10TH ANNUAL

DIGESTIVE DISEASES: NEW ADVANCES

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Wilson Disease:
What's New in the 2022 Guidelines

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Agenda

1. Review updated 2022 Wilson Disease Guidelines
2. Presentation
3. Diagnosis
4. Family Screening
5. Treatment

Relevant Disclosures

Nancy Reau, MD

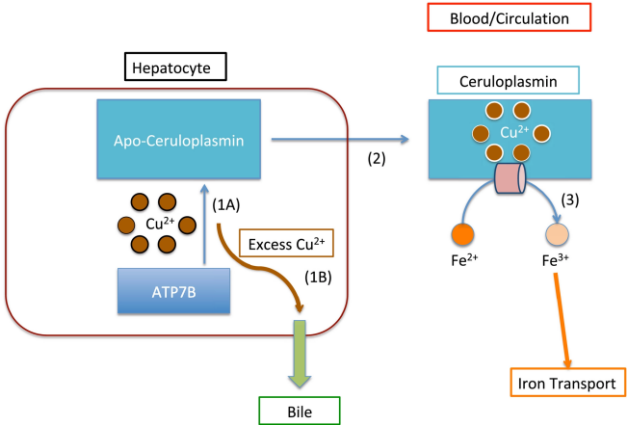
- **Research Support:** Gilead, AbbVie
- **Consultant:** Salix, Intercept

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

Updated Guidelines:

Received: 13 September 2022 | Accepted: 13 September 2022

DOI: 10.1002/hep.32805

PRACTICE GUIDANCE

A multidisciplinary approach to the diagnosis and management of Wilson disease: Executive summary of the 2022 Practice Guidance on Wilson disease from the American Association for the Study of Liver Diseases

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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
- **<u>Universally fatal if untreated</u>**

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 Guideline Recommendations: Clinical Spectrum

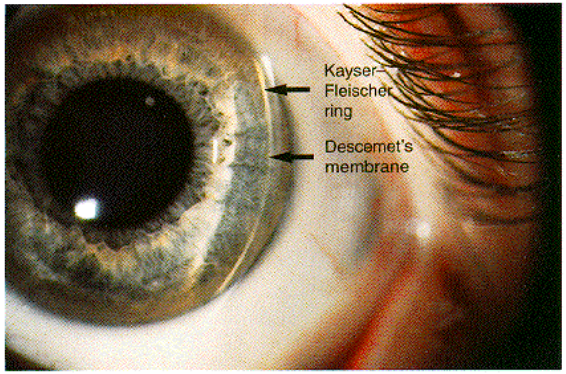
1. WD should be **considered in any individual with liver abnormalities of uncertain cause**. Age alone should not be the basis for eliminating a diagnosis of WD.
2. WD must be **excluded in any patient with unexplained liver disease associated with neurological or psychiatric disorder**.
3. WD should be suspected in any patient presenting with **ALF with nonimmune hemolytic anemia** including acute intravascular hemolysis. These patients require urgent evaluation for liver transplantation.
4. Evaluation for WD is critical in patients exhibiting **recurrent self-limited nonimmune hemolysis**.
5. At clinical presentation, WD **may involve organ systems besides the liver and nervous system** (such as renal, musculoskeletal, cardiac, or endocrine).

Hepatology. December 7, 2022.

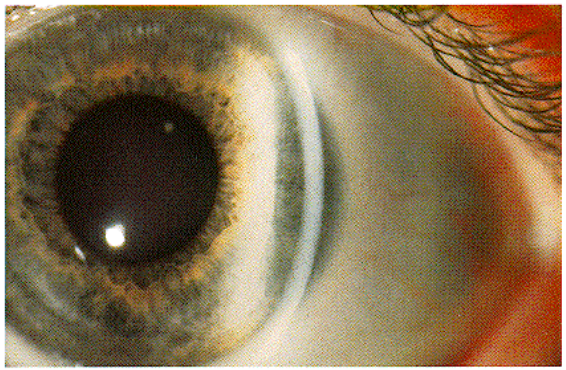
3. Diagnosis

Diagnosis

- Kayser–Fleischer rings and a low serum ceruloplasmin (<0.1 g/L)
- Hepatic presentation: no KF rings, ceruloplasmin not reliable



A



B

- Algorithms provide a structured approach to diagnosis.
- Different clinical presentations demand different algorithms.
- Alternatively, an arithmetic “scoring system,” such as the Leipzig score uses weighted scores for parameters valuable for disease diagnosis.
- The two may be complementary

Leipzig Score (for Diagnosis of WD)

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.

Ceruloplasmin

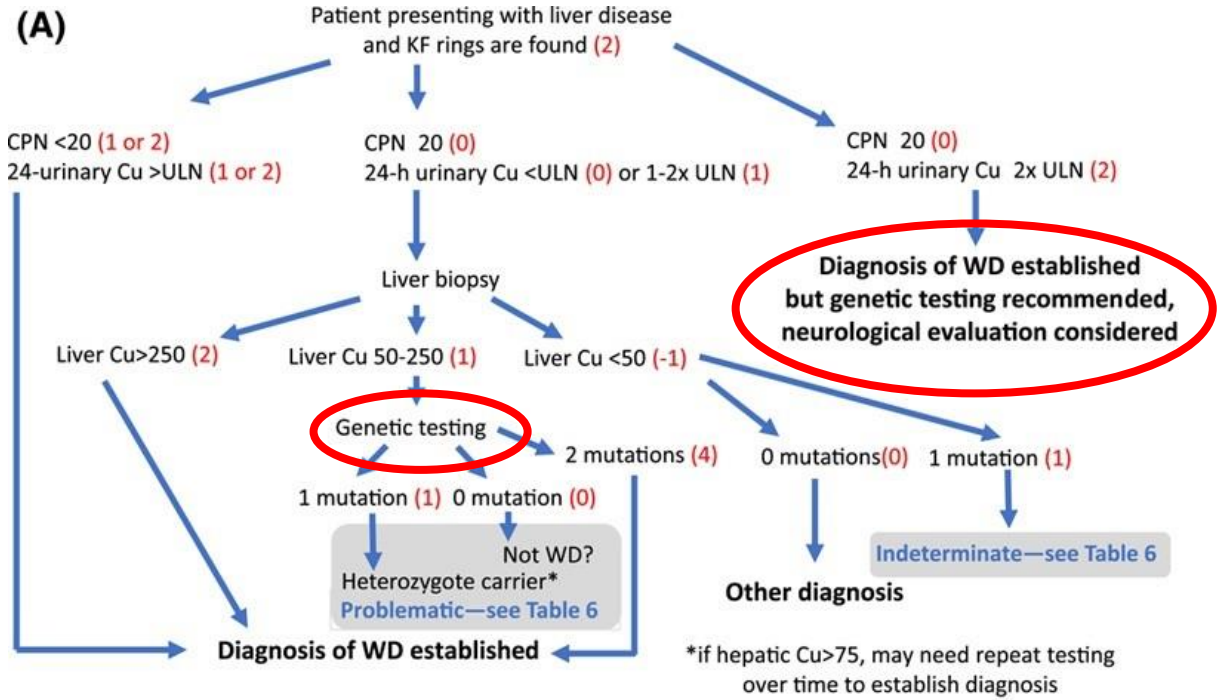
- Synthesized in hepatocytes w/ 6 Cu atoms → circulation (holoceruloplasmin)
- Acute phase reactant
- Inc w/ estrogen
- Serum ceruloplasmin within the normal range does not exclude the diagnosis of WD

Serum ceruloplasmin concentrations <14 mg/dl -PPV of 100% and NPV of 97.1%

TABLE 3 - Other disorders associated with low serum ceruloplasmin

Nonselective renal protein loss
Protein-losing enteropathy
Severe chronic liver disease with global hepatic synthetic deficit
Neurological disorders (cervical dystonia)
Absolute copper deficiency
Improper formulation of TPN omitting copper
After gastric or bariatric surgery
Chronic Ingestion of zinc in excess
Menkes disease
Aceruloplasminemia
MEDNIK syndrome (*AP1S1* disorder)
AP1B1 disorder
Congenital glycosylation disorder
PGM1-CDG
CCDC115-CGD
TMEM119-CDG
Niemann-Pick type C

Algorithmic Approach to Diagnosis of Wilson Disease (WD) in a Patient With Unexplained Liver Disease



Hepatology. December 07, 2022. doi: 10.1002/hep.32801.

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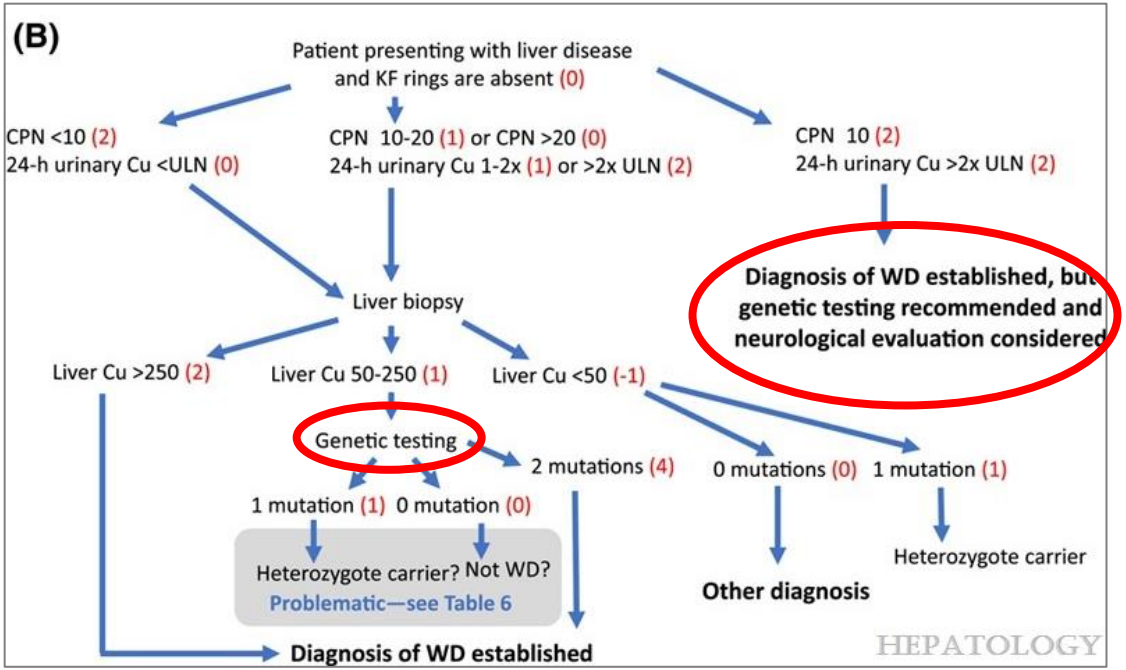

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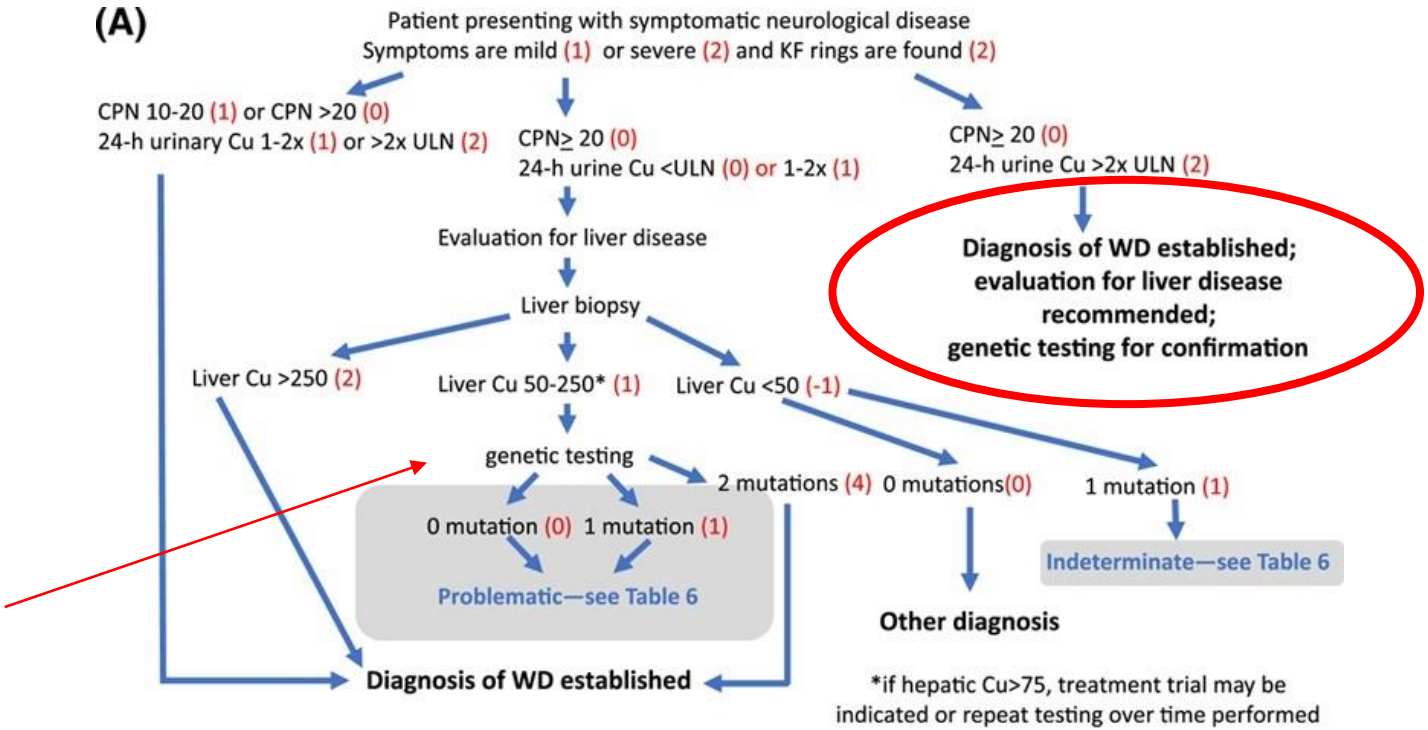
Algorithmic Approach to Diagnosis of Wilson Disease (WD) in a Patient With a Neurological Disorder



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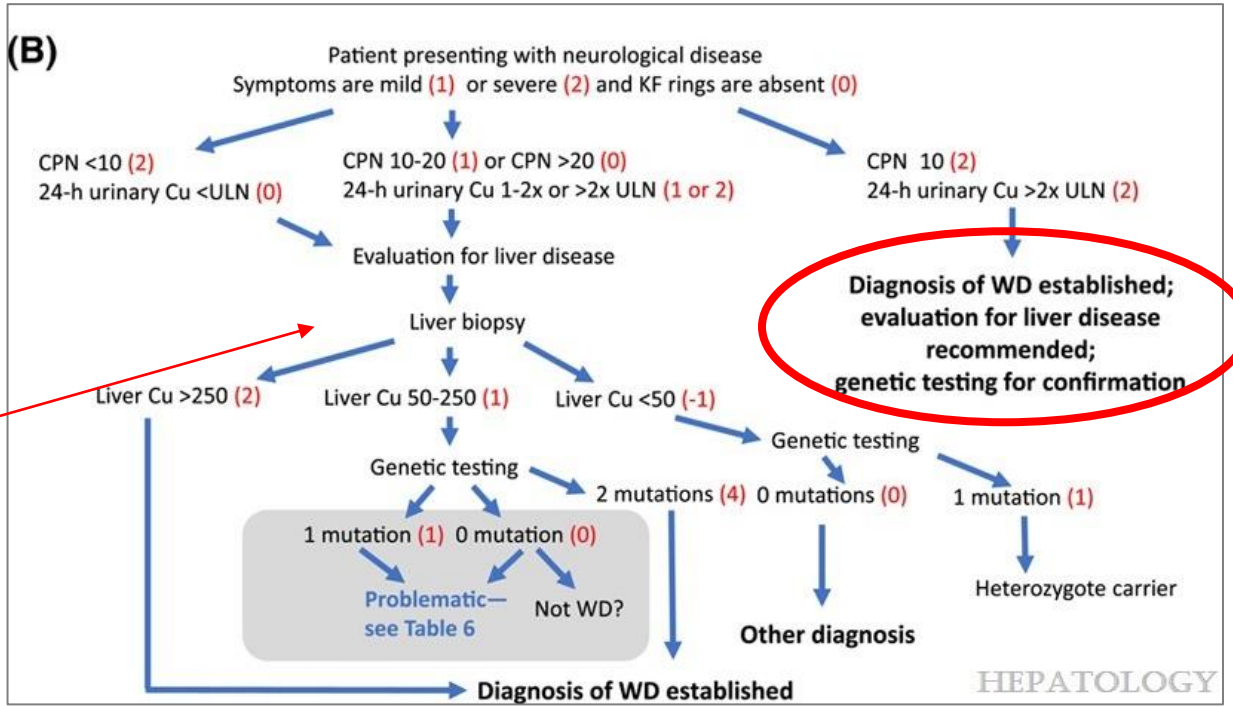

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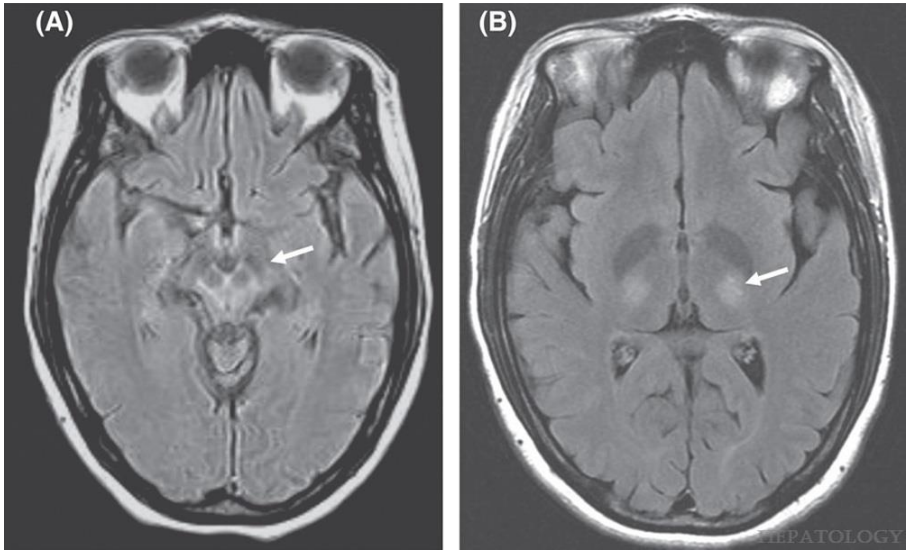
Magnetic Resonance Imaging (MRI) Brain

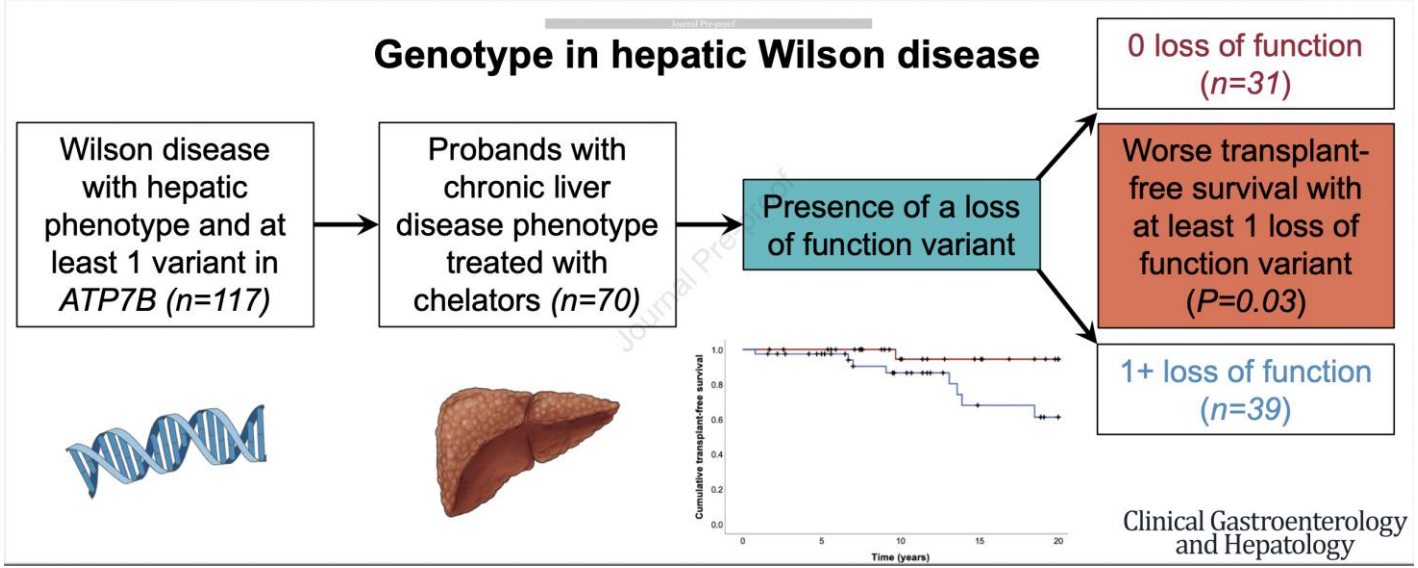


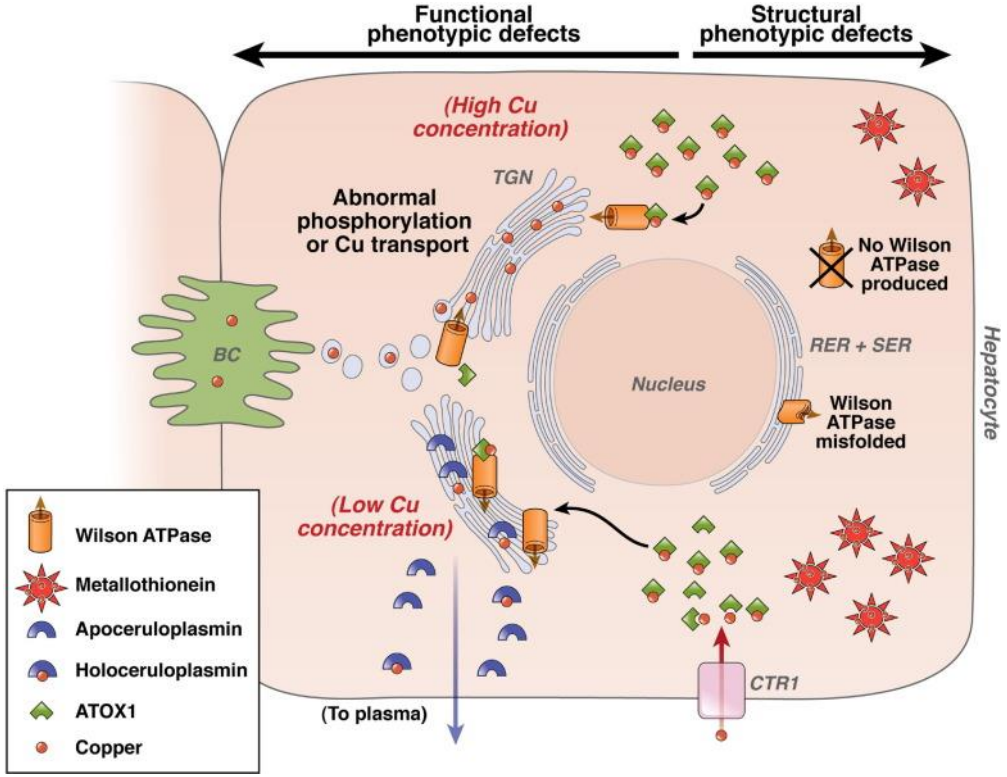
- Helpful esp with unexplained neurological and psychiatric symptoms
- MRI findings: signal changes in the basal ganglia, thalami, pons, and white matter, as well as atrophy
- “face of the giant panda sign”: increased T2 signal in the midbrain has been considered pathognomonic

FIGURE 1: Magnetic resonance images of a 32-year-old woman with Wilson disease. (A) Flair image of the midbrain showing the “face of the giant panda sign” (arrow). (B) T2 image showing thalamic lesions (arrow).

Loss of Function (LOF) Variant

- LOF variants: Earlier onset of disease, lower caeruloplasmin and copper, and a higher prevalence of FHF




Functional phenotypic defects
Structural phenotypic defects
(High Cu concentration)
TGN
Abnormal phosphorylation or Cu transport
No Wilson ATPase produced
BC
RER + SER
Nucleus
Wilson ATPase misfolded
Hepatocyte
(Low Cu concentration)
CTR1
(To plasma)
Wilson ATPase
Metallothionein
Apoceruloplasmin
Holoceruloplasmin
ATOX1
Copper

WD: ALF Typical Acute Presentation

- Severe Coombs-negative hemolytic anemia (acute intravascular hemolysis)
- Coagulopathy unresponsive to parenteral vitamin K
- Modest rises in serum aminotransferases (< 2000 IU/L)
- Normal or subnormal serum alkaline phosphatase (< 40 IU/L)
- ALP:Tbili < 2
- Rapid progression to renal failure
- Female: male ratio of 2:1.

Expeditious diagnosis is critically as urgent evaluation for liver transplantation needed
High mortality (80%–99%) without liver transplantation

WD: ALF Typical Acute Presentation

Diagnostics for WD differ in ALF

- KF rings are absent in 50%
- AST is higher than ALT
  - Mitochondrial damage
- Ceruloplasmin decreased, but poor predictive value
- Serum copper and 24-h urinary excretion of copper are greatly elevated
  - Serum copper is usually >200 μg/dl
  - BUT copper results are often not available in a timely manner
  - Diagnosis relies on clinical and biochemical features

WD ALF Diagnostic Clues

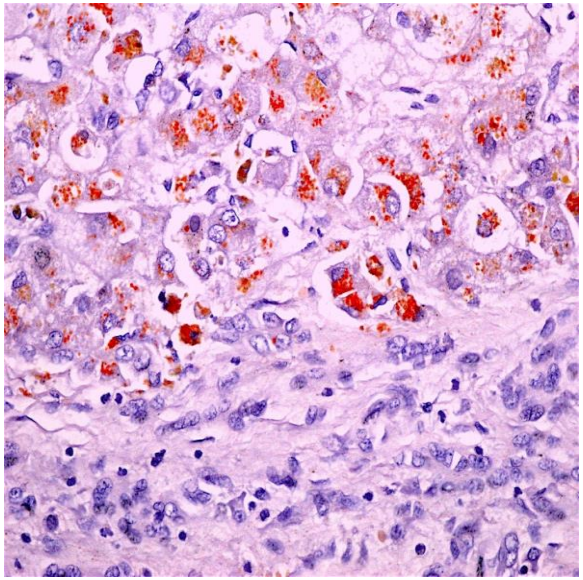
- Alkaline phosphatase : total bilirubin <4 was 94% sensitive and 96% specific,
- AST : ALT >2.2 - 94% sensitive but only 86% specific.
- Combination of both ratios 100% sensitive and 100% specific
  - Less accurate in the pediatric age bracket

Can have a viral or DILI trigger – important to recognize esp for family screening

Korman et al. *Hepatology*. 2008; 48:1167-74.

Wilson’s Disease Pathology

1. Early: EM: mitochondrial changes
   - LM: fat, glycogen, Cu stains –
   - hepatic Cu: highest
2. Mid: EM: Mitochondrial improving
   - LM: steatohepatitis, Cu-stain +
3. Late: EM: Mitochondria normal
   - LM: Cirrhosis (HCC rare)
   - Hepatic Cu: lowest (regenerating nodules)



Copper stain (rhodamine)

4. Family Screening

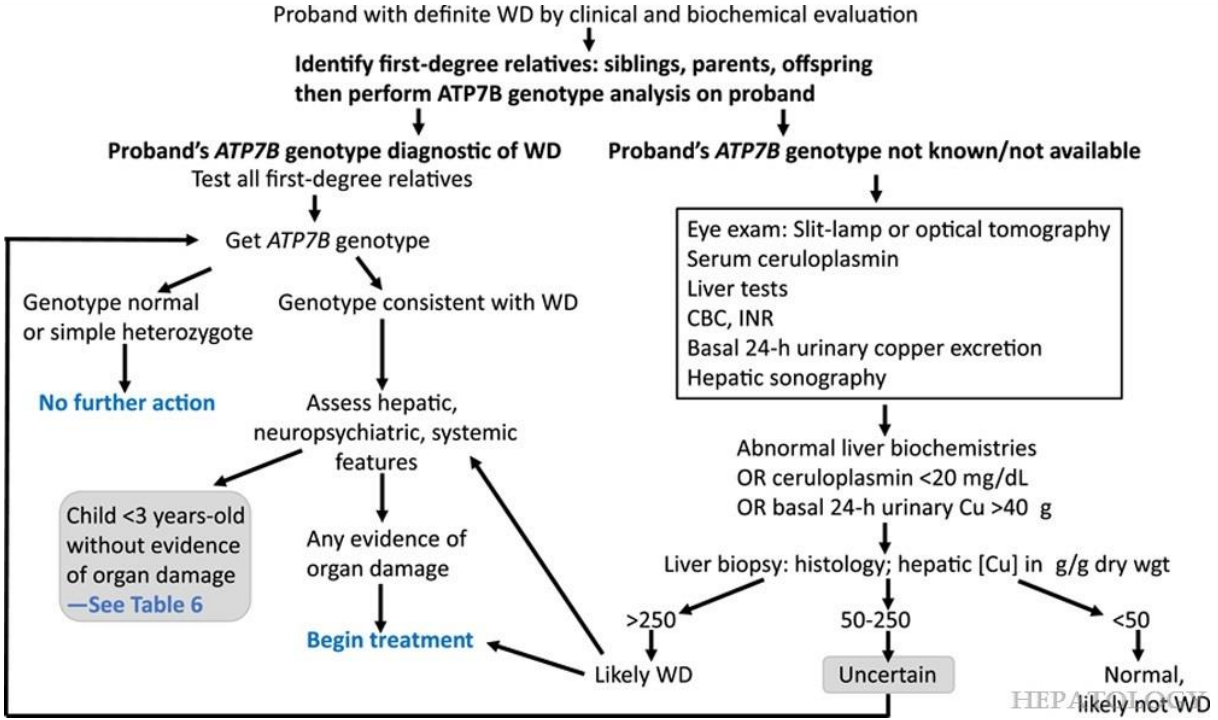
Screening for Wilson Disease (WD) in First-Degree Relatives

Guidance statement 14

14 First-degree relatives of patients newly diagnosed with WD must be screened for WD. Within a pedigree where there is one or more individuals with WD, any person with signs or symptoms consistent with WD, irrespective of closeness of relationship, should be evaluated for WD. Available strategies are genotype assessment of *ATP7B* and comprehensive clinical evaluation (summarized in Figure 4).

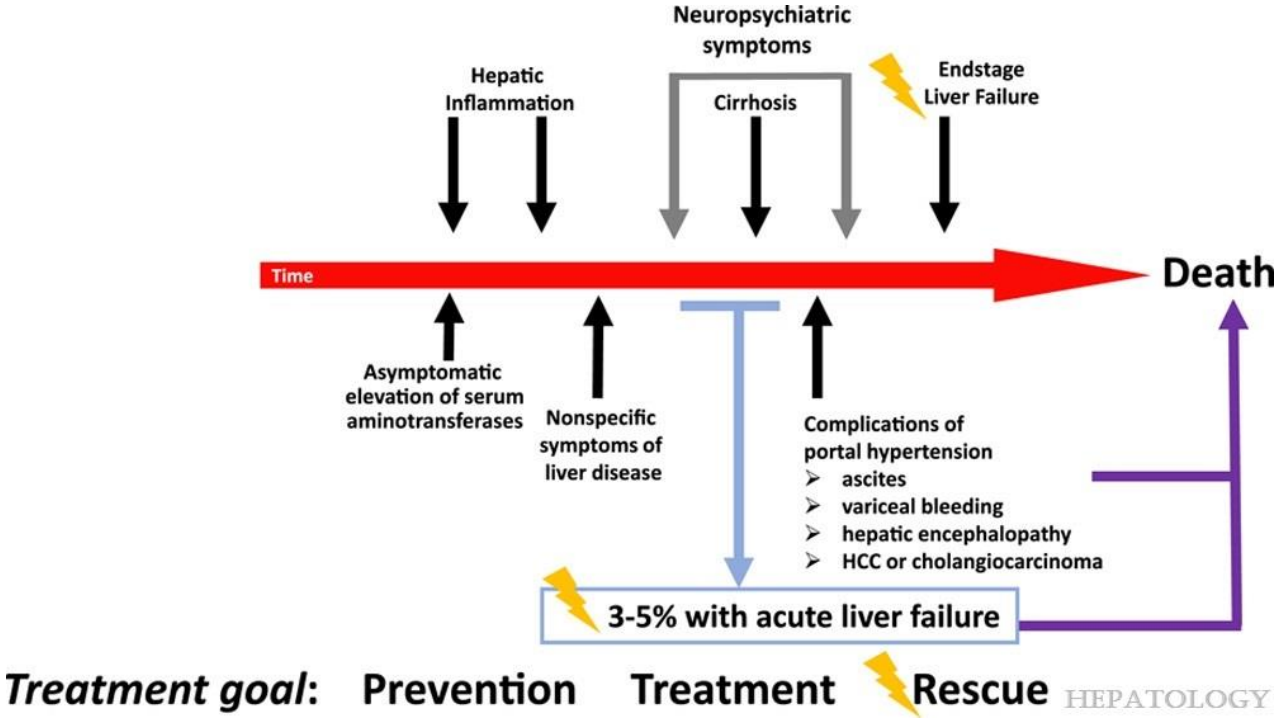
Although WD is suitable for newborn screening, no testing strategy has yet been established

Screening for Wilson disease (WD) in First-Degree Relatives



5. Treatment

Customizing Wilson Disease (WD) Treatment to the Character of Clinical Disease



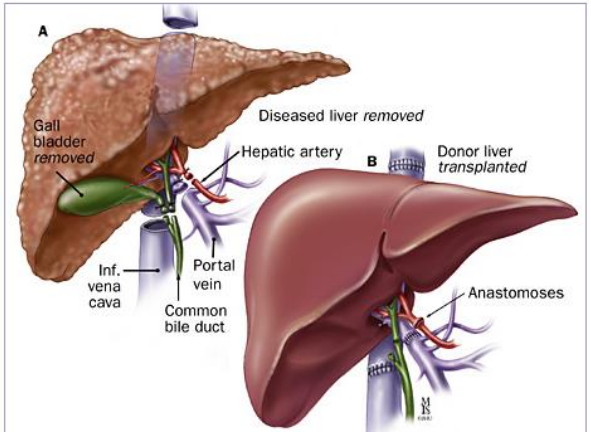
Treatment: Initial

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

- Initial therapy 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

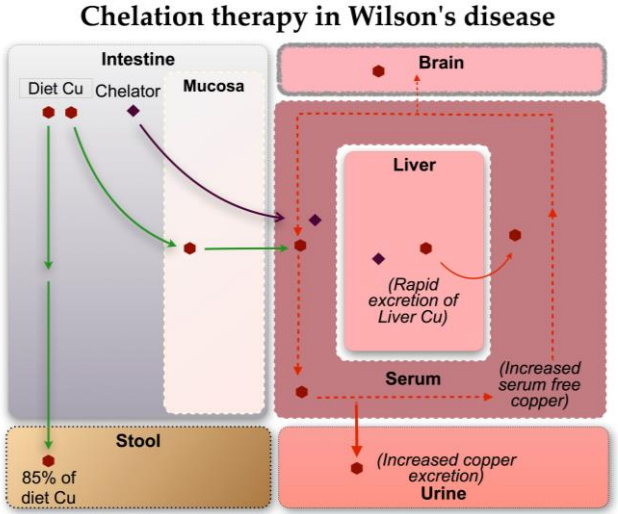
***WD with an* acute failure presentation**

- **Liver transplant**



D-Penicillamine

- Promote urinary copper excretion
- Absorption is decreased by approximately 50% with food
- Renally excreted
- “Paradoxical” worsening of neurological symptoms in 10%–50% during the initial phase of treatment
- Incremental dosing may enhance tolerability
  - 250–500 mg/day and then increasing by 250-mg increments every 4–7 days to approximately 1000–1500 mg/day (15–20 mg/kg/day) in 2–4 divided doses
  - Maintenance dose in adults is 10–15 mg/kg/day (approximately 750–1000 mg/day) administered in two divided doses.
  - Pyridoxine is also routinely administered although interference with pyridoxine action is rarely encountered because the racemic mixture of D,L-penicillamine is no longer in use



D-Penicillamine: Treatment Target

- Clinical and biochemical improvement
- 24-h urinary copper excretion on treatment
  - Chronic (maintenance) treatment: UCu excretion 200–500 μg/24 h (3–8 μmol/24 h)
  - >500 μg/24 worry about absorption, adherence and diet
  - <100 μg/24 over treatment
  - Normalization of serum NCC

D-Penicillamine: Lots of Side Effects!

Early sensitivity reactions: fever, cutaneous eruptions, lymphadenopathy, neutropenia, thrombocytopenia, and proteinuria first 1–3 weeks → STOP

Nephrotoxicity: proteinuria or cellular elements in the urine → STOP

Bone marrow toxicity: severe thrombocytopenia or total aplasia that may be irreversible

Dermatological: progeric changes in the skin and elastosis perforans serpiginosa, pemphigus or pemphigoid lesions, lichen planus, and aphthous stomatitis.

Other: lupus-like syndrome marked by hematuria, proteinuria, and positive ANA, Goodpasture syndrome, severe allergic response upon restarting the drug after prior discontinuation, myasthenia gravis, polymyositis, loss of taste, immunoglobulin A depression, and serous retinitis.

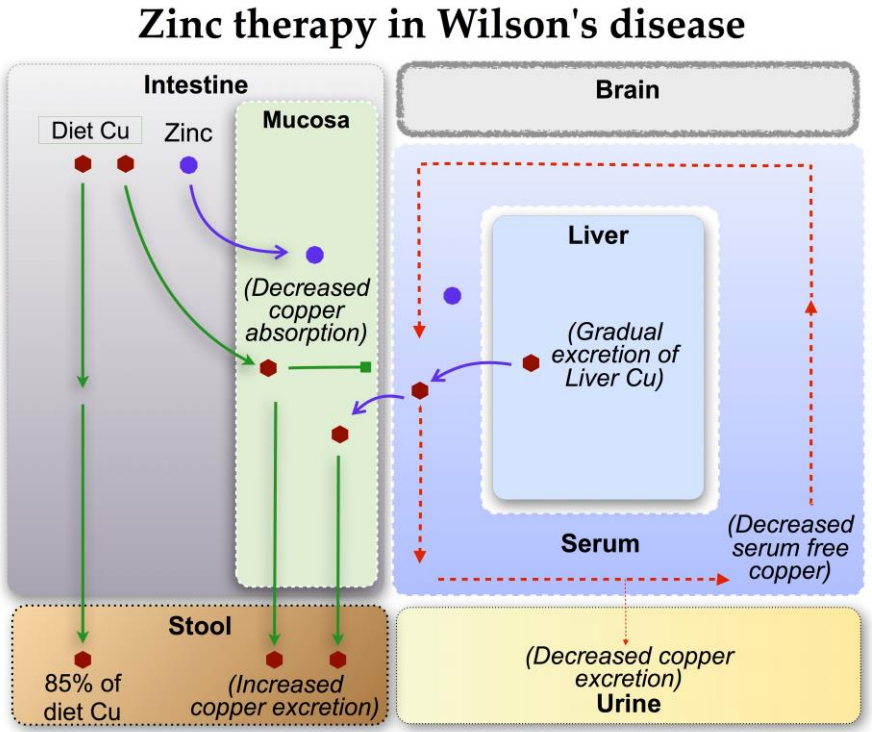
Hepatotoxicity and Hepatic siderosis

Trientine

- Promotes renal copper excretion.
- Blocks dietary copper absorption when given with food
  - Poorly absorbed from the gastrointestinal tract
- Indicated for those intolerant of D-penicillamine
  - Severe thrombocytopenia or neutropenia that can occur with splenomegaly.
- Paradoxical neurological worsening less common
- The tetrahydrochloride form of trientine was approved in 2022 by the Food and Drug Administration (FDA) for previously treated D-penicillamine–tolerant patients with WD.
  - Bioequivalence between trientine dihydrochloride and trientine tetrahydrochloride not established
- Trientine has few side effects.
  - Trientine also chelates iron do NOT Coadminister
- Similar treatment targets as D-Penicillamine

Zinc

- Inhibits intestinal uptake of copper by inducing enterocyte metallothionein, an endogenous chelator with a greater affinity for copper than for zinc.
- Copper-metallothionein is excreted in the feces as enterocytes are shed in normal turnover
- Zinc has very few side effects.
  - Gastric one third of patients (try a different zinc salt)
- Effective in the majority of but not all
- Paradoxical neurological deterioration is uncommon
- Can be used with impaired renal function
- Adults 150 mg/day elemental zinc in 2-3 divided doses without food



Zinc Treatment Targets:

- Clinical and biochemical improvement (ALT normalization)
  - Zinc lacks efficacy in a subset of patients with WD
- 24-h urinary excretion of copper: <100 µg (<1.6 µmol)/24 h
  - Overtreatment: Urinary copper excretion <20 µg [<0.3 µmol]/24 h with low serum copper and ceruloplasmin
- Clinical monitoring needs to be stringent.
  - Increased 24-h urinary copper excretion suggests poor adherence or increased dietary copper intake.
  - Urinary excretion of zinc, with target values of >1–2 mg/24 h, may be measured from time to time to check adherence
  - Rise in serum aminotransferases early sign of poor adherence or of treatment failure.

Treatment: Maintenance

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

Mainstay of treatment for WD lifelong oral pharmacotherapy and dietary copper restriction.

Monitoring of Treatment

- **21** Liver biochemistries, INR, CBC, urinalysis, and PE should be performed at least twice per year.
- **22** The 24-h urinary copper excretion while on medication, or in patients on D-penicillamine or trientine after a temporary period (48 h) off drug, should be measured yearly and more frequently if there are questions regarding adherence or if the medication dosage is adjusted.
  - Serum copper and ceruloplasmin may be followed for trends: very high or very low serum copper or serum copper disproportionately high for simultaneous serum ceruloplasmin. These may disclose exogenous copper intake (higher copper) or total-body depletion (lower copper and ceruloplasmin).
- **23** Overtreatment of WD may be indicated by development of cytopenias or retention of tissue iron associated with raised serum ferritin. It is confirmed by a low serum copper and a very low 24-h urinary copper output.
  - Oral chelators: 24-h urinary copper excretion disproportionately low for the dose of chelator being administered (below therapeutic target, specifically <100 μg/24 h or <1.6 μmol/24 h) suggests overtreatment.
  - Zinc therapy: 24-h urinary copper <20 μg/24 h (<0.3 μmol/24 h) suggests overtreatment.
- **24** Treatment failure may occur during treatment initiation or while on chronic treatment. It can complicate any WD medication. Concurrent diseases and nonadherence must be excluded. Pharmacological therapy should be revised in patients with treatment failure; however, with more advanced liver disease or liver failure, liver transplantation may be required.

Copper Levels in Food: *An Approximate Guide*

Average Copper (*Cu*) Content in *mg* per *100g* Portion

LOW <0.2 mg Cu/100g	mg	MEDIUM 0.2–1.0 mg Cu/100g	mg	HIGH 1.0–3.0 mg Cu/100g	mg	VERY HIGH ≥ 3 mg Cu/100g	mg
Meat		**Offal:**		**Liver Pâté - HIGH**		**Liver:**	
All fresh, frozen & tinned meat;	L	Brain – calves'	0.42	(varies according to animal - consult list on right...)		Calves'	23.86
Poultry (dark meat higher in *cu*)	O	Heart – lambs'	0.66			Lambs'	13.54
Fish - White/Oily	W	Kidney – pigs'	0.84			Cows'	6.40
Salmon/Tuna		**Meat:** Duck/goose	0.34			Pigs'	3.75
		Venison	0.36			*Chicken*	*0.52*
		Stock Cubes (Beef)	0.70				
Dairy		**Nuts:**		**Nuts:**			
Milk: Cows'	0.02	Peanut Butter	0.70	Cashews	2.20		
Goats'	0.05	Mixed Nuts	0.79	Brazil	1.76		
Butter:	0.03	Peanuts—roasted	0.60	Walnuts	1.34		
Cream: Single/Double	0.02	Coconut	0.56	Pine Nuts	1.32		
Cheese: Cheddar	0.03	Macademia Nuts	0.43	Hazelnuts	1.23		
Yogurt: Natural	0.04	Chestnuts	0.23	Pecan	1.07		
Flavoured	0.08	Marzipan - homemade	0.49	Peanuts (plain)	1.02		
		- shop bought	0.24	Pistachios	1.00		
				Almonds	1.00		
Eggs:		**Dried Fruits:**		**Shellfish**		**Shellfish:**	
Whole	0.10	Apricots	0.35	Crayfish	2.00	Scallops	10.00
White	0.05	Dates	0.26	Calamari (squid)	2.10	Whelks	7.00
Yolk	0.30	Figs	0.30	*Prawns*	*0.70*	Oysters	7.60
Oils/Fats		Raisins	0.39	*Shrimps*	*0.80*	Crab	4.80
Cooking Oils	*Trace*	Sultanas	0.40	*Mussels*	*0.48*	Clams	5.00
Butter/ Margarine	0.04	Dried Mixed Fruit	0.47	*Cockles*	*0.38*	*Lobster*	*2.90*
		Currants	0.81				
Fruits: Fresh		**Fruits:** Fresh		**Candied Fruit**			
Apples	0.02	Olives	0.23	Glace Cherries	1.28		
Oranges	0.05	Avocados	0.20	**Seeds**			
Pears	0.06	Banana	0.21	Sunflower	2.27		
Grapes	0.12	Kiwi	0.30	Sesame	1.46		
Prunes	0.14	Lemons	0.26	Pumpkin/Squash	1.40		
Berries (average)	0.16						
Vegetables/Tomatoes		**Vegetables/legumes**		**Legumes/sauces**			
Potatoes - new/old	0.07	Mushrooms	0.72	Beans-Butter (raw)	1.22		
- with skins	0.14	Asparagus	0.20	Soy (Edamame)	1.10		
- Sweet	0.14	Beans - Broad	0.43	Tomatoes - sun dried	1.40		
Root	≥0.08	Haricot (raw)	0.61	*Tomato Puree*	*0.53*		
Greens	≥0.06	Mung (raw)	0.97	*Tomato Ketchup*	*0.40*		
Salads	≥0.05	Red Kidney (raw)	0.68	*Brown Sauce*	*0.33*		
Lettuce, peppers		Baked	0.21	*Bovril*	*0.45*	Bakers' Yeast (dried)	5.00
Tomatoes - raw	0.01	Peas (raw)	0.23	*Marmite*	*0.30*		
- tinned	0.07	Chick Peas (cooked)	0.33	*Stock Cubes*	*0.71*		
Lentils, split boiled	0.19	Chips	>0.24	**Herbs:** Pepper	1.13		
		Spinach (boiled)	0.26	Basil (dried)	1.40		
		Parsley	0.52				
Bread/Rice/Pasta		**Pasta/Preserves/Cakes**		**Cereals**			
White bread (premium)	0.19	Pasta (cooked)	>0.46	Bran	1.34		
Wholemeal bread	*0.26*	Treacle (black)	0.43	All Bran	1.20		
White rice (cooked)	0.12	Jams (berries)	0.23	*Puffed Wheat*	*0.56*		
Brown rice	*0.33*	Mincemeat & fruit cake	0.20	*Weetabix*	*0.54*		
Porridge	0.06	Xmas Pudding	0.25	*Shredded Wheat*	*0.40*		
Spaghetti (white cooked)	0.10			*Muesli*	*0.36*		
Sweets/Desserts		**Confectionery/snacks**		**Chocolate/Sweets**		**Cocoa Powder**	
White chocolate bar	0.06	Milk Chocolate Bar	0.32	Dark chocolate (check amt of cocoa solids on packet)	>1.8	Cocoa powder (unsweetened)	3.80
Twix	0.08	Liquorice	0.39				
Cream Egg	0.10	Mars Bar	0.31				
Boiled sweets	0.09	Bounty Bar	0.47	Fruit Gums	1.43		
Pastries) Not con-	L	Bombay Mix	0.62	Drinking chocolate (sweetened)	1.10		
Cakes) taining	O	Twiglets	0.32				
Ice Cream) cocoa	W	Crisps	0.22				
		Cereal Crunchy bar	0.29				

Compiled from the Food Standards Agency (2002): **McCance & Widdowson's** *The Composition of Foods:* 6th Summary Ed., Cambridge: Royal Society of Chemistry

MYFOODDATA

Top 10 Foods Highest in Copper

0.9mg of Copper = 100% of the Daily Value (%DV)

1 Oysters

419% DV (3.8mg)
per 6 oysters

67 calories

2 Shiitake Mushrooms

144% DV (1.3mg)
per cup cooked

81 calories

3 Firm Tofu

106% DV (1mg)
per cup

363 calories

4 Sweet Potatoes

79% DV (0.7mg)
per cup mashed

258 calories

5 Sesame Seeds

78% DV (0.7mg)
per oz

160 calories

6 Cashews (Dry Roasted)

70% DV (0.6mg)
per 1 oz handful

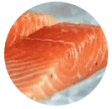
163 calories

7 Chickpeas (Garbanzo Beans)

64% DV (0.6mg)
per cup

269 calories

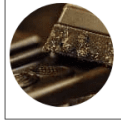
8 Salmon



61% DV (0.5mg)
per 6oz fillet

309 calories

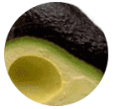
9 Dark Chocolate (70-85% Cocoa)



56% DV (0.5mg)
per 1oz square

170 calories

10 Avocados



42% DV (0.4mg)
per avocado

322 calories

https://wilsondisease.org/living-with-wilson-disease/copper-conscious-eating/;
https://www.wilsonsdisease.org.uk/store/pages/42870fb9-1af7-4e23-bcec-3eb7b451d1b0_WDSG_UK_Food_Copper_Content_of_Foods_081019.pdf.

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.