9TH ANNUAL
DIGESTIVE DISEASES: NEW ADVANCES

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W Hotel
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Wilson Disease: New Guidelines?

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- Nancy Reau, MD
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Agenda

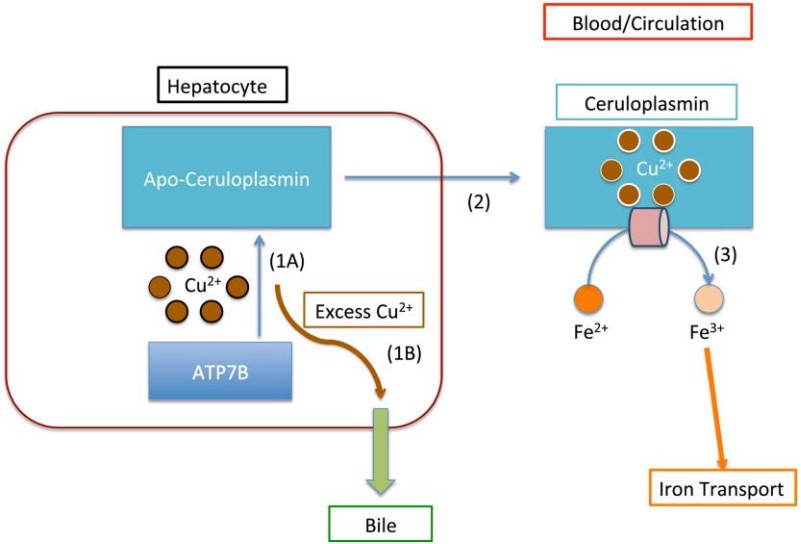
1. Review current Wilson Disease Guidelines
2. Presentation
3. Diagnosis
4. Family Screening
5. Treatment

What Is Wilson Disease

- Inherited disorder in which defective biliary excretion of copper leads to accumulation especially in liver and brain
- Mutation of *ATP7B* gene on chromosome 13
- Autosomal Recessive

ATP7B

- Transports copper from intracellular chaperone proteins into the secretory pathway → excretion into bile and for incorporation into apo-ceruloplasmin



Clinical Liver Disease. Volume: 17, Issue: 2, Pages: 61-66.

1 Current Guidelines

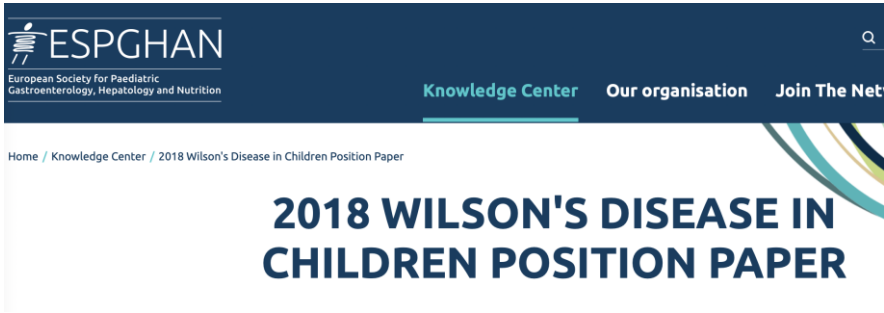
Guidelines

2003, revised 2008…soon

AASLD PRACTICE GUIDELINES

Diagnosis and Treatment of Wilson Disease: An Update

Eve A. Roberts[1] and Michael L. Schilsky[2]



Clinical Practice Guidelines 2012

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

EASL Clinical Practice Guidelines: Wilson's disease

European Association for the Study of the Liver*

2 Clinical Presentation

Clinical Presentation

- Liver disease + neuropsychiatric disturbances, Kayser–Fleischer rings
- Acute hemolysis +/-ALF
- Liver disease: asymptomatic to cirrhosis or ALF with Coombs-negative hemolytic anemia and ARF
- **Universally fatal if untreated**

Include Wilson Disease on the differential, especially if <40 yo

Table 2. Clinical Features in Patients with Wilson Disease

Hepatic	• Asymptomatic hepatomegaly • Isolated splenomegaly • Persistently elevated serum aminotransferase activity (AST, ALT) • Fatty liver • Acute hepatitis • Resembling autoimmune hepatitis • Cirrhosis: compensated or decompensated • Acute liver failure
Neurological	• Movement disorders (tremor, involuntary movements) • Drooling, dysarthria • Rigid dystonia • Pseudobulbar palsy • Dysautonomia • Migraine headaches • Insomnia • Seizures
Psychiatric	• Depression • Neurotic behaviours • Personality changes • Psychosis
Other systems	• Ocular: Kayser-Fleischer rings, sunflower cataracts • Cutaneous: lunulae ceruleae • Renal abnormalities: aminoaciduria and nephrolithiasis • Skeletal abnormalities: premature osteoporosis and arthritis • Cardiomyopathy, dysrhythmias • Pancreatitis • Hypoparathyroidism • Menstrual irregularities; infertility, repeated miscarriages

AASLD and EASL Guideline Recommendations

1. WD should be considered in any individual between the ages of 3 and 55 years with liver abnormalities of uncertain cause. Age alone should not be the basis for eliminating a diagnosis of WD (Class I, Level B).
2. WD must be excluded in any patient with unexplained liver disease along with neurological or neuropsychiatric disorder (Class I, Level B).
3. 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 neurological disease (Class I, Level B).

3 Diagnosis

Guidelines: Diagnosis and Screening

- AASLD 2008
  - Dx: Clinical and biochemical algorithm
  - Screen: siblings – genetic testing
  - Children/1st degree relatives – clinical
- EASL 2012
  - Dx: Leipzig Score
  - Screen: 1st degree relatives – genetic testing
- ESPGHAN 2018 Algorithm and Leipzig score (Ferenci)
  - Screen: 1st degree relatives -- Clinical and genetic testing

Diagnosis

- Kayser–Fleischer rings and a low serum ceruloplasmin (<0.1 g/L)
- Hepatic presentation: no KF rings, ceruloplasmin not reliable
  - Ceruloplasmin alone is not sufficient to diagnose or to exclude Wilson's disease.

Test	Typical finding	False "negative"	False "positive"
Serum ceruloplasmin	Decreased by 50% of lower normal value	Normal levels in patients with marked hepatic inflammation Overestimation by immunologic assay Pregnancy, estrogen therapy	Low levels in: - malabsorption - aceruloplasminemia - heterozygotes
24-hour urinary copper	>1.6 µmol/24 h >0.64 µmol/24 h in children	Normal: - incorrect collection - children without liver disease	Increased: - hepatocellular necrosis - cholestasis - contamination
Serum "free" copper	>1.6 µmol/L	Normal if ceruloplasmin overestimated by immunologic assay	
Hepatic copper	>4 µmol/g dry weight	Due to regional variation - in patients with active liver disease - in patients with regenerative nodules	Cholestatic syndromes
Kayser-Fleischer rings by slit lamp examination	Present	Absent - in up to 50% of patients with hepatic Wilson's disease - in most asymptomatic siblings	Primary biliary cirrhosis

-Advanced liver disease

Journal of Heptology. 2012 vol. 56; 671-685.

AASLD

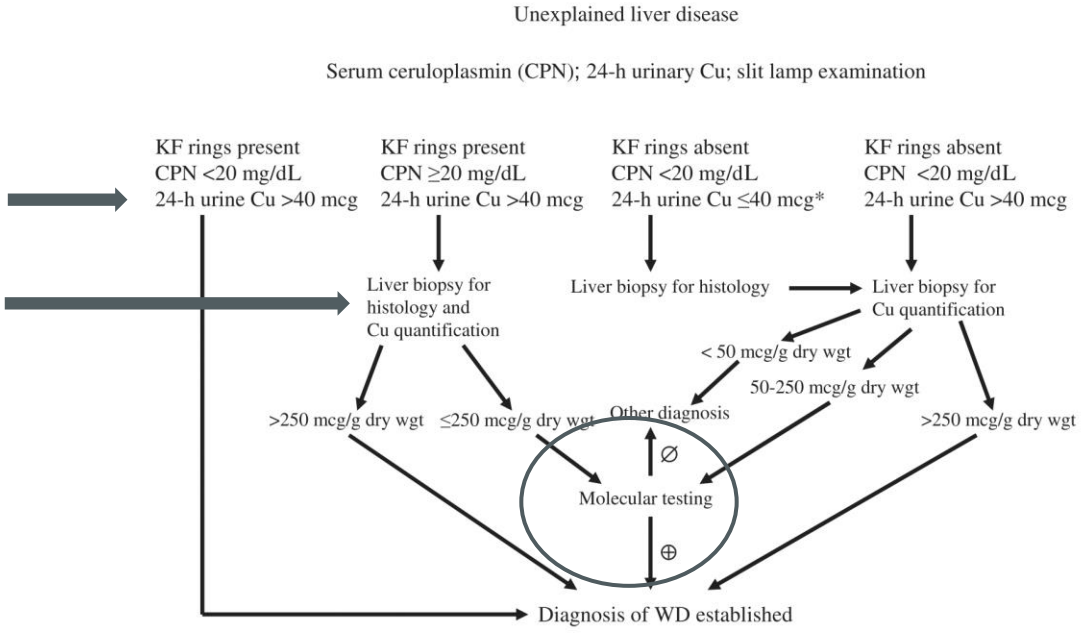
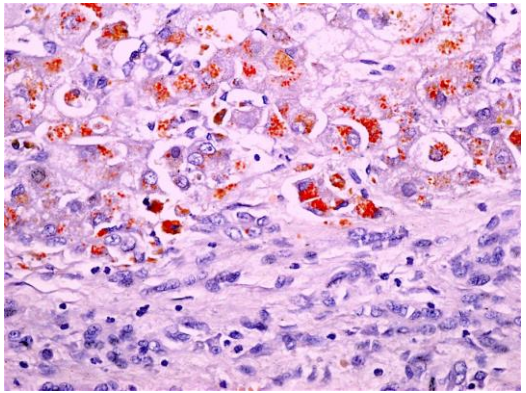


Fig. 1. Approach to diagnosis of Wilson disease (WD) in a patient with unexplained liver disease. Molecular testing means confirming homozygosity for one mutation or defining two mutations constituting compound heterozygosity. *Assure adequacy of urine collection. Conversion to SI units: CPN <20 mg/dL or 0.2 g/L; 24-hour urinary Cu >40 μg/day or 0.6 μmol/day. Note that normal ranges for CPN may vary slightly between laboratories. Abbreviations: CPN, ceruloplasmin; KF, Kayser-Fleischer.



EASL: The Wilson's Disease Scoring System

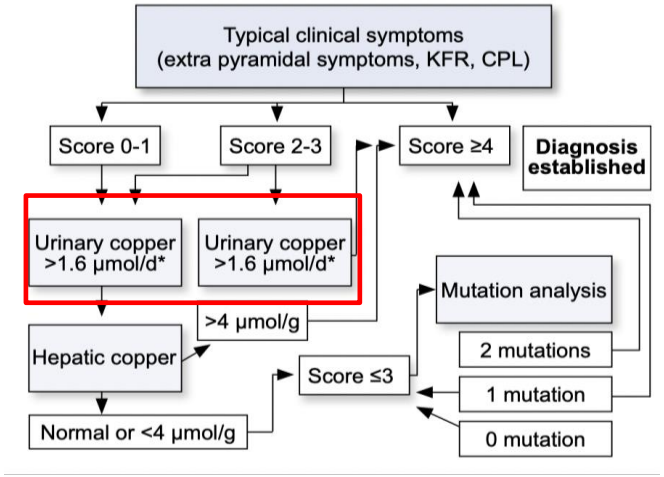


Table 5. Scoring system developed at the 8th International Meeting on Wilson's disease, Leipzig 2001 [44].

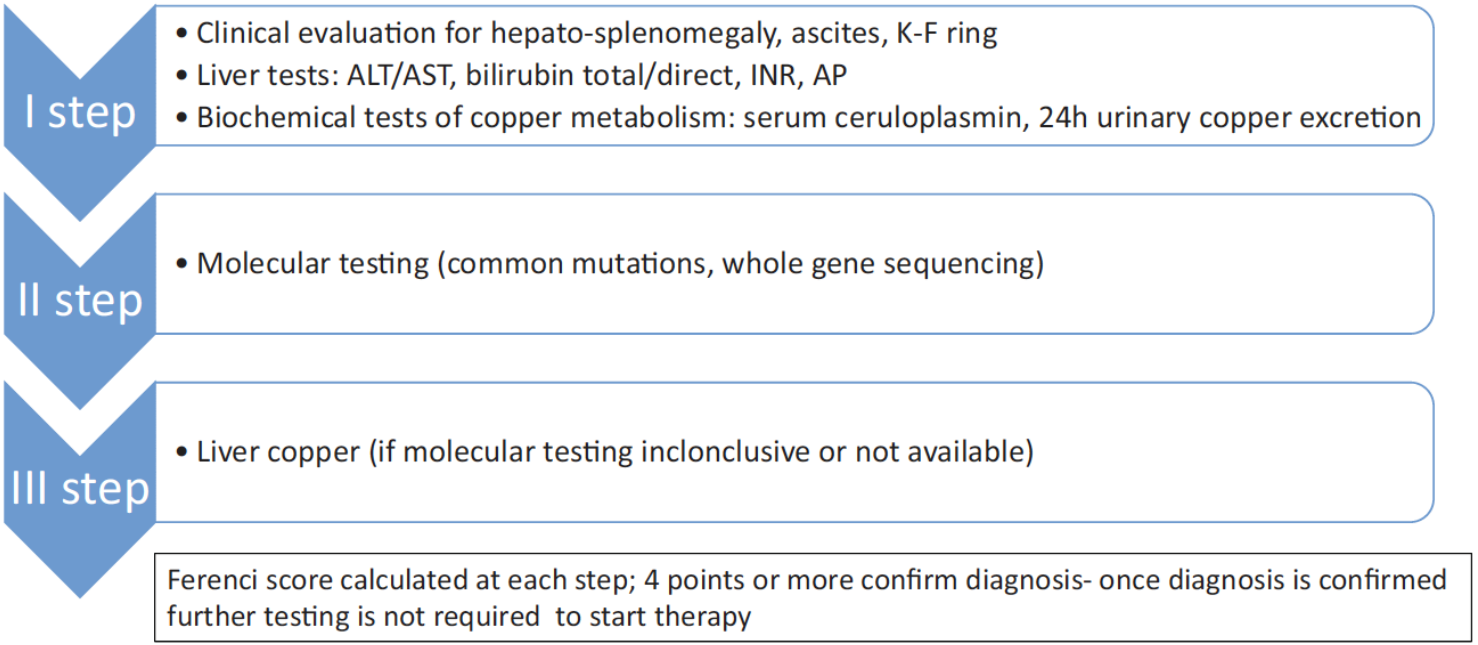
Typical clinical symptoms and signs	
KF rings	
Present	2
Absent	0
Neurologic symptoms**	
Severe	2
Mild	1
Absent	0
Serum ceruloplasmin	
Normal (>0.2 g/L)	0
0.1-0.2 g/L	1
<0.1 g/L	2
Coombs-negative hemolytic anemia	
Present	1
Absent	0

Other tests	
Liver copper (in the absence of cholestasis)	
>5x ULN (>4 µmol/g)	2
0.8-4 µmol/g	1
Normal (<0.8 µmol/g)	-1
Rhodanine-positive granules*	1
Urinary copper (in the absence of acute hepatitis)	
Normal	0
1-2x ULN	1
>2x ULN	2
Normal, but >5x ULN after D-penicillamine	2
Mutation analysis	
On both chromosomes detected	4
On 1 chromosome detected	1
No mutations detected	0

TOTAL SCORE	Evaluation:
4 or more	Diagnosis established
3	Diagnosis possible, more tests needed
2 or less	Diagnosis very unlikely

*If no quantitative liver copper available, **or typical abnormalities at brain magnetic resonance imaging.
KF, Kayser-Fleischer; ULN, upper limit of normal.
Journal of Heptology. 2012 vol. 56; 671-685.

ESPGHAN 2018



JPGN. Volume 66, Number 2, February 2018.

ESPGHAN 2018

TABLE 4. Diagnostic score in Wilson's disease, agreed at a consensus meeting (64)

Score	−1	0	1	2	4
Kayser-Fleischer rings		Absent		Present	
Neuropsychiatric symptoms suggestive of WD (or typical brain MRI)		Absent		Present	
Coombs negative hemolytic anemia + high serum copper		Absent	Present		
Urinary copper (in the absence of acute hepatitis)		Normal	1–2 × ULN	>2 × ULN, or normal but >5 × ULN 1 day after challenge with 2 × 0.5 g D-penicillamine	
Liver copper quantitative	Normal		<5 × ULN (<250 μg/g)	>5 × ULN (>250 μg/g)	
Rhodanine positive hepatocytes (only if quantitative Cu measurement is not available)		Absent	Present		
Serum ceruloplasmin (nephelometric assay)		>0.2 g/L	0.1–0.2 g/L	<0.1 g/L	
Disease-causing mutations detected		None	1		2

Assessment of the Wilson's disease diagnostic score

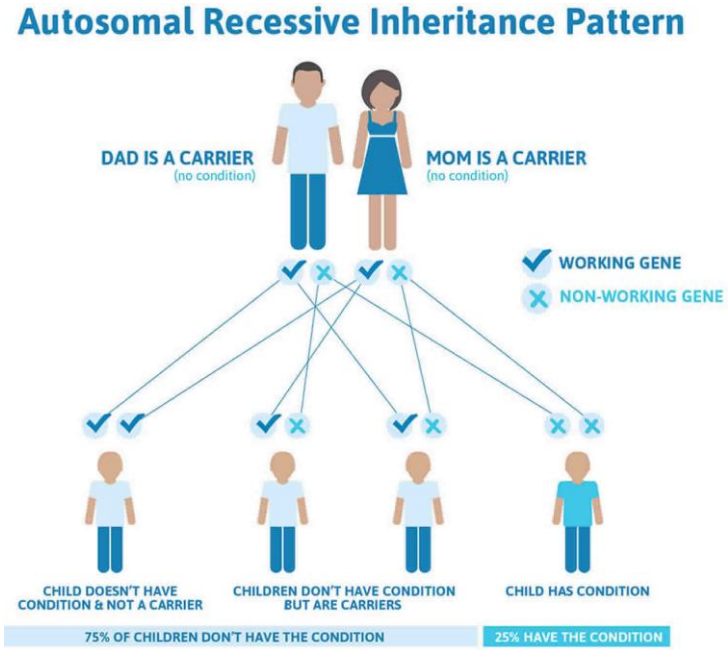
0–1: Unlikely	2–3:Probable	4 or more: highly likely

JPGN. Volume 66, Number 2, February 2018.

Genetic Testing – Role Is Evolving

- >500 possible mutations
- Most compound heterozygotes
- Perform molecular in any patient who has a provisional diagnosis of Wilson's disease
  - Confirmation
  - Family screening
- **AASLD Recommendation:**

  9. Mutation analysis by whole-gene sequencing is possible and should be performed on individuals in whom the diagnosis is difficult to establish by clinical and biochemical testing. Haplotype analysis or specific testing for known mutations can be used for family screening of first-degree relatives of patients with WD. A clinical geneticist may be required to interpret the results (Class I, Level B).



WD: ALF

- ***Acute Liver Failure. WD* acute failure presentation**
  - Coombs-negative hemolytic anemia with features of acute intravascular hemolysis
  - Coagulopathy unresponsive to parenteral vitamin K
  - Rapid progression to renal failure
  - Relative modest rises in serum aminotransferases (typically 2000 IU/L)
  - Normal or subnormal serum alkaline phosphatase (typically 40 IU/L) ALP:Tbili < 2
  - Female: male ratio of 2:1.

4 Family Screening

Family Screening

- Siblings have a 25% risk of being a homozygote – and therefore developing clinical disease

Recommendation:

First-degree relatives of any patient newly diagnosed with WD must be screened for WD (Class I, Level A).

- Analysis of the ATP7B gene for mutations in the children of an index patient
- Siblings of an index case with a documented mutation can be screened by mutational analysis.

– Mutation analysis should be the primary mode for screening of first-degree relatives of patients with Wilson's disease
GRADE II-2, B, 1 AASLD Class I, Level B

5 Treatment

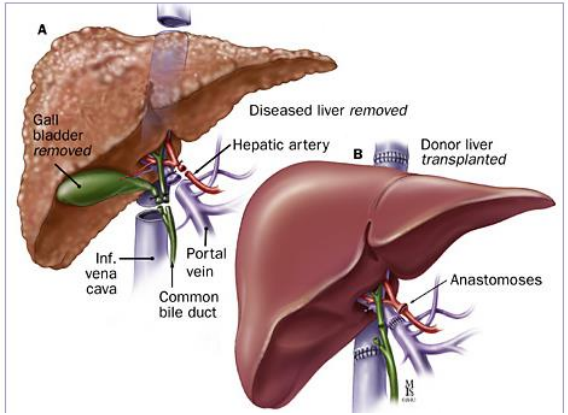
Treatment: Initial

***WD without an* acute failure presentation**

- Initial therapy in a symptomatic patient should be a chelating agent (penicillamine or trientene).
  - AASLD and ESPGHAN specify a potential role for combination therapy with zinc in the setting of decompensated cirrhosis.
  - EASL guidelines also propose a role for zinc as initial choice in neurological patients.
  - Zinc can be used in asymptomatic patients
  - Low Cu diet

***WD with an* acute failure presentation**

- **Liver transplant**



Treatment: Maintenance

- AASLD and EASL both suggest maintenance-dose chelator or zinc as acceptable options for maintenance therapy.
- ESPGHAN favors zinc.

Treatment: Monitoring

- Copper Balance: 24-hour urine copper and non-ceruloplasmin bound copper
- Urinary copper excretion target: 200–500 µg (3–8 µmol) per day
  - EASL: 24-hour urinary Cu be measured after 2 days of cessation of chelation therapy,
  - < 100 µg (1.6 µmol) per day = adequate control
  - Zinc therapy.
    - AASLD – urinary copper excretion < 75 µg (1.2 µmol) per day
    - EASL allows up to 100 µg (1.6 µmol) per day,
    - ESPGHAN: 30–75 µg (0.5–1.2 µmol) per day.
  - Serum and urinary zinc should be monitored while on zinc therapy.
- Normalization of non-ceruloplasmin bound copper
- Follow liver biochemistry and function, serum copper, ceruloplasmin and physical exam twice yearly, and urinary copper at least yearly.

Treatment

TABLE 5. Dosage and treatment monitoring

	Zinc salts	D-penicillamine	Trientine
Dosage in children	Zinc acetate, zinc sulphate Age >16 years and body weight >50 kg: 150 mg* day in 3 divided doses. Age 6–16 years and body weight <50 kg: 75 mg* day in 3 divided doses younger than 6 years of age: 50 mg* day in 2 divided doses	Starting dose: 150–300 mg/day, gradually increasing once a week up to 20 mg/kg/day given in 2 or 3 divided doses or 1000 mg (max 1500 mg) in young adults given in 2 or 4 divided doses. Maintenance dose: 10–20 mg/kg/day up to 750 mg–1000 mg/day in 2 divided doses	Starting dose: 20 mg/kg/day or 1000 mg (max 1500 mg) in young adults given in 2 or 3 divided doses. Maintenance dose: 900–1500 mg/day in 2 or 3 divided doses.
Administration	1 hour before meal or 2 hours after meal	1 hour before meal or 2 hours after meal	1 hour before meal or 3 hours after meal
Adequacy of treatment parameters	Urinary copper excretion: 30–75 μg (0.5–1.2 μmol/L) /24 hours on maintenance treatment Serum zinc level >125 μg/dL Urinary zinc >2 mg/24 h on maintenance treatment	Urinary copper excretion: 200–500 μg (3–8 μmol/L)/24 hours on maintenance treatment	Urinary copper excretion: 200–500 μg (3–8 μmol/L)/24 hours on maintenance treatment
Liver function improvement	Usually 2–6 months, ALT normalization within 1 year	Usually 2–6 months	Usually 2–6 months
Indication for a drug change	Persistent ALT >3× upper limit of normal and/or INR >1.5 Poor tolerance, for example, nausea, abdominal pain, gastric ulcerations	Poor tolerance or side effects, for example, hypersensitivity reactions, fever, neutropenia, thrombocytopenia, lymphadenopathy or proteinuria	Poor tolerance or side effects, for example, allergic reactions, arthralgia, sideroblastic anemia

ALT = alanine aminotransferase.
* - elemental zinc.

Conclusions

- WD should be considered in all individuals with unexplained liver disease
- WD should be evaluated for in all patients with liver and neurologic disease
- The role of molecular testing is changing
- WD is universally fatal without therapy
- Chelation and zinc therapy are standard of care

Thank You.