



Complete Summary

GUIDELINE TITLE

Diagnosis and treatment of autoimmune hepatitis.

BIBLIOGRAPHIC SOURCE(S)

Czaja AJ, Freese DK. Diagnosis and treatment of autoimmune hepatitis. Hepatology 2002 Aug; 36(2):479-97. [216 references] [PubMed](#)

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SCOPE

DISEASE/CONDITION(S)

Autoimmune hepatitis

GUIDELINE CATEGORY

Diagnosis
Evaluation
Management
Treatment

CLINICAL SPECIALTY

Allergy and Immunology
Family Practice
Gastroenterology
Internal Medicine
Pediatrics

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To provide a data-supported approach to the diagnosis and management of patients with autoimmune hepatitis

TARGET POPULATION

Individuals with autoimmune hepatitis

INTERVENTIONS AND PRACTICES CONSIDERED

Diagnosis

1. Evaluation for hereditary, infectious, and drug-induced liver injury
2. Serum aminotransferase and gamma-globulin levels
3. Liver biopsy
4. Measurement of autoantibodies including antinuclear antibodies (ANA), smooth muscle antibodies (SMA), and antibodies to liver/kidney microsome type 1 (anti-LKM1)
5. Use of diagnostic criteria and/or a diagnostic scoring system for autoimmune hepatitis

Initial therapy

1. Prednisone alone
2. Prednisone with azathioprine
3. Adjunctive therapies such as regular exercise program, vitamin D and calcium supplementation, estrogen replacement, bisphosphonates

Management of relapse after drug withdrawal

1. Regular determinations of serum aminotransferase, bilirubin, and gamma-globulin levels
2. Combination prednisone and azathioprine; low dose prednisone, or azathioprine only

Management of suboptimal responses to initial therapy

NOTE: refer to the "Major Recommendations" field for appropriate clinical context.

1. High doses of prednisone alone or prednisone with azathioprine
2. Corticosteroid therapy
3. Liver transplantation
4. High-dose corticosteroid regimens and possible liver transplantation in children

Therapies considered but not recommended: cyclosporine, 6-mercaptopurine, ursodeoxycholic acid, budesonide, methotrexate, cyclophosphamide, and mycophenolate mofetil.

MAJOR OUTCOMES CONSIDERED

- Sensitivity and specificity of diagnostic tests and scoring systems for autoimmune hepatitis
- Rates of clinical, laboratory, and histologic remission
- Relapse rates
- Survival
- Drug-related adverse effects and complications

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

A formal review and analysis of the published world literature on autoimmune hepatitis (914 articles) (Medline Search from 1966-2002; using the search term autoimmune hepatitis) was conducted.

NUMBER OF SOURCE DOCUMENTS

914 articles were reviewed

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus
Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

In an attempt to standardize recommendations, the Practice Guidelines Committee of the American Association for the Study of Liver Diseases modified the categories of the Infectious Diseases Society of America's Quality Standards:

Grade I: Evidence from multiple well-designed randomized controlled trials each involving a number of participants to be of sufficient statistical power.

Grade II: Evidence from at least one large well-designed clinical trial with or without randomization, from cohort or case-control analytic studies, or well-designed meta-analysis.

Grade III: Evidence based on clinical experience, descriptive studies, or reports of expert committees.

Grade IV: Not rated

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Not stated

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Not applicable

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Recommendations are followed by quality of evidence ratings (Grades I-IV), which are defined at the end of the "Major Recommendations" field.

Diagnosis

1. The diagnosis of autoimmune hepatitis (AIH) requires determination of the serum aminotransferase and gamma-globulin levels; detection of antinuclear antibodies (ANA) and/or smooth muscle antibodies (SMA), or in their absence, antibodies to liver/kidney microsome type 1 (anti-LKM1); and liver tissue examination (Rating, III).
2. The diagnostic criteria for AIH that are defined in Table 1 below should be applied to all patients (Rating, III).

Table 1. Diagnostic Criteria for Autoimmune Hepatitis

	Diagnostic Criteria	
Requisites	Definite	Probable
No genetic liver disease	Normal alpha1-antitrypsin phenotype Normal serum ceruloplasmin, iron, and ferritin levels	Partial alpha1-antitrypsin deficiency Nonspecific serum copper, ceruloplasmin, iron, and/or ferritin abnormalities
No active viral infection	No markers of current infection with hepatitis A, B, and C viruses	No markers of current infection with hepatitis A, B, and C viruses
No toxic or alcohol injury	Daily alcohol < 25 g/d and no recent use of hepatotoxic drugs	Daily alcohol < 50 g/d and no recent use of hepatotoxic drugs
Laboratory features	Predominant serum aminotransferase abnormality Globulin, gamma-globulin or immunoglobulin G level ≥ 1.5 times normal	Predominant serum aminotransferase abnormality Hypergammaglobulinemia of any degree
Autoantibodies	ANA, SMA, or anti-LKM1 $\geq 1:80$ in adults and $\geq 1:20$ in children; no AMA	ANA, SMA, or anti-LKM1 $\geq 1:40$ in adults or other autoantibodies*
Histologic findings	Interface hepatitis No biliary lesions, granulomas, or prominent changes suggestive of another disease	Interface hepatitis No biliary lesions, granulomas, or prominent changes suggestive of another disease

Abbreviation: AMA, antimitochondrial antibodies.

* Includes perinuclear anti-neutrophil cytoplasmic antibodies and the not generally available antibodies to soluble liver antigen/liver pancreas, actin, liver cytosol type 1, and asialoglycoprotein receptor.

Based on recommendations of the International Autoimmune Hepatitis Group (J Hepatol 1999; 31: 929-38).

3. If the diagnosis of AIH is not clear, a scoring method should be used as shown in Table 2 of the original guideline document (Rating, II).

Treatment indications

1. Treatment should be instituted in patients with serum aminotransferase levels greater than 10-fold the upper limit of normal (Rating, I).
2. Patients with serum aminotransferase levels that are 5-fold the upper limit of normal in conjunction with a serum gamma-globulin level at least twice the upper limit of normal should be treated (Rating, I).
3. Histologic features of bridging necrosis or multiacinar necrosis compel therapy (Rating, I).
4. Patients not satisfying the criteria in recommendations 1 through 3 must be individualized and treatment should be based on clinical judgment. The presence of interface hepatitis without bridging necrosis or multiacinar necrosis on histologic examination does not compel treatment (Rating, III).
5. Treatment may not be indicated in patients with inactive cirrhosis, preexistent comorbid conditions, or drug intolerances (Rating, III).
6. Treatment is warranted in most children at the time of diagnosis (Rating, II).

Treatment regimens

1. Prednisone in combination with azathioprine or a higher dose of prednisone alone is the appropriate treatment for severe AIH in adults (Rating, I).
2. Prednisone in combination with azathioprine is the preferred initial treatment because of its lower frequency of side effects (Rating, II).
3. All patients treated with prednisone alone or in combination with azathioprine must be monitored for the development of drug-related side effects (Rating, III).
4. Azathioprine or 6-mercaptopurine is preferred as a corticosteroid-sparing agent in children, especially when high doses of prednisone are required for disease control (Rating, III).

Treatment end points

1. Conventional treatment regimens should be continued in adults and children until remission, treatment failure, incomplete response, or drug toxicity. Once disease remission has been achieved, drug withdrawal should be attempted (Rating, II).
2. Treatment in children should be adjusted to clinical and laboratory findings in an individualized fashion, recognizing that therapy is frequently long term (Rating, III).

Management of relapse after drug withdrawal

1. Relapse is common in adults and children after drug withdrawal, and patients should be monitored for this occurrence by regular determinations of serum aminotransferase, bilirubin, and gamma-globulin levels (Rating, II).
2. Adults who have relapsed more than once should be treated with combination prednisone and azathioprine therapy, low dose prednisone, or azathioprine only (Rating, II).

Management of suboptimal responses to initial therapy

1. High doses of prednisone alone or prednisone in combination with azathioprine should be used in treatment failure (Rating, III).
2. Corticosteroid therapy should be considered in the decompensated patient (Rating III).
3. Liver transplantation should be considered in the decompensated patient who is unable to undergo or be salvaged by drug therapy (Rating, III).
4. Children who have treatment failure should be treated with high-dose corticosteroid regimens and considered for liver transplantation (Rating, III).

Definitions:

Grade I : Evidence from multiple well-designed randomized controlled trials each involving a number of participants to be of sufficient statistical power.

Grade II : Evidence from at least one large well-designed clinical trial with or without randomization, from cohort or case-control analytic studies, or well-designed meta-analysis.

Grade III : Evidence based on clinical experience, descriptive studies, or reports of expert committees.

Grade IV: Not rated

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of evidence is specifically stated for each recommendation (see the "Major Recommendations" field).

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Three randomized, controlled treatment trials published between 1971 and 1974 have established that prednisone alone or in combination with azathioprine improves symptoms, laboratory tests, histologic findings, and immediate survival. Liver transplantation has been associated with 5-year patient and graft survivals that exceed 80%, and recurrent disease after transplantation has been usually mild and manageable.
- Three randomized, controlled trials have shown improvement in the clinical and histologic features and survival of severe autoimmune hepatitis (AIH) after corticosteroid therapy. Subsequent studies have indicated that patients with histologic cirrhosis respond as well to corticosteroid treatment as

- patients without cirrhosis. Furthermore, the 20-year life expectancy for all treated patients exceeds 80%, and survival is similar to that of age- and sex-matched normal subjects from the same geographical region.
- Prednisone alone or a lower dose of prednisone in conjunction with azathioprine induces clinical, laboratory, and histologic remission with similar frequency.
 - Eighty-seven percent of adult patients managed by the indefinite azathioprine strategy remain in remission during a median observation interval of 67 months.
 - Twelve percent of patients treated with these schedules were able to be permanently withdrawn from medication after 69 ± 8 months of follow-up, and the probability of a sustained remission after total drug withdrawal was 13% after 5 years.
 - Liver transplantation is effective in patients who deteriorate during or after corticosteroid treatment. The 5-year patient and graft survival after liver transplantation in adults ranges from 83% to 92%; the actuarial 10-year survival after transplantation is 75%; autoantibodies and hypergammaglobulinemia disappear within 1 year in most patients; and disease recurrence is typically mild and easily managed.

POTENTIAL HARMS

- Eighty percent of patients develop cosmetic changes, including facial rounding, acne, dorsal hump formation, and/or truncal obesity, after two years of corticosteroid therapy. Severe, potentially debilitating complications, such as osteoporosis, vertebral compression, diabetes, cataracts, hypertension, and psychosis, usually develop only after 18 months of continuous therapy and at doses of prednisone that exceed 10 mg daily. Only 13% of treated patients develop complications during therapy that necessitate dose reduction or premature drug withdrawal. The most common reasons for treatment withdrawal are intolerable cosmetic changes or obesity (47%), osteopenia with vertebral compression (27%), and brittle diabetes (20%).
- Complications of azathioprine include cholestatic hepatitis, veno-occlusive disease, pancreatitis, nausea, emesis, rash, and bone marrow suppression. Side effects develop in fewer than 10% of patients receiving 50 mg daily of azathioprine, and they can be improved by reduction of the dose or discontinuation of the drug.
- The long-term complications of immunosuppressive therapy include the theoretical possibility of oncogenicity. The frequency of extrahepatic malignancy is 5% in patients with a cumulative treatment duration of 42 months. The incidence of extrahepatic malignancy is 1 per 194 patient-years of surveillance, and the probability of tumor occurrence is 3% after 10 years. The risk of malignancy is 1.4-fold that of an age- and sex-matched normal population (range, 0.6 to 2.9), and no specific cell type predominates.
- The risk of primary hepatocellular cancer is related mainly to the presence of cirrhosis. It is rare in treated patients who do not have hepatitis B and C viruses. In a prospective study based on annual assessments of serum alpha-fetoprotein level and hepatic ultrasonography, only one patient (0.5%) developed primary hepatic malignancy in 1,732 patient-years of observation, and only one of 88 patients with cirrhosis (1%) developed malignancy during

1,002 patient-years after cirrhosis (mean observation interval after cirrhosis, 10 ± 1 years).

- Asymptomatic patients on long-term corticosteroid treatment should be monitored for bone disease by annual bone mineral densitometry of the lumbar spine and hip.
- Drug toxicity compels immediate adjustments in therapy. Cytopenia, nausea, emotional lability, hypertension, cosmetic changes, and diabetes are typically dose related. These consequences can improve with dose reduction. Severe reactions, including psychosis, extreme cytopenia, and symptomatic osteopenia with or without vertebral compression, justify immediate discontinuation of the offending agent. In these patients, treatment can usually be continued with the single tolerated drug (prednisone or azathioprine) in adjusted dose.
- Long-term intermediate- or high-dose corticosteroid therapy has significant deleterious effects on linear growth, bone development, and physical appearance in children; therefore, early use of azathioprine or 6-mercaptopurine is usually recommended for all children without contraindications.

Subgroups Most Likely to be Harmed:

Advanced age, postmenopausal status, and presence of cirrhosis are features associated with increased risk of drug-related complications.

QUALIFYING STATEMENTS

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The guidelines, intended for use by physicians, are meant to be flexible, in contrast to "standards of care," which are inflexible policies to be followed in almost every case.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness
Staying Healthy

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Czaja AJ, Freese DK. Diagnosis and treatment of autoimmune hepatitis. *Hepatology* 2002 Aug; 36(2): 479-97. [216 references] [PubMed](#)

ADAPTATION

Recommendations regarding the diagnosis of autoimmune hepatitis are based, in part, on recommendations of the International Autoimmune Hepatitis Group (*J Hepatol* 1999; 31: 929-38).

DATE RELEASED

2002 Aug

GUIDELINE DEVELOPER(S)

American Association for the Study of Liver Diseases - Private Nonprofit Research Organization

SOURCE(S) OF FUNDING

American Association for the Study of Liver Diseases

GUIDELINE COMMITTEE

Practice Guidelines Committee

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the [American Association for the Study of Liver Diseases Web site](#).

Print copies: Available from the American Association for the Study of Liver Diseases, 1729 King Street, Suite 200; Alexandria, VA 22314; Phone: 703-299-9766; Web site: www.aasld.org; e-mail: aasld@aasld.org.

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on May 9, 2003. The information was verified by the guideline developer as of June 12, 2003.

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