms</td>
<td>Asymptomatic with minimal laboratory changes.</td>
</tr>
<tr>
<td></td>
<td>Relentless clinical progression</td>
<td></td>
<td>Previous intolerance of prednisone and/or azathioprine</td>
</tr>
<tr>
<td>Laboratory</td>
<td>AST ≥10-fold ULN AST ≥5-fold ULN and gamma globulin ≥2-fold ULN</td>
<td>AST 3- to 9.9-fold ULN AST ≥5-fold ULN and gamma globulin &lt;2-fold ULN</td>
<td>AST &lt;3-fold ULN Severe cytopenia</td>
</tr>
<tr>
<td>Histologic</td>
<td>Bridging necrosis Multilobular necrosis</td>
<td>Interface hepatitis Portal cirrhosis Decompensated cirrhosis with variceal bleeding.</td>
<td></td>
</tr>
</tbody>
</table>

**Table 6: Immunosuppressive Treatment Regimens for Adults in AIH**

<table>
<thead>
<tr>
<th>Monotherapy</th>
<th>Combination Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisone only* (mg/day)</td>
<td>Prednisone* (mg/day)</td>
</tr>
<tr>
<td>Week 1</td>
<td>60</td>
</tr>
<tr>
<td>Week 2</td>
<td>40</td>
</tr>
<tr>
<td>Week 3</td>
<td>30</td>
</tr>
<tr>
<td>Week 4</td>
<td>30</td>
</tr>
<tr>
<td>Maintenance</td>
<td>Until end-point</td>
</tr>
</tbody>
</table>

**Reasons for preference**

- Cytopenia
- Thiopurin methyltransferase deficiency
- Pregnancy
- Malignancy
- Shot course (< 6 months)

*Prednisolone can be used in place of prednisone in equivalent doses.

**Table 7: Immunosuppressive Treatment Regimens for Children in AIH**

<table>
<thead>
<tr>
<th>Initial Regimen</th>
<th>Maintenance Regimen</th>
<th>Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisone, 1.2 mg/kg</td>
<td>Prednisone taper over 6</td>
<td>Normal liver tests for 1 daily (up to 60 mg/day), 8 weeks to 0.1-0.2 mg/2 yrs during treatment. for two weeks either kg daily or 5 mg daily alone or in combination with azathioprine, 1.2 mg/kg daily.</td>
</tr>
<tr>
<td>Azathioprine at constant dose if added initially.</td>
<td>Continue daily prednisone dose with or without azathioprine or switch alternate day prednisone dose adjusted to response with or without azathioprine</td>
<td></td>
</tr>
</tbody>
</table>

**TREATMENT REGIMEN IN CHILDREN:**

Treatment regimen is less rigorously established in children than adults & reflects the preferences of individual centres. But several report shows, children show similar efficacy as adults. Prednisone is the mainstay in virtually all reported regimen, at the dose of 1.2mg/kg of body wt daily. Tapering schedule vary widely.

**RECOMMENDATIONS**

- Diagnosis of AIH should be made when compatible clinical signs & symptoms, lab abnormalities, serological and histological findings are present and other conditions that can cause chronic hepatitis including viral, hereditary, metabolic, and cholestatic & drug induced disease have been excluded.
- Diagnostically challenging cases that have few or atypical clinical, laboratory, serological or histological findings should be assessed by the diagnostic scoring system.
- In pts negative for conventional auto-antibodies in AIH is suspected, other serological marker e.g. Anti-SLA and atypical pANCA, should be tested.
• In pts with AIH & multiple endocrine disorders, the APECED syndrome must be excluded by testing for typical mutation in the AIRE gene.

• Classification of AIH into two types based on the presence of ANA and SMA (type 1 AIH) or anti-LKM1 and anti LCI (type 2 AIH)

• Diagnosis of AIH should be considered in all pts with acute or chr. Hepatitis of undermined cause including pts with acute severe hepatitis.

• Cholangiographic studies should be considered to exclude PSC in adults if no response to corticosteroid therapy after 3 months.

• All children with AIH and all adult with both AIH & IBD should undergo cholangiographic studies to exclude PSC.

• Immunosuppressive treatment should be instituted in pts with serum AST or ALT level ≥ 10-fold ULN, at least 5-fold ULN in connection with serum x-globulin level, at-least 2-fold ULN, and/or histological features of bridging necrosis or multilobular necrosis.

• Immunosuppressive treatment may be considered in adult pts without symptoms & mild laboratory and histologic changes, but the decision is individualized & against possible risk.

• Immunosuppressive treatment should not be instituted in pts with minimal or no disease activity or inactive cirrhosis, but pts should follow closely.

• Immunosuppressive therapy should not be given in pts with serious pre-existent co-morbid condition (psychosis, vertebral compression, brittle diabetes, uncontrolled hypertension).

• Azathioprine should not be started in pts with severe pre-treatment cytopenia.

• Immunosuppressive treatment should be started in children at the time of diagnosis regardless of symptoms.

• Treatment should start with prednisone (starting with 30 mg daily & tapering down to 10 mg daily within 4 wks) in combination with azathioprine (50 mg daily or 1-2 mg/ kg body wt wkly. Combination regimen is preferred.

• In children prednisone (1-2 mg/kg daily, max 60 mg daily with azathioprine (1-2 mg/kg daily) or 6 mercaptopurine (1.5 mg/kg daily)

• Pts on long term corticosteroid should monitor for bone disease at base line and then annually & pre-treatment vaccination against HAV & HBV to be given.

• Pts to be counseled for risk of azathioprine in pregnancy & should be discontinued.

• Improvements of serum AST or ALT level, and also total bilirubin concentration & y-globulin or IgG level should be monitored at 3-6 months interval during treatment.

• Treatment should be continued until normal AST or ALT level, total bilirubin, y-globulin or IgG level and normal liver histology.

• 1st relapse after drug withdrawal should be retreated with combination of prednisone plus azathioprine with same treatment regimen.

• Treatment failure in adults should be managed with high dose prednisone (60 mg daily) or 30 mg daily in combination with azathioprine (150 mg daily). Other alternative medication e.g., mycofenolate mofetil, cyclosporine mycophenolate mofetil (2 gm daily orally) is the most promising agent.

• Liver transplantation should be considered in pts with acute liver failure, decompensated cirrhosis or HCC.

REFERENCES:


3. Czaja AJ. Autoimmune hepatitis: Diagnosis.


