



## Complete Summary

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### GUIDELINE TITLE

A practice guideline on Wilson disease.

### BIBLIOGRAPHIC SOURCE(S)

Roberts EA, Schilsky ML. A practice guideline on Wilson disease. Hepatology 2003 Jun;37(6):1475-92. [208 references] [PubMed](#)

### GUIDELINE STATUS

**Note:** This guideline has been updated. The National Guideline Clearinghouse (NGC) is working to update this summary.

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## SCOPE

### DISEASE/CONDITION(S)

Wilson disease (WD; hepatolenticular degeneration)

### GUIDELINE CATEGORY

Diagnosis  
Management  
Treatment

### CLINICAL SPECIALTY

Gastroenterology  
Internal Medicine

Medical Genetics  
Pediatrics

## **INTENDED USERS**

Physicians

## **GUIDELINE OBJECTIVE(S)**

To direct patient care with up-to-date approaches in the diagnosis and treatment of Wilson disease

## **TARGET POPULATION**

- Children and adults with suspected Wilson disease (e.g., persons between 3 and 45 years of age with unexplained hepatic, neurologic, or psychiatric abnormalities)
- Children and adults diagnosed with Wilson disease
- First-degree relatives of persons diagnosed with Wilson disease

## **INTERVENTIONS AND PRACTICES CONSIDERED**

### **Diagnosis**

1. History and physical examination
2. Diagnostic testing
  - Complete blood count
  - Serum ceruloplasmin
  - Slit-lamp examination (Kayser-Fleischer rings)
  - Basal 24-hour urinary excretion
  - Penicillamine challenge studies in children
  - Hepatic parenchymal copper content
  - Liver biopsy (discussed but not specifically recommended)
  - Neurologic evaluation and radiologic imaging of the brain by magnetic resonance imaging (MRI)
  - Genetic screening of first-degree relatives based on haplotype analysis

### **Treatment**

1. Chelating agent (D-penicillamine or trientine)
2. Zinc
3. Liver transplantation
4. Treatment options considered but not specifically recommended:
  - Antioxidants
  - Diet
  - Tetrathiomolybdate

### **Management/Monitoring**

1. Serum copper and ceruloplasmin
2. Liver biochemistries and international normalized ratio

3. Physical examination
4. Complete blood count with differential
5. Urinalysis for patients receiving chelators.
6. Repeat Kayser-Fleischer ring examination for patients with questionable compliance.
7. Yearly measurement of 24-hour urinary excretion of copper for patients on medication or more frequently if there are issues of compliance.
8. Lifelong treatment unless a liver transplantation has been performed.

## **MAJOR OUTCOMES CONSIDERED**

- Clinical findings, laboratory results (i.e., biochemical liver testing, serum concentrations), neurologic and psychiatric testing
- Side effects of pharmacologic treatment
- Effectiveness of treatment options (e.g., survival rates following liver transplantation, associated morbidity)

## **METHODOLOGY**

### **METHODS USED TO COLLECT/SELECT EVIDENCE**

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

### **DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE**

A broad-based review of the published literature in pediatrics and medicine including Medline searches on hepatolenticular degeneration and related subjects was conducted.

### **NUMBER OF SOURCE DOCUMENTS**

Not stated

### **METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE**

Weighting According to a Rating Scheme (Scheme Given)

### **RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE**

The standardized guidelines of the Practice Guideline Committee of the American Association for the Study of Liver Diseases were modified from 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**

External Peer Review  
Internal Peer Review

## **DESCRIPTION OF METHOD OF GUIDELINE VALIDATION**

This guideline was produced in collaboration with the American Association for the Study of Liver Diseases Practice Guidelines Committee in concert with additional external reviewers who supplied peer review of the guideline.

# **RECOMMENDATIONS**

## **MAJOR RECOMMENDATIONS**

**Note:** This guideline has been updated. The National Guideline Clearinghouse (NGC) is working to update this summary. The recommendations that follow are based on the previous version of the guideline.

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

### **Clinical Features**

Wilson disease (WD) should be considered in any individual between the ages of 3 and 45 years with liver abnormalities of uncertain cause (**Grade III**).

In a patient in whom WD is suspected Kayser-Fleischer rings should be sought by slit-lamp examination by a skilled examiner. The absence of Kayser-Fleischer rings does not exclude the diagnosis of WD, even in patients with predominantly neurologic disease (**Grade III**).

### **Diagnostic Testing**

#### *Ceruloplasmin*

Serum ceruloplasmin should be routinely measured during the evaluation of unexplained hepatic, neurologic, or psychiatric abnormalities in children and adults through middle age. An extremely low serum ceruloplasmin level (<50 mg/L or <5 mg/dL) should be taken as strong evidence for the diagnosis of WD. Modestly subnormal levels suggest that further evaluation is necessary. Serum ceruloplasmin within the normal range does not exclude the diagnosis (**Grade III**).

#### *Urinary Copper Excretion*

The basal 24-hour urinary excretion should be measured as an aid to the diagnosis of WD. Basal 24-hour urinary excretion of copper in WD is typically greater than 100 micrograms (1.6 micromoles) in symptomatic patients, but a finding greater than 40 micrograms (>0.6 micromoles or >600 nmoles) may indicate WD and requires further investigation (**Grade II**).

In children, penicillamine challenge studies may provide evidence for the diagnosis of WD if urinary excretion of greater than 1,600 micrograms copper/24 hours (>25 micromoles/24 hours) is found following the administration of 500 mg of D-penicillamine at the beginning and again 12 hours later during the 24-hour urine collection. The predictive value of this test in adults is unknown (**Grade II**).

#### *Hepatic Parenchymal Copper Concentration*

Hepatic parenchymal copper content greater than 250 micrograms/g dry weight provides critical diagnostic information and should be obtained in cases where the diagnosis is not straightforward and in younger patients. In untreated patients, normal hepatic copper content (<40 to 50 micrograms/g dry weight) excludes a diagnosis of WD (**Grade III**).

#### *Neurological Evaluation and Radiologic Imaging of the Brain*

Neurologic evaluation and radiologic imaging of the brain, preferably by magnetic resonance imaging (MRI), should be considered prior to treatment in all patients

with neurologic WD and should be part of the evaluation of any patient presenting with neurologic symptoms consistent with WD (**Grade III**).

#### *Genetic Studies*

When possible, genetic diagnosis based on haplotype analysis should be used for family screening of first-degree relatives of patients with WD (**Grade III**).

### **Diagnostic Considerations in Specific Target Populations**

#### *"Mimic" Liver Diseases*

Patients in the pediatric age bracket who present a clinical picture of autoimmune hepatitis should be investigated for WD. Adult patients with atypical autoimmune hepatitis or who respond poorly to standard corticosteroid therapy should also be investigated for WD (**Grade III**).

WD should be considered in the differential diagnosis of patients presenting with nonalcoholic fatty liver or who have pathologic findings of nonalcoholic steatohepatitis (NASH) (**Grade IV**).

#### *Fulminant Liver Failure*

WD should be suspected in any patient presenting with fulminant hepatic failure with Coombs-negative intravascular hemolysis, modest elevations in serum aminotransferases, low serum alkaline phosphatase, and ratio of alkaline phosphatase to bilirubin of less than 2 (**Grade III**).

#### *Family Screening*

First-degree relatives of any patient newly diagnosed with WD must be screened for WD. Assessment should include history and physical examination, serum aminotransferases and biochemical tests of hepatic synthetic function, complete blood count, and ceruloplasmin. Kayser-Fleischer rings should be sought by slit-lamp examination. The basal 24-hour urinary copper excretion should be measured. Genotype or haplotype studies based on findings in the proband should be performed (**Grade II**).

### **Treatment**

Initial treatment for symptomatic patients should include a chelating agent (penicillamine or trientine) (**Grade II**).

Treatment of presymptomatic patients or maintenance therapy of successfully treated symptomatic patients can be accomplished with the chelating agent penicillamine or trientine, or with zinc (**Grade II**).

### **Treatment in Specific Clinical Situations**

#### *Fulminant Hepatic Failure*

Patients with fulminant hepatic failure or patients with severe liver disease unresponsive to chelation treatment should be treated with liver transplantation (**Grade II**).

#### *Pregnancy*

Treatment for WD should be continued during pregnancy, but dosage reduction is advisable for D-penicillamine and trientine (**Grade III**).

#### *Liver Transplantation*

Treatment is lifelong and should not be discontinued, unless a liver transplantation has been performed (**Grade II**).

#### **Monitoring**

For routine monitoring, serum copper and ceruloplasmin, liver biochemistries and international normalized ratio, and physical examination should be performed regularly (**Grade III**).

Twenty-four-hour urinary excretion of copper while on medication should be measured yearly, or more frequently if there are issues of compliance or if dosage of medications is adjusted. The serum nonceruloplasmin-bound copper may be estimated in these situations (**Grade III**).

Patients receiving chelators require a complete blood count with differential and urinalysis regularly no matter how long they have been on treatment (**Grade III**).

#### **Definitions:**

#### **Quality of Evidence**

**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)**

An algorithm is provided in the original guideline document for assessment of suspected Wilson disease.

## EVIDENCE SUPPORTING THE RECOMMENDATIONS

### TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The guidelines are based on review of the published literature and the personal experience of the authors. The type of supporting evidence is identified and graded for selected recommendations (see "Major Recommendations").

## BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

### POTENTIAL BENEFITS

#### Overall Benefits

Effective and timely diagnosis and treatment of persons with Wilson disease (WD)

#### Specific Benefits

##### *D-Penicillamine*

Numerous studies attest to the effectiveness of penicillamine as treatment for WD.

##### *Trientine*

Trientine is an effective treatment for WD and is indicated especially in patients who are intolerant of penicillamine or have clinical features indicating potential intolerance (history of renal disease of any sort, congestive splenomegaly causing severe thrombocytopenia, or autoimmune tendency). It has also been shown to be an effective initial therapy for patients, even with decompensated liver disease at the outset. Trientine has few side effects. No hypersensitivity reactions have been reported although a fixed drug reaction was observed in one patient. Pancytopenia has rarely been reported.

##### *Zinc*

Zinc has very few side effects. Although zinc is currently reserved for maintenance treatment, it has been used as first-line therapy, most commonly for asymptomatic or presymptomatic patients. It appears to be equally effective as penicillamine but much better tolerated. Reports of extensive series of adults with WD indicate good efficacy. A child who presented with ascites and coagulopathy was effectively treated only with zinc; a few other favorable reports in children have appeared.

### POTENTIAL HARMS

#### D-Penicillamine

Worsening of neurologic symptoms has been reported in 10 to 50% of those treated with penicillamine during the initial phase of treatment. Penicillamine use

is associated with severe side effects requiring the drug to be discontinued in 20 to 30% of patients. Early sensitivity reactions include fever and cutaneous eruptions, lymphadenopathy, neutropenia or thrombocytopenia, and proteinuria during the first 1 to 3 weeks. Late reactions include nephrotoxicity, usually heralded by proteinuria or the appearance of other cellular elements in the urine. Other late reactions include a lupus-like syndrome marked by hematuria, proteinuria, positive antinuclear antibody, and with higher dosages of penicillamine, Goodpasture syndrome. Significant bone marrow toxicity includes severe thrombocytopenia or total aplasia. Dermatologic toxicities reported include progeric changes in the skin and elastosis perforans serpiginosa, and pemphigus or pemphigoid lesions, lichen planus, and aphthous stomatitis. Very late side effects include nephrotoxicity, severe allergic response upon restarting the drug after it has been discontinued, myasthenia gravis, polymyositis, loss of taste, immunoglobulin A depression, and serous retinitis. Hepatotoxicity has been reported. Hepatic siderosis has been reported in association with treated patients with reduced levels of serum ceruloplasmin and nonceruloplasmin-bound copper.

### **Trientine**

Treatment with trientine in patients with primary biliary cirrhosis revealed that trientine may cause hemorrhagic gastritis, loss of taste, and rashes. Recent evidence suggests that copper deficiency induced by trientine can result in iron overload in livers of patients with Wilson disease.

### **Zinc**

Gastric irritation is the main problem and may be dependent on the salt employed. Hepatic deterioration has been occasionally reported when zinc was commenced, fatal in one case. Also, zinc may have immunosuppressant effects and reduce leukocyte chemotaxis. Elevations in serum lipase and/or amylase may occur, without clinical or radiologic evidence of pancreatitis. Whether high-dose zinc is safe for patients with impaired renal function is not yet established.

## **QUALIFYING STATEMENTS**

### **QUALIFYING STATEMENTS**

- As their purpose is to direct patient care, these guidelines should not be considered inflexible mandates.
- A significant problem with the literature on Wilson disease is that patients are sufficiently rare to preclude large cohort studies or randomized controlled trials; moreover, most treatment modalities were developed at a time when conventions for drug assessment were less stringent than currently.

## **IMPLEMENTATION OF THE GUIDELINE**

### **DESCRIPTION OF IMPLEMENTATION STRATEGY**

An implementation strategy was not provided.

## **IMPLEMENTATION TOOLS**

Clinical Algorithm  
Personal Digital Assistant (PDA) Downloads

For information about [availability](#), see the "Availability of Companion Documents" and "Patient Resources" fields below.

## **INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES**

### **IOM CARE NEED**

Getting Better  
Living with Illness

### **IOM DOMAIN**

Effectiveness

## **IDENTIFYING INFORMATION AND AVAILABILITY**

### **BIBLIOGRAPHIC SOURCE(S)**

Roberts EA, Schilsky ML. A practice guideline on Wilson disease. Hepatology 2003 Jun;37(6):1475-92. [208 references] [PubMed](#)

### **ADAPTATION**

Not applicable: The guideline was not adapted from another source.

### **DATE RELEASED**

2003 Jun

### **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**

**Note:** This guideline has been updated. The National Guideline Clearinghouse (NGC) is working to update this summary.

## **GUIDELINE AVAILABILITY**

Electronic copies of the updated guideline: 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](http://www.aasld.org); e-mail: [aasld@aaasld.org](mailto:aasld@aaasld.org).

## **AVAILABILITY OF COMPANION DOCUMENTS**

This guideline is available as a Personal Digital Assistant (PDA) download via the APPRISOR™ Document Viewer from [www.apprisor.com](http://www.apprisor.com).

## **PATIENT RESOURCES**

None available

## **NGC STATUS**

This NGC summary was completed by ECRI on February 17, 2004. The information was verified by the guideline developer on March 16, 2004.

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