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Enfermedades Hepáticas y Digestivas

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INSTITUTO DE BIOMEDICINA DE SEVILLA

Hospital U Virgen del Rocío
UGC Aparato Digestivo

Universidad de Sevilla

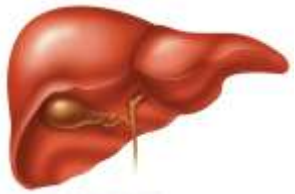
22 JORNADAS DE AVANCES EN HEPATOLOGIA

18/19 Mayo 2023

AULA MAGNA
(Facultad de Medicina)
Málaga
Asistencia libre

PROGRAMA DE DOCTORADO
Biomedicina, Investigación Traslacional y Nuevas Tecnologías en Salud.

Enfermedad de Wilson
Actualización de guías clínicas



Dr. Javier Ampuero
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Sevilla, España

PRACTICE GUIDANCE

A multidisciplinary approach to the diagnosis and management of Wilson disease: 2022 practice guidance on Wilson disease from the American Association for the Study of Liver Diseases

Michael L. Schilsky[1] | Eve A. Roberts[2] | Jeff M. Bronstein[3] | Anil Dhawan[4] | James P. Hamilton[5] | Anne Marie Rivard[6] | Mary Kay Washington[7] | Karl Heinz Weiss[8] | Paula C. Zimbrean[9]

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

Review

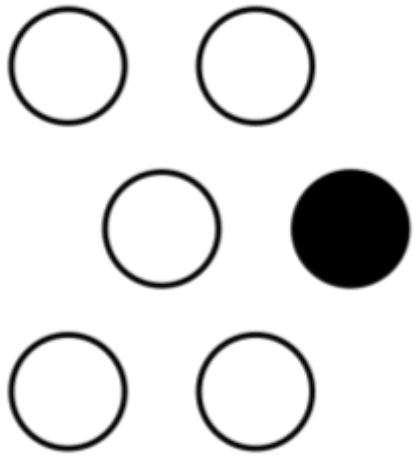
Investigation and management of Wilson's disease: a practical guide from the British Association for the Study of the Liver

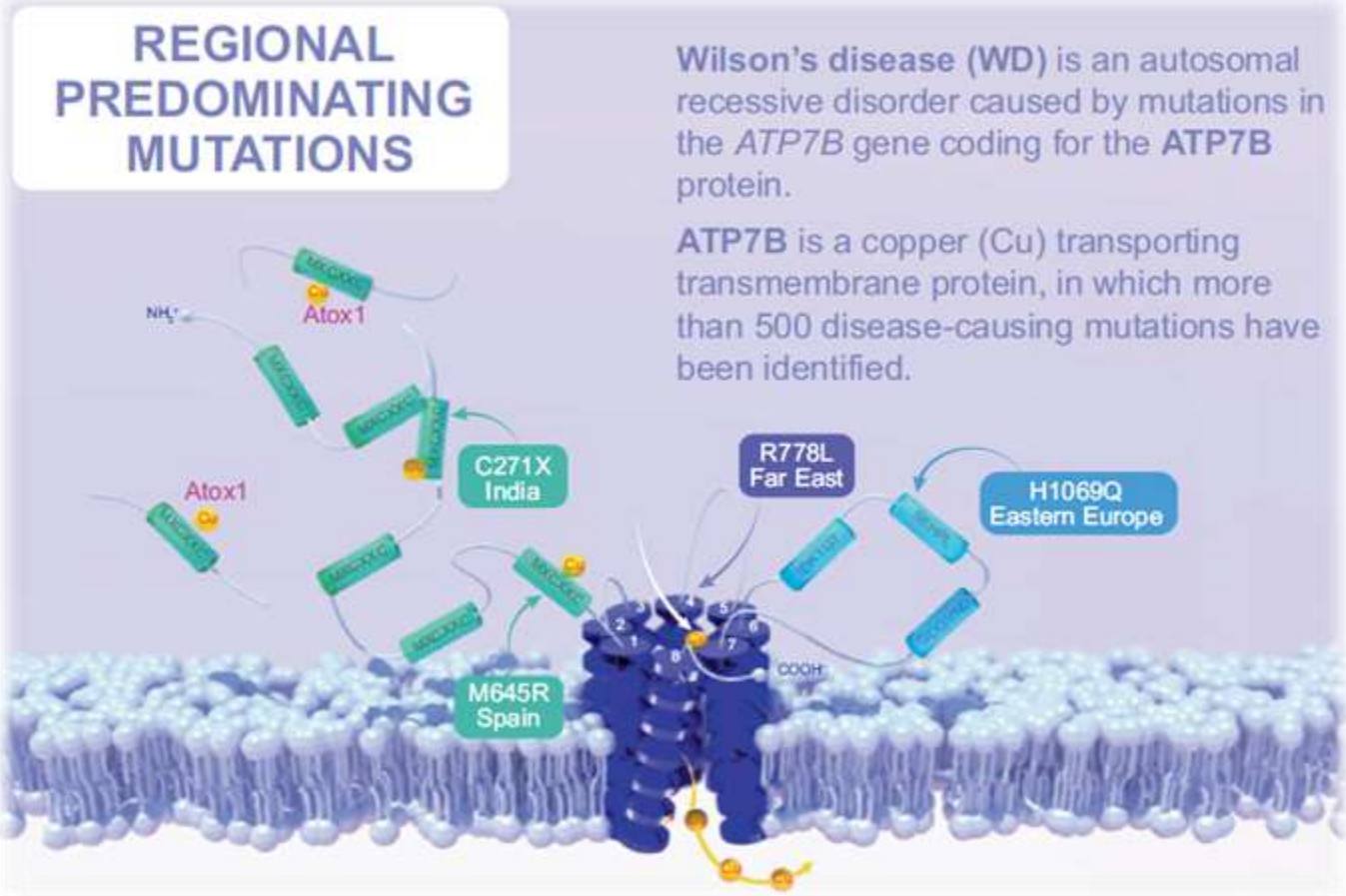
Samuel Shribman, Thomas Marjot*, Abubakar Sharif*, Sunitha Vimalesvaran*, Aftab Ala, Graeme Alexander, Anil Dhawan, James Dooley, Godfrey T Gillett, Deirdre Kelly, Alisdair McNeill, Thomas T Warner, Valerie Wheater, William Griffiths†, and Oliver Bandmann†, on behalf of the British Association for the Study of the Liver Rare Diseases Special Interest Group*

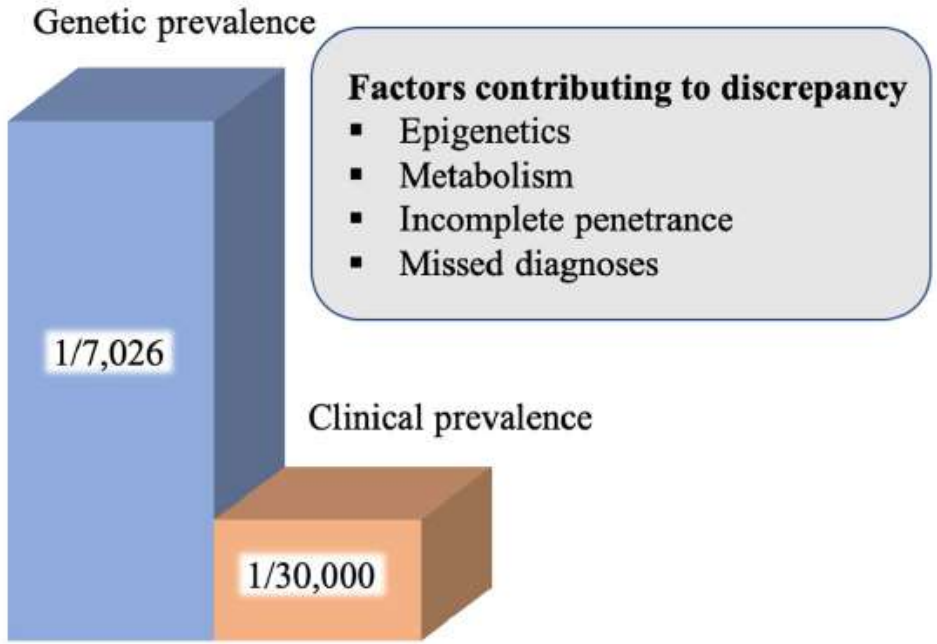
BASL
British Association for the Study of the Liver

Cuestiones generales

¿Algo especial?



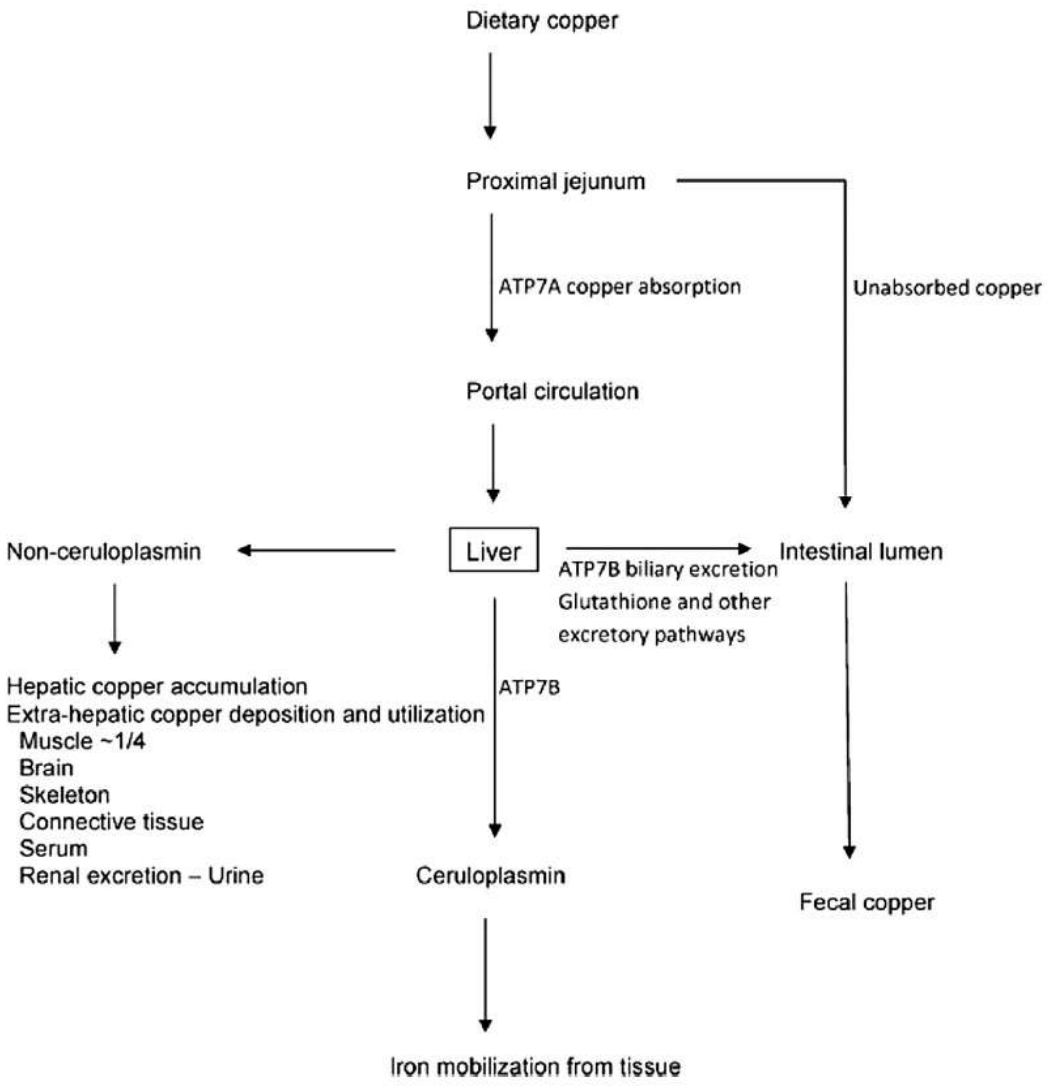


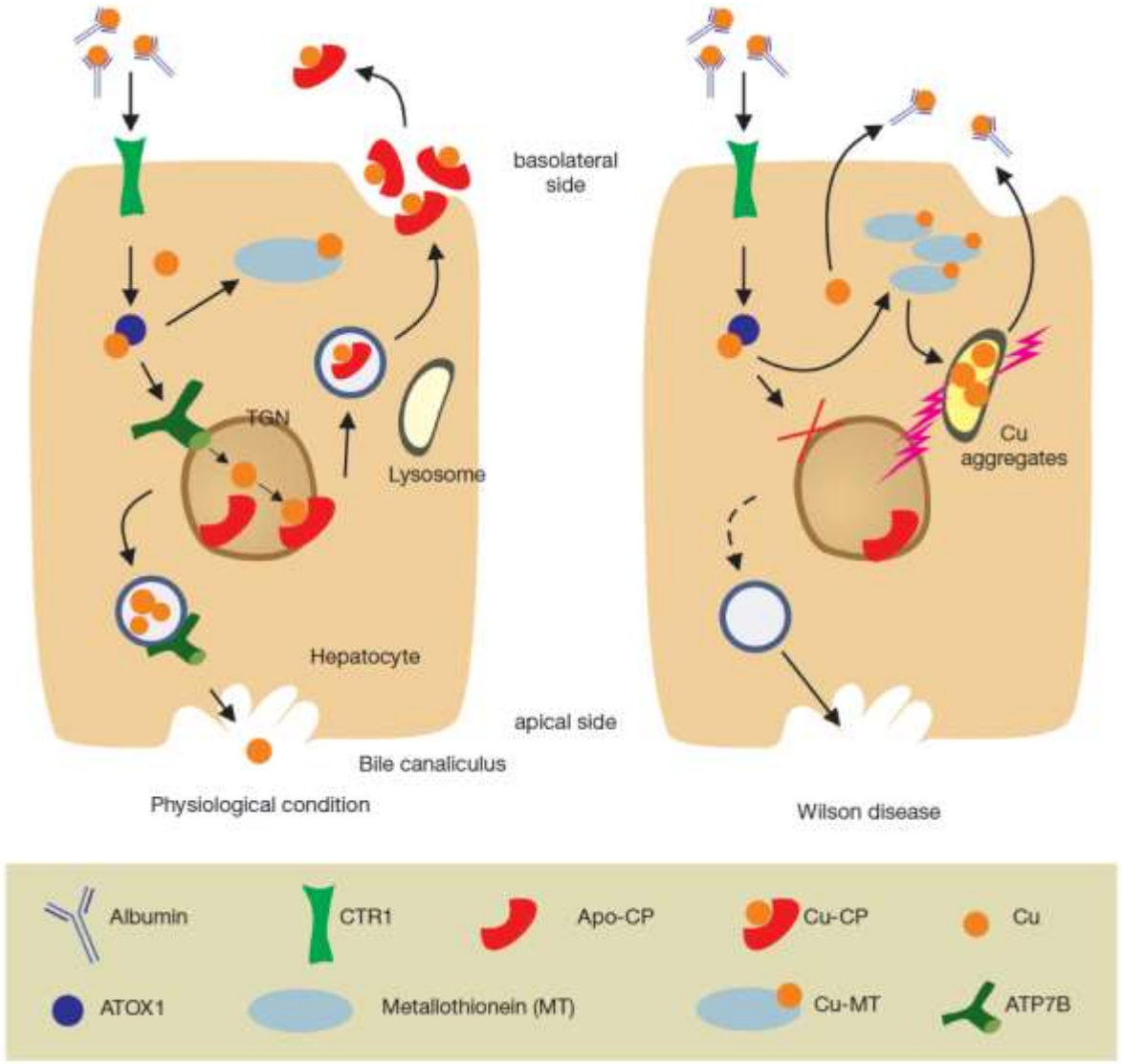


Ferenci et al. J Hepatol 2019

Leung et al. Clin Liver Dis 2021

PATOGENIA

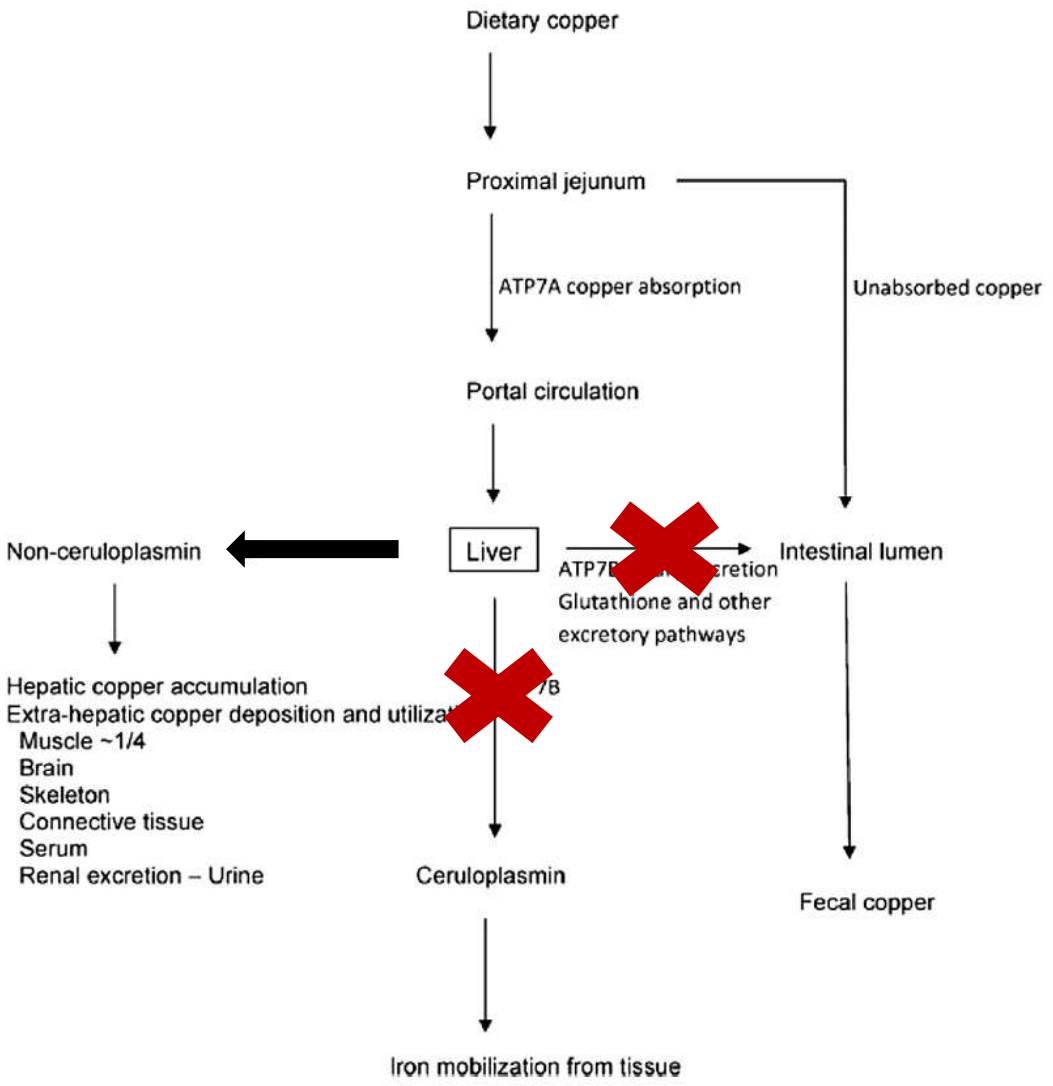




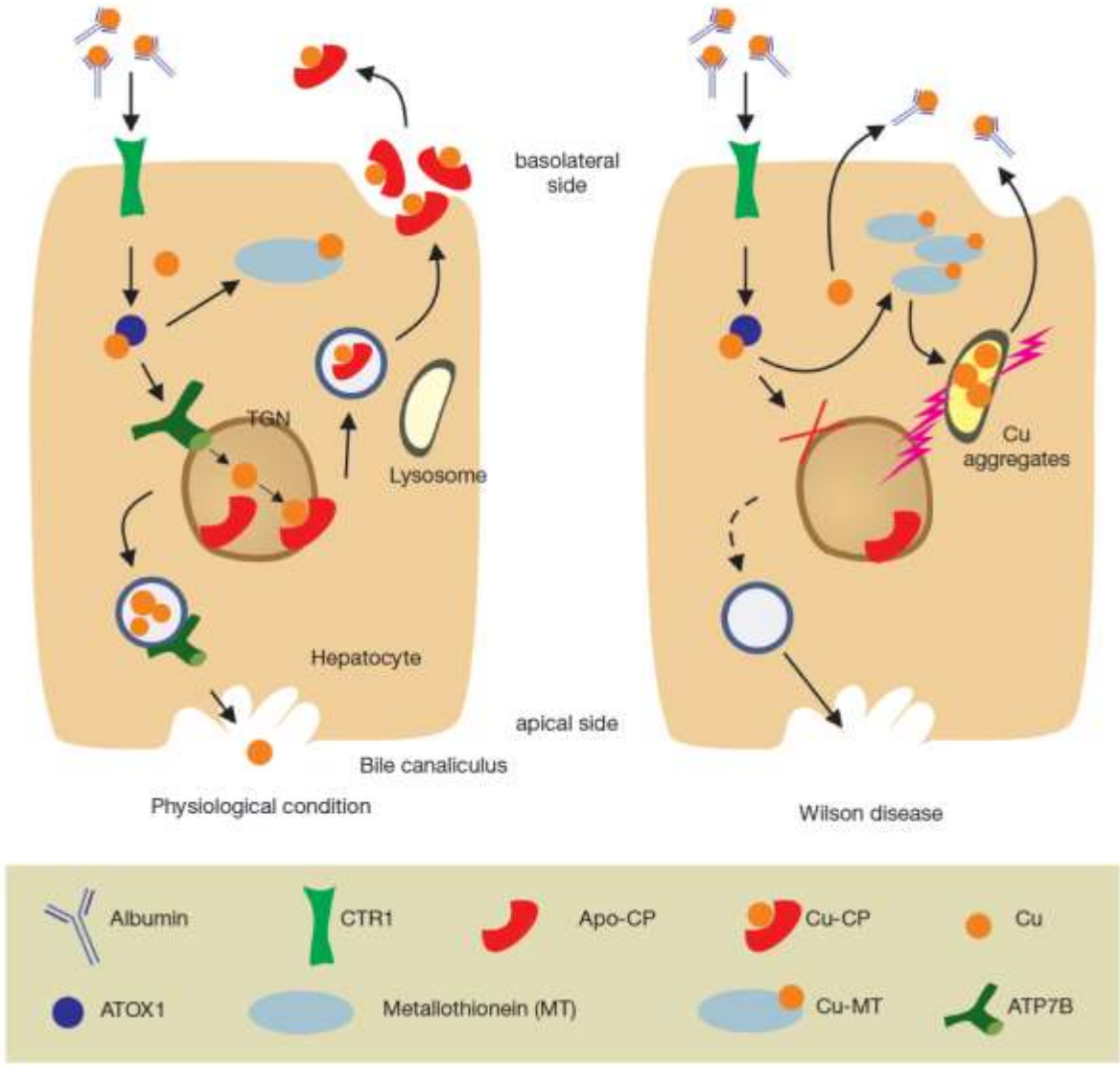
Rosencrantz et al. Semin Liver Dis 2011

Stremmel et al. Ann Transl Med 2021

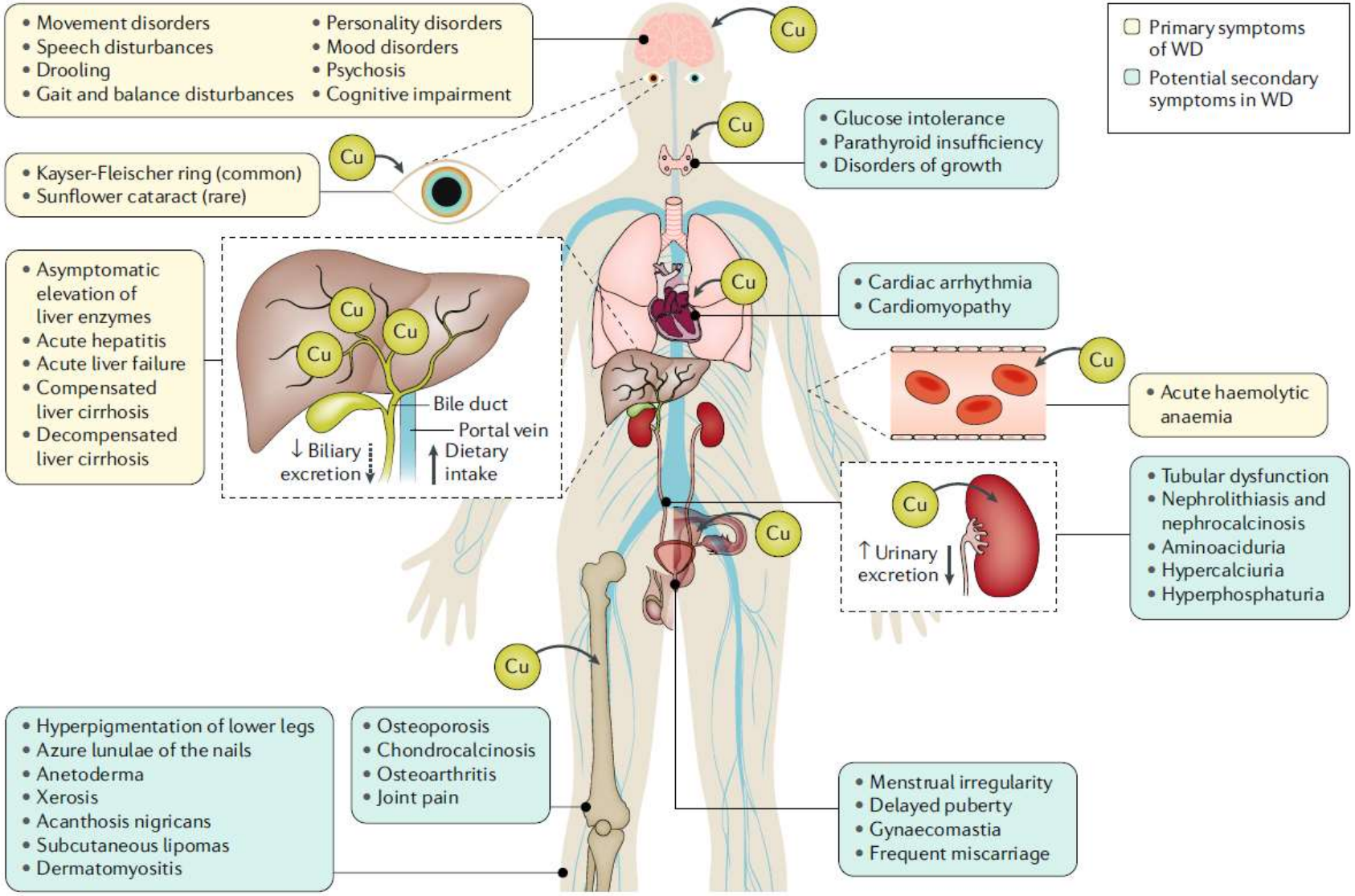
PATOGENIA



Rosencrantz et al. Semin Liver Dis 2011

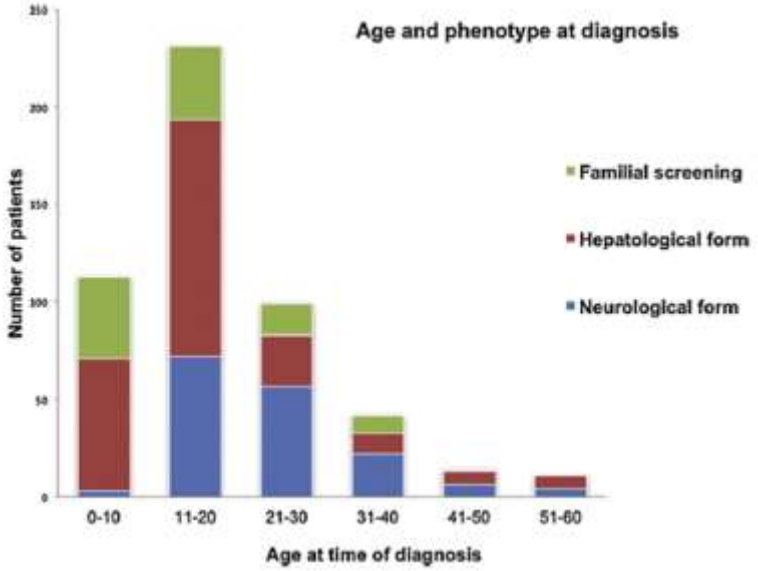


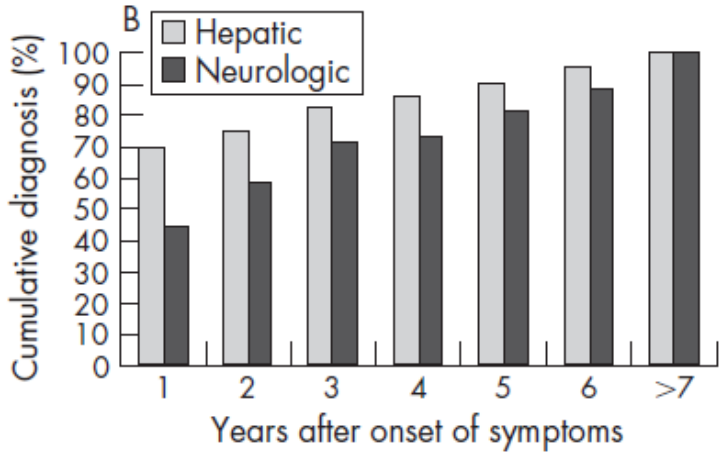
Stremmel et al. Ann Transl Med 2021



Członkowska et al. Nat Rev Dis Primers 2018

CLÍNICA: EDAD Y FORMA DE PRESENTACIÓN





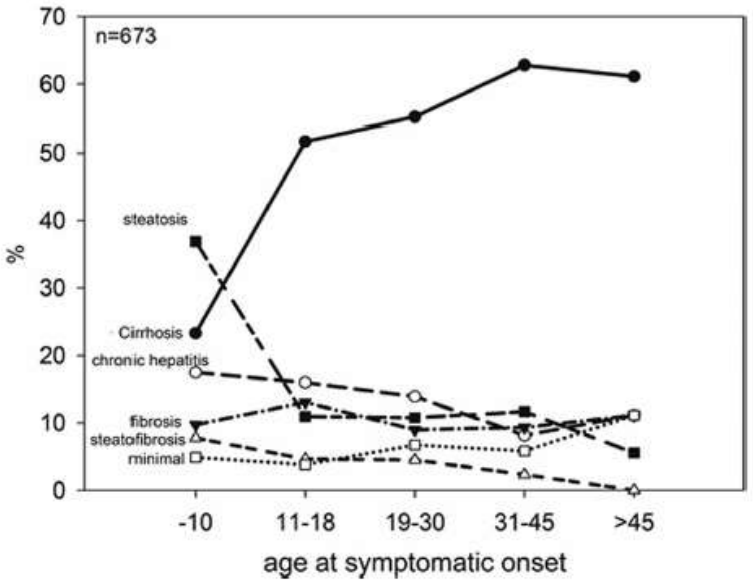


Table 1
Summary of neurologic symptoms at presentation based on 4 independent case series

Neurologic Manifestations at Onset	Patients (%)
Dysarthria	46–97
Gait abnormality/ataxia/cerebellar	28–75
Dystonia	38–69
Parkinsonism	12–58
Postural tremor	55
Dysphagia	50
Chorea/athetosis	6–30
Seizures	6–28
Rest tremor	4

Table 2. Clinical symptoms in Wilson's disease patients presenting with liver disease.

Author, Country, [Ref.]	Walshe, UK, [157]	Stremmel *et al.*, Germany, [39]	Schilsky *et al.*, USA, [142]	Scott *et al.*, UK, [158]	Ferenci, Austria, [
N with liver disease (out of)	87 (>250)	n.a. (51)	20* (320)	17* (45)	30 (64)
Presenting symptom					
Jaundice, anorexia, vomiting (%)	44	14	15	41	37
Ascites/edema (%)	26	14	50	24	23
Variceal hemorrhage (%)	6		10	6	3
Hemorrhagic diathesis (%)	8				3
Hemolysis (%)	20	10	5		10
Hepatomegaly/splenomegaly (%)	16	49	15	29	17
Acute liver failure (%)	n.a.	n.a.	n.a.	n.a.	17
Asymptomatic[§] (%)		18	5		23

¿Cómo abordar el diagnóstico?

Desafío en el horizonte

Síntomas y signos clínicos típicos	
Anillos de Kayser-Fleischer	
Presentes	2
Ausentes	0
Síntomas neurológicos**	
Severos	2
Moderados	1
Ausentes	0
Ceruloplasmina sérica	
Normal (>0,2g/L)	0
0,1-0,2g/L	1
<0,1g/L	2
Anemia hemolítica Coombs-negativa	
Presente	1
Ausente	0

Otros tests	
Cobre hepático (en ausencia de colestasis)	
>5x LSN (>4µmol/g)	2
0,8-4µmol/g	1
Normal (<0,8µmol/g)	-1
Gránulos Rodanina-positivos*	1
Cobre urinario (en ausencia de hepatitis aguda)	
Normal	0
1-2xLSN	1
>2xLSN	2
Normal, pero >5xLSN después de la D-penicilmamina	2
Análisis de mutaciones	
Detectadas en ambos cromosomas	4
Detectadas en 1 cromosoma	1
Sin mutaciones detectadas	0

PUNTUACIÓN TOTAL	Resultado evaluación:
4 o más	Diagnóstico confirmado
3	Diagnóstico posible, se necesitan más tests
2 o menos	Diagnóstico poco probable

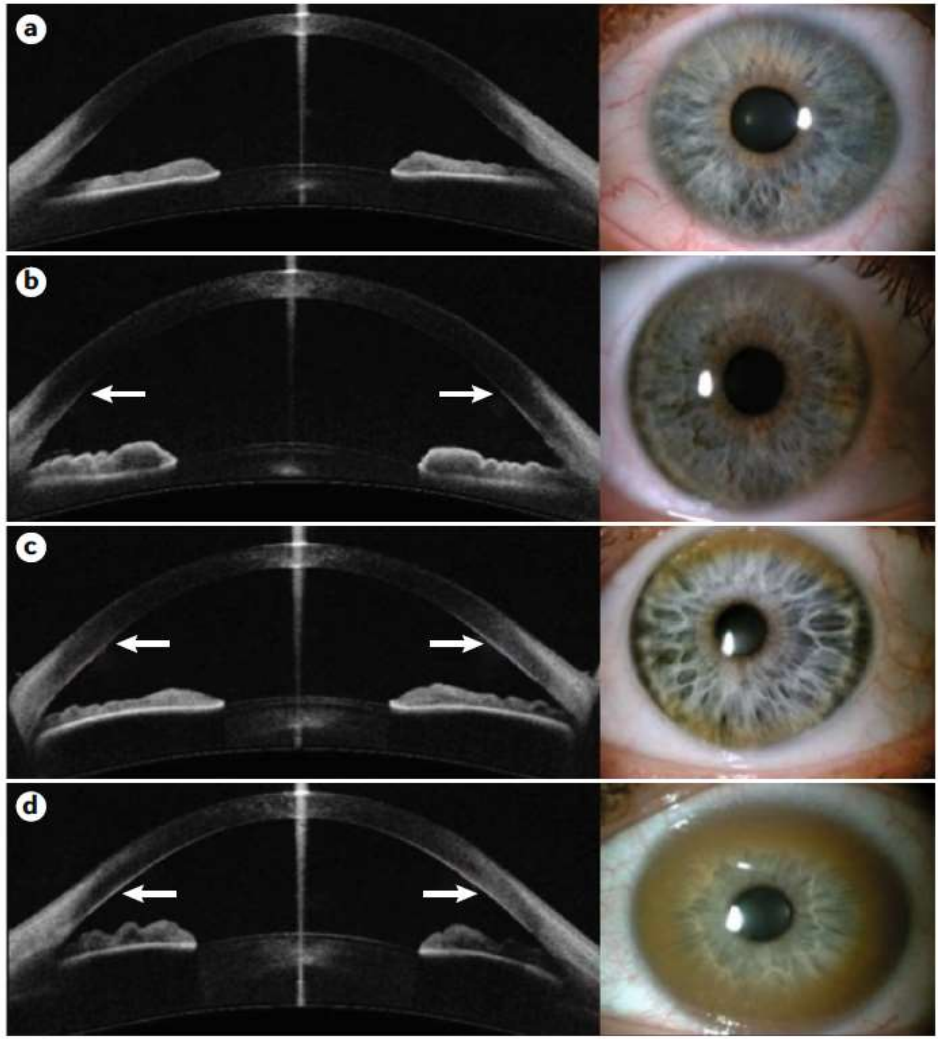
TABLE 2. NEW DIAGNOSTIC TOOLS

Parameter	Description	WD Diagnosis
Radioactive copper (^{64}Cu) ratio	^{64}Cu infused intravenously and measured within the liver and serum after 2, 24, and 48 hours[14]	
24 hours/2 hours		<0.3
48 hours/2 hours		<0.395[14]
Genetic analysis	Polymerase chain reaction amplification of *ATP7B* mutations Whole-genome sequencing: assesses all liver disease genes, not just WD	Disease-causing mutations
REC	Serum assay. REC = exchangeable copper/serum copper	>2.08 µmol/L for extrahepatic disease >1.53 µmol/L for hepatic disease Normal range: 0.62 and 1.15 µmol/L[15]

CRITERIOS DIAGNÓSTICOS: ANILLO KF

Typical clinical symptoms and signs		Other tests	
Kayser-Fleischer rings		**Liver copper** (in the absence of cholestasis)	
Present	2	>250 µg (>4 µmol)/g dry weight	2
Absent	0	50–249 µg (0.8–4 µmol)/g	1
Neurologic symptoms **		Normal: <50 µg (<0.8 µmol)	−1
Severe	2	Rhodanine-pos. granules *	1
Mild	1	**Urinary copper** (in the absence of acute hepatitis)	
Absent	0	Normal	0
Serum ceruloplasmin		1–2 × ULN	1
Normal (>0.2 g/l)	0	>2 × ULN	2
0.1–0.2 g/l	1	Normal but >5 × ULN after d-penicillamine	2
<0.1 g/l	2	**Mutation analysis**	
Coombs-negative haemolytic anaemia		On both chromosomes detected	4
Present	1	On 1 chromosome detected	1
Absent	0	No mutations detected	0

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



Członkowska et al. Nat Rev Dis Primers 2018

CRITERIOS DIAGNÓSTICOS

Typical clinical symptoms and signs		Other tests	
Kayser-Fleischer rings		**Liver copper** (in the absence of cholestasis)	
Present	2	>250 µg (>4 µmol)/g dry weight	2
Absent	0	50–249 µg (0.8–4 µmol)/g	1
Neurologic symptoms**		Normal: <50 µg (<0.8 µmol)	−1
Severe	2	Rhodanine-pos. granules*	1
Mild	1	**Urinary copper** (in the absence of acute hepatitis)	
Absent	0	Normal	0
Serum ceruloplasmin		1–2 × ULN	1
Normal (>0.2 g/l)	0	>2 × ULN	2
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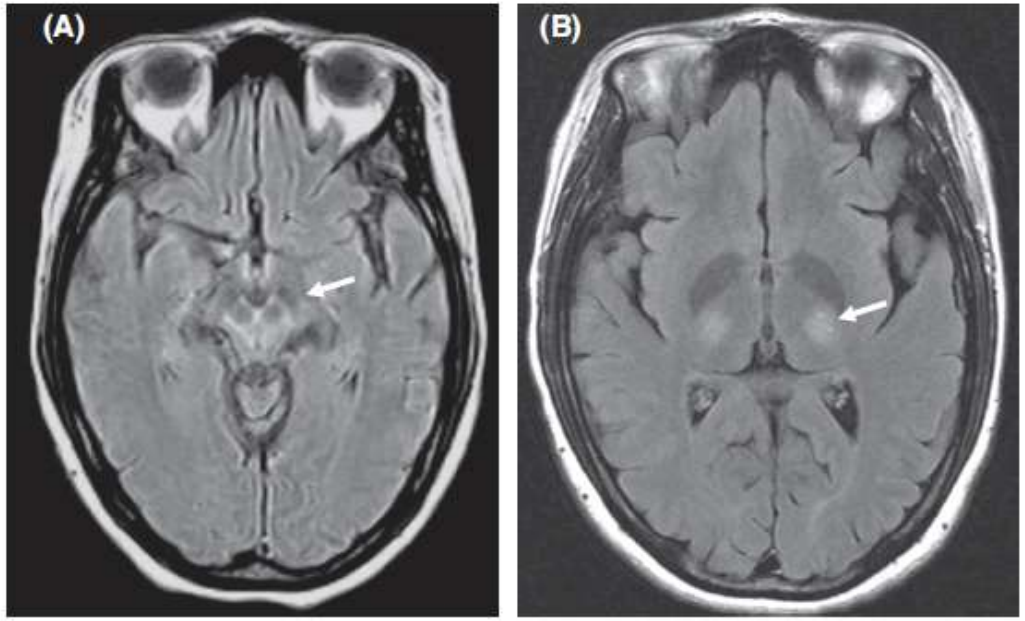

3.8 All patients with a confirmed diagnosis of Wilson's disease should have an MRI brain scan, irrespective of their initial presentation

Shribman et al. Lancet Gastroenterol Hepatol 2022

Schilsky et al. Hepatology 2022

CRITERIOS DIAGNÓSTICOS: BIOPSIA HEPÁTICA

Typical clinical symptoms and signs		Other tests	
Kayser-Fleischer rings		**Liver copper** (in the absence of cholestasis)	
Present	2	>250 μg (>4 μmol)/g dry weight	2
Absent	0	50–249 μg (0.8–4 μmol)/g	1
Neurologic symptoms **		Normal: <50 μg (<0.8 μmol)	−1
Severe	2	Rhodanine-pos. granules *	1
Mild	1	**Urinary copper** (in the absence of acute hepatitis)	
Absent	0	Normal	0
Serum ceruloplasmin		1–2 × ULN	1
Normal (>0.2 g/l)	0	>2 × ULN	2
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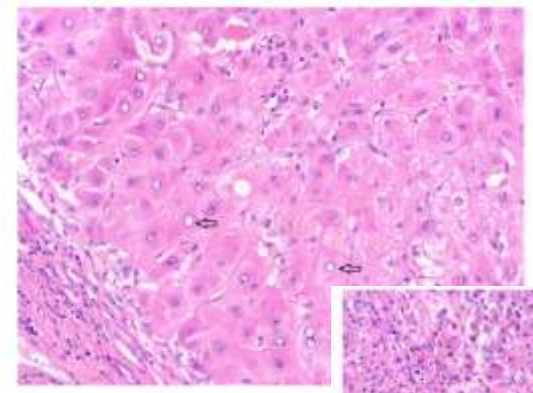
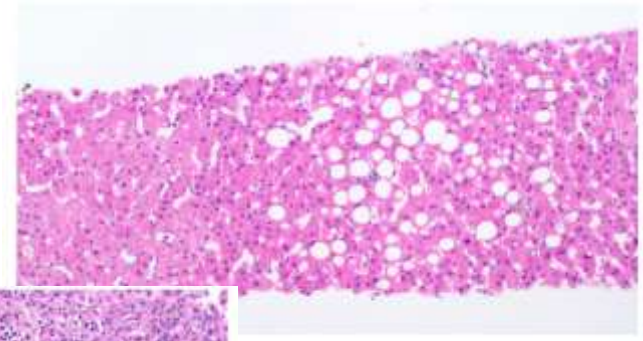


Fig. 3. Glycogenated nuclei in WD liver (arrow) magnification).



/D showing only mild large droplet steatosis × magnification).

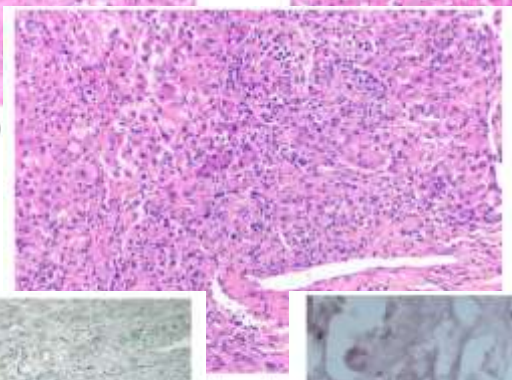


Fig. 6. Variable copper staining by Rhodanine in cirrhotic liver. Nodule to the right shows many brown red copper granules (arrows) and nodule to the left shows scant staining (asterisks) (Rhodanine stain, 20× magnification).

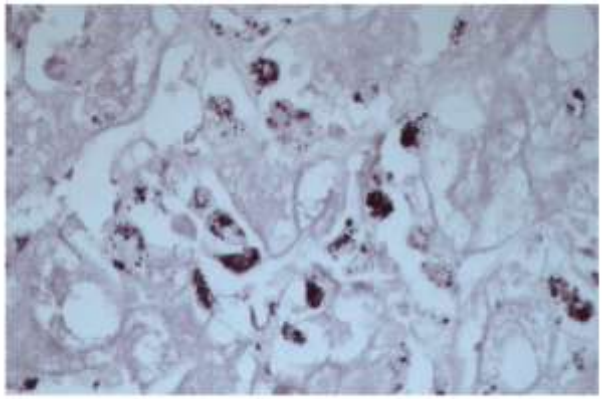


Fig. 8. Copper associated protein staining black in hepatocytes with orcein stain (40× magnification).

Guindi et al. Semin Diagn Pathol 2019

CRITERIOS DIAGNÓSTICOS: GENÉTICA

Typical clinical symptoms and signs		Other tests	
Kayser-Fleischer rings		**Liver copper** (in the absence of cholestasis)	
Present	2	>250 µg (>4 µmol)/g dry weight	2
Absent	0	50–249 µg (0.8–4 µmol)/g	1
Neurologic symptoms **		Normal: <50 µg (<0.8 µmol)	−1
Severe	2	Rhodanine-pos. granules *	1
Mild	1	**Urinary copper** (in the absence of acute hepatitis)	
Absent	0	Normal	0
Serum ceruloplasmin		1–2 × ULN	1
Normal (>0.2 g/l)	0	>2 × ULN	2
0.1–0.2 g/l	1	Normal but >5 × ULN after d-penicillamine	2
<0.1 g/l	2	**Mutation analysis**	
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Present	1	On 1 chromosome detected	1
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TOTAL SCORE	Evaluation:
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3	Diagnosis possible, more tests needed
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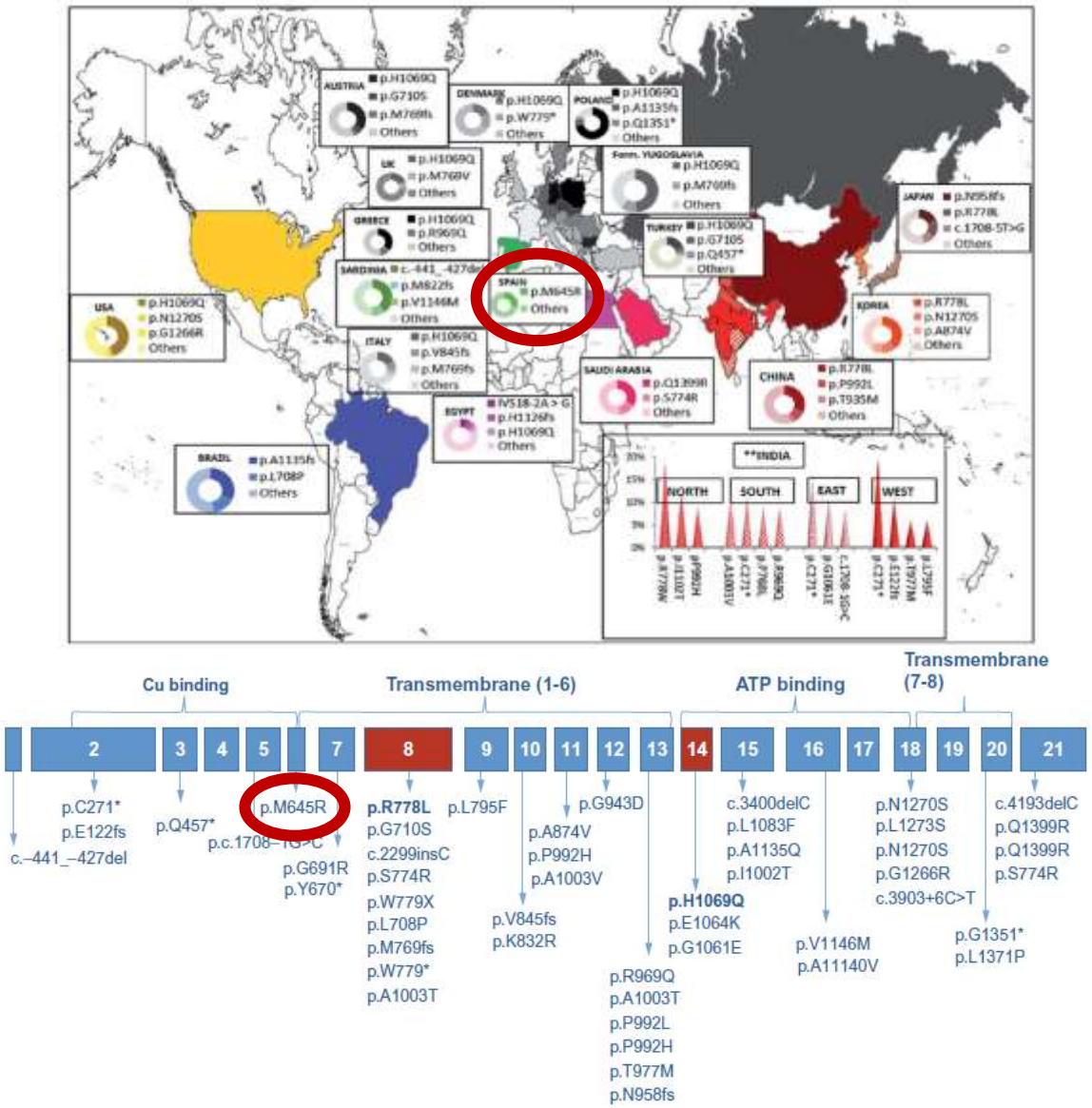


Chang et al. Handb Clin Neurol 2017

CRITERIOS DIAGNÓSTICOS: A TENER EN CUENTA

Typical clinical symptoms and signs		Other tests	
Kayser-Fleischer rings		**Liver copper** (in the absence of cholestasis)	
Present	2	>250 µg (>4 µmol)/g dry weight	2
Absent	0	50–249 µg (0.8–4 µmol)/g	1
Neurologic symptoms **		Normal: <50 µg (<0.8 µmol)	−1
Severe	2	Rhodanine-pos. granules #	1
Mild	1	**Urinary copper** (in the absence of acute hepatitis)	
Absent	0	Normal	0
Serum ceruloplasmin		1–2 × ULN	1
Normal (>0.2 g/l)	0	>2 × ULN	2
0.1–0.2 g/l	1	Normal but >5 × ULN after d-penicillamine	2
<0.1 g/l	2	**Mutation analysis**	
Coombs-negative haemolytic anaemia		On both chromosomes detected	4
Present	1	On 1 chromosome detected	1
Absent	0	No mutations detected	0
TOTAL SCORE		**Evaluation:**	
4 or more		Diagnosis established	
3		Diagnosis possible, more tests needed	
2 or less		Diagnosis very unlikely	

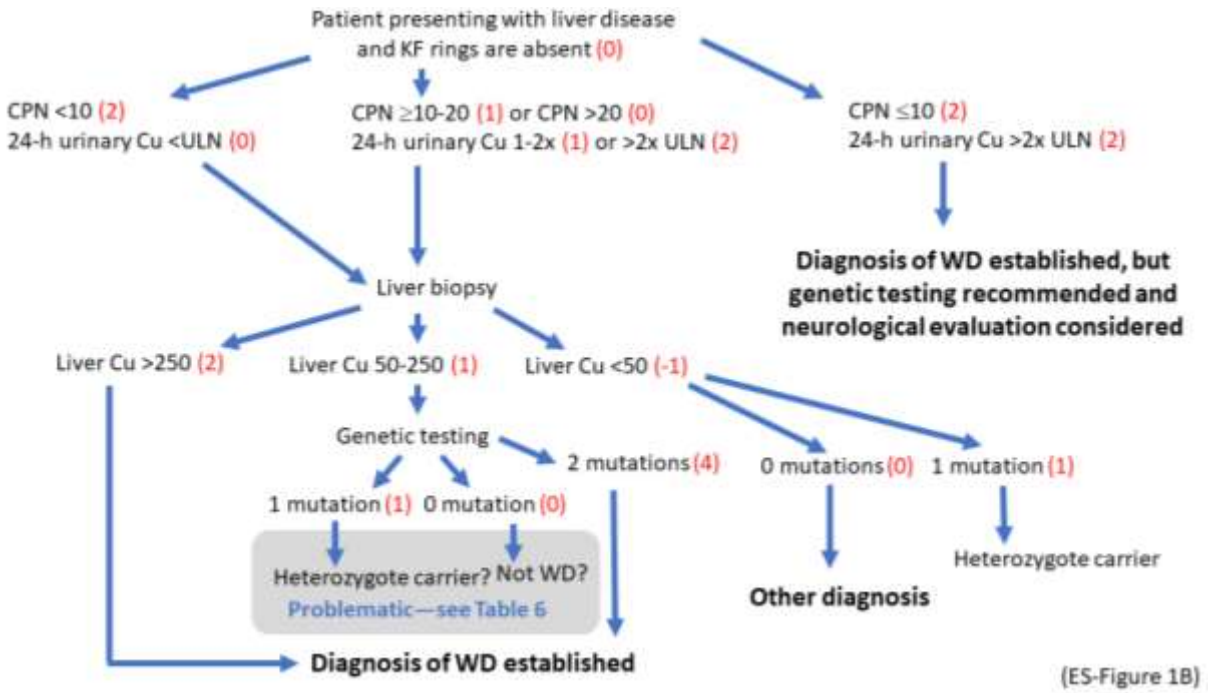
Subgroup	Hepatic (%)	Neurologic (%)
Serum ceruloplasmin (<20 mg/dL)	59	85
Urine copper (>100 µg/day)	90	78
Liver copper content (>250 µg/gm)	90	93
KF rings (on slit lamp examination)	41	90

Test	Typical finding	False 'negative'	False 'positive'
Serum ceruloplasmin	Decreased in patients with WD compared with healthy controls	• Normal levels in patients with marked hepatic inflammation • Overestimation by immunological assay • Pregnancy • Oestrogen therapy	Low levels in patients with malabsorption, malnutrition and/or aceruloplasminemia and in heterozygotes
24 h urinary copper	• Adults: >100 µg (1.6 µmol) per 24 h • Child: >40 µg (0.64 µmol) per 24 h	• Normal levels caused by incorrect collection • Normal levels in children without liver disease	• Increased in hepatocellular necrosis • Increased in cholestasis • May appear increased owing to sample contamination
Non-ceruloplasmin-bound copper	>10 µg dl^{-1} (1.6 µmol per litre)	May appear normal or negative if ceruloplasmin is measured by immunological assay	NA
Hepatic copper	250 µg (4 µmol) g^{-1} dry weight	• Regional variation in patients with active liver disease • Regional variation in patients with regenerative nodules	• Increased in cholestatic syndromes • Increased in idiopathic copper toxicosis disorders
Kayser-Fleischer rings by slit-lamp examination	Present	• Absent in up to 50% of patients with hepatic WD • Absent in most asymptomatic siblings	May be present in primary biliary cholangitis (primary biliary cirrhosis)

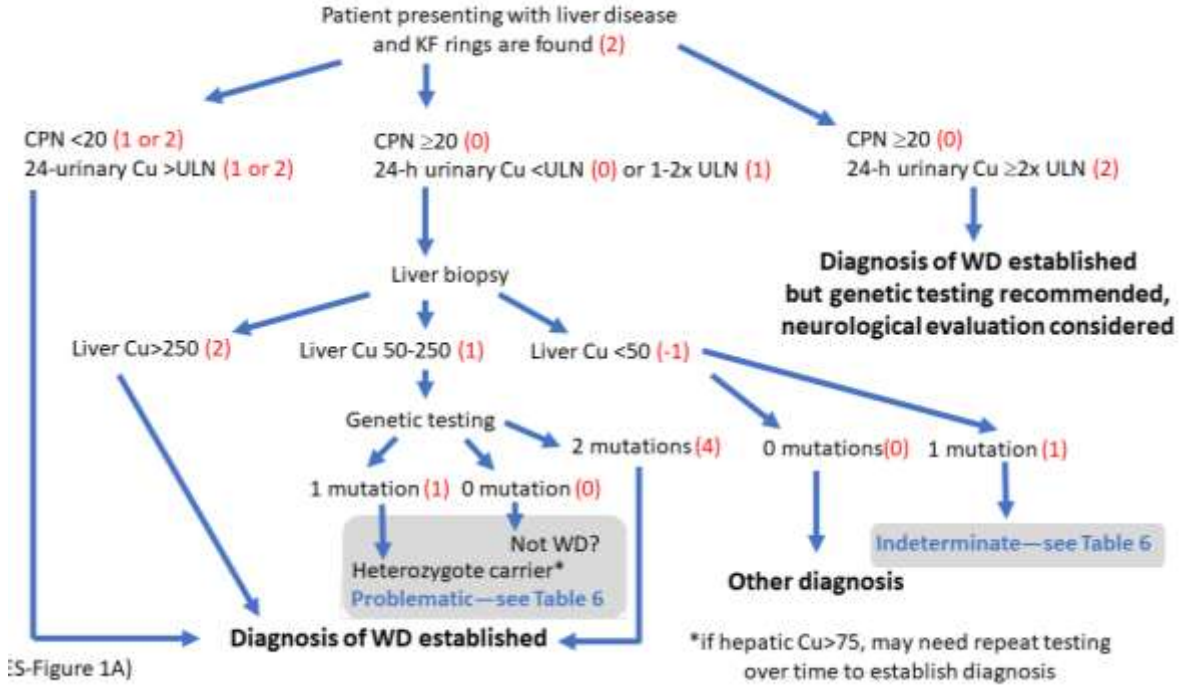
Shribman et al. Ann Trans Med 2019

Członkowska et al. Nat Rev Dis Primers 2018

DIAGNÓSTICO: APROXIMACIÓN SEGÚN ESCENARIO



(ES-Figure 1B)



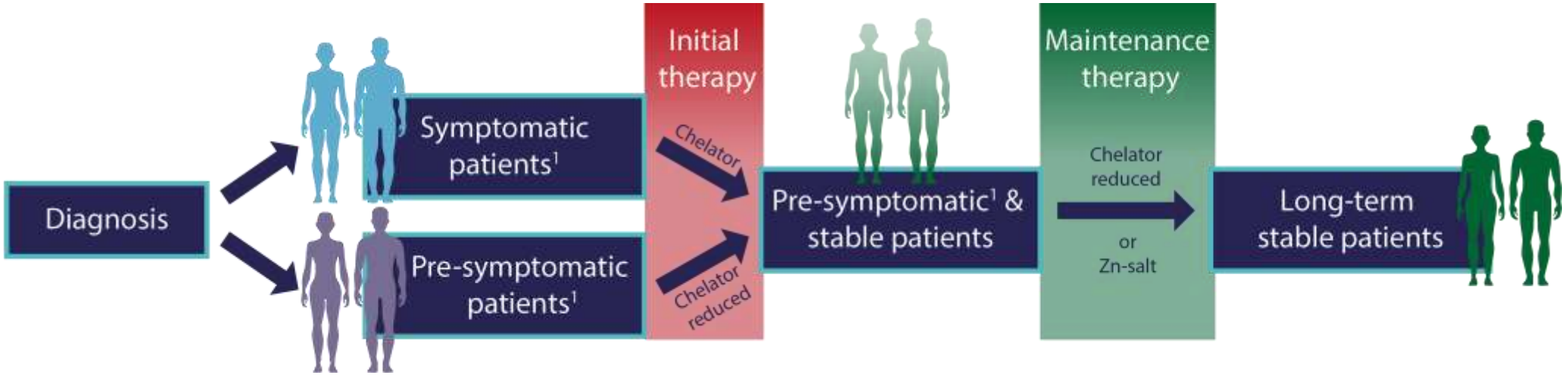
(ES-Figure 1A)

Schilsky et al. Hepatology 2022

¿Se tratan todos los pacientes?

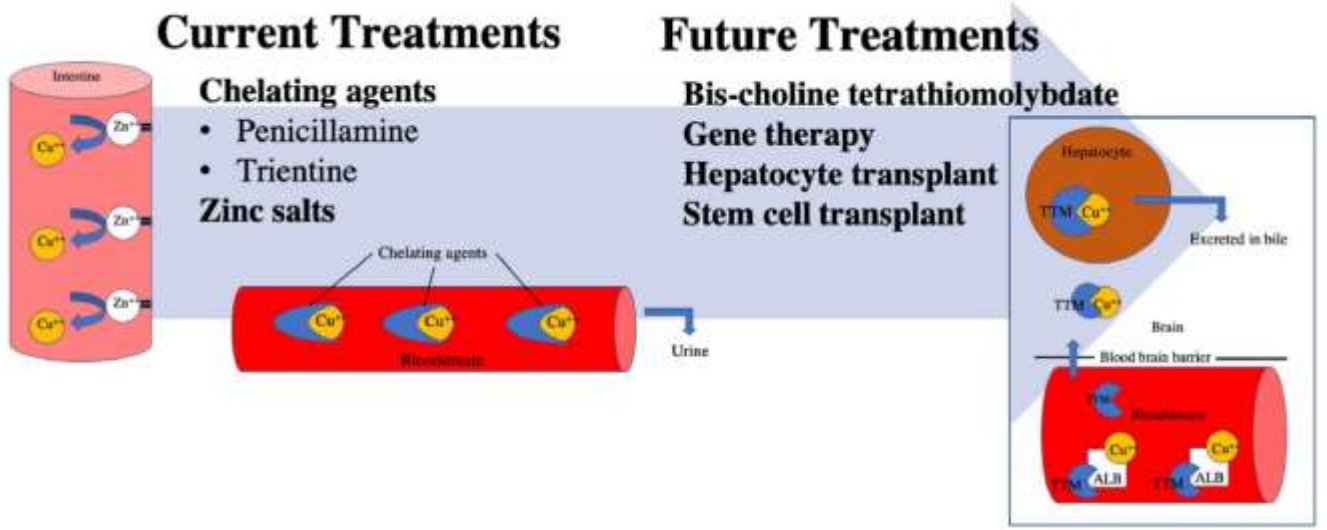
Sí o no, esa es la cuestión

ESQUEMA DE TRATAMIENTO



Guidance statements 15–18

15. All patients with a newly-established diagnosis of WD should be initiated on lifelong medical therapy for WD. Timing of treatment in children who are less than 3 years-old should be individualized to the degree of organ damage.
16. Initial treatment for symptomatic patients with WD should include a chelating agent (D-penicillamine or trientine). Trientine may be better tolerated.
17. Treatment of asymptomatic patients with WD can be a chelating agent (D-penicillamine or trientine at a lower dose than for initial therapy) or zinc.
18. The suitability for transition to maintenance therapy for WD includes time on therapy (generally more than 1 year) and favorable clinical and biochemical response to therapy. Maintenance therapy may be a lower dose of chelating agent (D-penicillamine or trientine) or full-dose zinc.



Leung et al. Clin Liver Dis 2021

Schilsky et al. Hepatology 2022

¿Cuál es el tratamiento actual?

Las piezas del puzzle

Guidance statements 15–18

15. All patients with a newly-established diagnosis of WD should be initiated on lifelong medical therapy for WD. Timing of treatment in children who are less than 3 years-old should be individualized to the degree of organ damage.
16. Initial treatment for symptomatic patients with WD should include a chelating agent (D-penicillamine or trientine). Trientine may be better tolerated.
17. Treatment of asymptomatic patients with WD can be a chelating agent (D-penicillamine or trientine at a lower dose than for initial therapy) or zinc.
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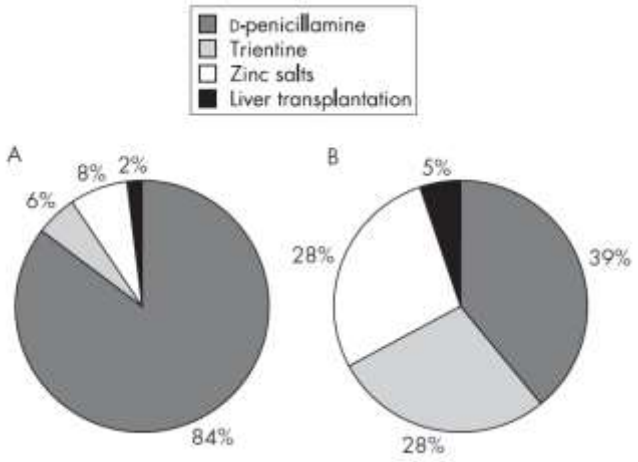

	Level of evidence
(Continued from previous page)	
Initial management	
4.1 All children with paediatric acute liver failure or decompensated liver disease should be urgently referred to a paediatric liver transplant centre	2
4.2 Adults with acute liver function should be urgently referred to a liver transplant centre	2
4.3 Liver transplantation is indicated in children who have decompensated liver disease with encephalopathy	2
4.4 Liver transplantation should be considered in all adults with acute liver failure	2
4.5 The new Wilson index should be used for prognosis and to facilitate decision making for liver transplantation in children	3
4.6 Penicillamine monotherapy is the first-line treatment for children and adults in the UK and should be introduced in consultation with a specialist centre for Wilson's disease	3
4.7 Trientine dihydrochloride or tetrahydrochloride can be used in children and adults intolerant to penicillamine or at increased risk of adverse effects	3
4.8 Penicillamine should be introduced gradually with dose increments of 125–250 mg per week in children	4
4.9 Penicillamine should be introduced gradually with dose increments of 125–250 mg per week in adults with neurological or psychiatric symptoms	4
4.10 Penicillamine can be introduced more quickly in adults presenting with decompensated liver disease in the absence of neurological symptoms or neuroimaging abnormalities	4
4.11 A full blood count, liver function tests, renal profile, and urine dipstick should be performed to monitor for adverse effects before starting penicillamine, after 1 week of treatment and then every 2 weeks for 3 months	4
4.12 Zinc salts are considered a third-line treatment for adults in the UK and should only be initiated by specialist centres; they are not recommended as monotherapy in patients with cirrhosis unless other treatments are unavailable or contraindicated	3
4.13 We cannot make a strong recommendation for the use of zinc salts in children because of inadequate data; zinc salts have been used by paediatric hepatologists in children identified through family screening, or as maintenance therapy with or without chelators	NA
4.14 Dietary copper intake should be restricted in the first year of treatment; decisions to continue this after 1 year should consider response to treatment, and adherence and impact on quality of life	4
4.15 Patients with neurological symptoms should have regular follow up with a movement disorders specialist for a minimum of 12 months after treatment initiation	4
4.16 24-h urinary copper output while continuing medication (on treatment) should be measured within the first 2 months to confirm an adequate copper excretion	4

	Children	Adults without neurological or psychiatric symptoms	Adults with neurological or psychiatric symptoms	Maintenance dose (typically after 2 years)	Adverse effects
Penicillamine	125–250 mg per day slowly increasing by 125–250 mg per week to 20 mg/kg per day in two divided doses (maximum 1500 mg/day)	1000–1500 mg per day in two divided doses	125–250 mg per day, slowly increasing by 125–250 mg per week, to 1000–1500 mg per day in two divided doses	10–20 mg/kg per day in two divided doses	Early reactions: hypersensitivity reactions (fever and rash), proteinuria, bone marrow suppression (thrombocytopenia and neutropenia), altered sense of taste or smell, and paradoxical neurological worsening. Late reactions: lupus-like syndrome, Goodpastures syndrome, elastosis perforans serpiginosa, cutis laxa, and poor wound healing
Trientine	150–200 mg per day, slowly increasing by 150–200 mg per week to 400–1000 mg per day for trientine dihydrochloride (Cufence) or 225–600 mg per day for trientine tetrahydrochloride (Cuprior) in two divided doses	800–1600 mg per day for trientine dihydrochloride (Cufence) or 450–975 mg per day for trientine tetrahydrochloride (Cuprior) in two divided doses	150–200 mg per day, slowly increasing by 150–200 mg per week to 800–1600 mg per day for trientine dihydrochloride (Cufence) or 450–975 mg per day for trientine tetrahydrochloride (Cuprior) in two divided doses	800–1600 mg per day for trientine dihydrochloride (Cufence) or 450–975 mg per day for trientine tetrahydrochloride (Cuprior) in two divided doses	Urticaria or other rashes, arthralgia, myalgia, proteinuria, haematuria, sideroblastic anaemia, and paradoxical neurological worsening
Zinc salts	25 mg daily if patient <6 years; 25 mg three times daily if patients aged 6–16 years or <50 kg; 50 mg three times daily if patient >16 years or >50 kg	50 mg three times daily if patient >50 kg	50 mg three times daily if patient >50 kg	25–50 mg three times a day	Nausea, abdominal pain, gastritis, and paradoxical neurological worsening

Dosing for penicillamine and zinc salts are based on experience of the authors, and dosing for trientine dihydrochloride and trientine tetrahydrochloride on the basis of the summary of product characteristics by the manufacturer. The recommended doses of trientine dihydrochloride and tetrahydrochloride are expressed as mg of trientine base as opposed to trientine salt. Chelating agents and zinc salts should be taken on an empty stomach.

Table 2: **Dosing and adverse effects for penicillamine, trientine, and zinc salts**

Shribman et al. Lancet Gastroenterol Hepatol 2022

Table 3. Details of Patients Who Failed to Respond to Treatment

						Event "treatment failure" occurred				
Patient no.	Sex	Diagnosis by family screening	Initial presentation	Kayser-Fleischer rings at diagnosis	Liver cirrhosis at diagnosis	Under therapy with	Time on this medication (*y*)	Time from diagnosis to failure (*y*)	First-line therapy	Rescue therapy
7	Female	No	Hepatic	None	None	Zinc	9.93	17.05	D-penicillamine	Trientine
15	Male	No	Hepatic	Yes	Yes	Zinc	1.16	34.75	D-penicillamine	Trientine
25	Female	No	Asymptomatic	Yes	None	Zinc	3.63	7.99	D-penicillamine	Trieninte
31	Female	Yes	Hepatic	Not determined	None	Zinc	1.00	13.01	D-penicillamine	D-penicillamine
39	Female	Yes	Hepatic	None	Yes	Zinc	3.11	3.11	Zinc	Trientine
69	Male	No	Mixed	Yes	Yes	Zinc	1.18	27.26	D-penicillamine	D-penicillamine
72	Female	No	Neurological	Yes	None	Zinc	18.34	34.35	D-penicillamine	Trientine
88	Female	Yes	Asymptomatic	None	None	Trientine	1.45	14.06	D-penicillamine	Zinc (in follow-up: zinc failure; final successful rescue treatment: D-penicillamine)
88	Female	Yes	Asymptomatic	None	None	Zinc	3.94	18.00	D-penicillamine	D-penicillamine
91	Male	Yes	Hepatic	None	None	Zinc	2.70	6.65	D-penicillamine	D-penicillamine
94	Female	No	Hepatic	None	None	Zinc	3.50	3.75	D-penicillamine	Combination
94	Female	No	Hepatic	None	None	Trientine	2.30	14.90	D-penicillamine	D-penicillamine
104	Male	Yes	Hepatic	None	None	Zinc	0.67	0.83	Zinc	D-penicillamine
127	Male	No	Neurologic	None	None	Zinc	1.06	1.96	Zinc	Combination
135	Male	Yes	Hepatic	Yes	None	Zinc	2.52	15.33	D-penicillamine	Trientine
177	Female	No	Neurologic	None	Yes	Trientine	0.50	0.76	Zinc	D-penicillamine
184	Male	No	Hepatic	Yes	Yes	D-penicillamine	26.68	26.68	D-penicillamine	Trientine
205	Male	No	Hepatic	Not determined	Yes	Zinc	8.33	8.50	D-penicillamine	OLT
215	Male	No	Hepatic	None	None	Combination	2.08	2.08	Combination	D-penicillamine

Weiss et al. Gastroenterology 2011

ES-TABLE 10 General laboratory parameter targets for Wilson disease treatment modalities, including findings with excessive or inadequate treatment

	Treatment initiation[a]	Maintenance treatment				Overtreatment			Treatment failure on chronic therapy (nonadherence, drug failure)		
	Urinary copper	24-h urinary Cu excretion, µg/24-h	NCC, µg/dl	AST, ALT	TBili, INR	24-h urinary Cu excretion, µg/24-h	NCC, µg/dl	Other	24-h urinary Cu excretion, µg/24-h	NCC, µg/dl	AST, ALT
D-Penicillamine	Increases	~200–500 (≈3–8 µmol/24-h)	5–15	Trend to normal[b]	↓	<100	<5	↓↓CPN, ↓↓Cu; sideroblastic anemia; ↓WBC; ↑Fe indices	>500 (previously in range)[c]	>25	↑
Trientine	Increases	~150–500 (≈2.4–8 µmol/24-h)	5–15	Trend to normal[b]	↓	<100	<5	↓↓CPN, ↓↓Cu; sideroblastic anemia; ↓WBC; ↑Fe indices;	>500 (previously in range)[c]	>25	↑
Zinc	No change, then ↓	<100 (<1.6 µmol/24-h)	5–15	Trend to normal[b]	↓	<20	<5	↓↓CPN, ↓↓Cu; sideroblastic anemia; ↓WBC; ↑Fe indices;	>100 (previously normal/ near-normal)	>25	↑

4.11 A full blood count, liver function tests, renal profile, and urine dipstick should be performed to monitor for adverse effects before starting penicillamine, after 1 week of treatment and then every 2 weeks for 3 months

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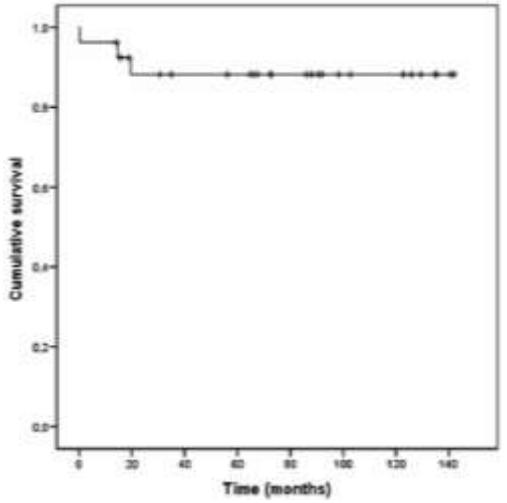
PAPEL DEL TRASPLANTE HEPÁTICO

Enfermedad de Wilson

Guidance statements 28–31

28. Patients with ALF due to WD should be referred for a liver transplant evaluation and potential liver transplantation immediately.
29. Patients with ALI due to WD may respond to medical therapy or may progress to ALF. They require early transplant referral and evaluation.
30. After liver transplantation, medical treatment specific for WD is unnecessary.
31. Liver failure and HCC are well-accepted indications for liver transplantation in WD; however, neurologic WD remains a controversial indication.



Patient Number	Sex	Age, years	Transplant	ALT, IU/L	AST, IU/L	ALP, IU/L	TB, mg/dL	INR	Albumin, g/dL	Creatinine, mg/dL	Lactate, mmol/L	Platelets, ×1000/mm³	Hb, g/dL
1	Male	19	No	48	77	47	4.9	2.3	2.2	NA	NA	119	7.6
2	Male	19	No	52	102	90	4.9	2.6	2	0.55	NA	77	9
3	Female	49	No	714	585	46	9.5	2.4	1.9	0.7	1.3	159	12.5
4	Female	57	Yes	44	198	39	10.42	2.17	2.2	0.6	1.8	106	10.2
5	Female	21	Yes	16	83	25	35	2.5	2.4	0.6	NA	173	8.2
6	Female	18	Yes	20	125	24	48.1	2.8	2.8	0.82	1.7	195	5.7
7	Female	25	Yes	255	364	184	16.7	3.7	2	0.63	NA	46	9.7
8	Female	20	Yes	52	181	44	11.7	5.4	1.4	0.53	NA	88	9.1

Patient Number	Leipzig Score*	K-F Rings	Ceruloplasmin, mg/dL	24-Hour Urine Copper, µg	ATP7B Mutation Analysis†	Hemolytic Anemia‡	Liver Copper, µg/g dry weight of liver
1	6	Yes	4	7583	NA	NA	NA
2	7	No	16	3235	Homozygous	NA	NA
3	5	Inconclusive	17	146	1 exon loci	NA	70
4	5	Yes	23	NA	NA	Yes	1122
5	8	Yes	4	4702	Heterozygous	Yes	NA
6	6	No	13	17,210	NA	Yes	1525
7	10	No	9	3991	Homozygous	NA	1374
8	8	Yes	9	1094	NA	Yes	§

(Continued from previous page)

Initial management

	Lev
4.1 All children with paediatric acute liver failure or decompensated liver disease should be urgently referred to a paediatric liver transplant centre	2
4.2 Adults with acute liver function should be urgently referred to a liver transplant centre	2
4.3 Liver transplantation is indicated in children who have decompensated liver disease with encephalopathy	2
4.4 Liver transplantation should be considered in all adults with acute liver failure	2
4.5 The new Wilson index should be used for prognosis and to facilitate decision making for liver transplantation in children	3
4.6 Penicillamine monotherapy is the first-line treatment for children and adults in the UK and should be introduced in consultation with a specialist centre for Wilson's disease	3
4.7 Trientine dihydrochloride or tetrahydrochloride can be used in children and adults intolerant to penicillamine or at increased risk of adverse effects	3
4.8 Penicillamine should be introduced gradually with dose increments of 125–250 mg per week in children	4
4.9 Penicillamine should be introduced gradually with dose increments of 125–250 mg per week in adults with neurological or psychiatric symptoms	4
4.10 Penicillamine can be introduced more quickly in adults presenting with decompensated liver disease in the absence of neurological symptoms or neuroimaging abnormalities	4
4.11 A full blood count, liver function tests, renal profile, and urine dipstick should be performed to monitor for adverse effects before starting penicillamine, after 1 week of treatment and then every 2 weeks for 3 months	4
4.12 Zinc salts are considered a third-line treatment for adults in the UK and should only be initiated by specialist centres; they are not recommended as monotherapy in patients with cirrhosis unless other treatments are unavailable or contraindicated	3
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4.15 Patients with neurological symptoms should have regular follow up with a movement disorders specialist for a minimum of 12 months after treatment initiation	4
4.16 24-h urinary copper output while continuing medication (on treatment) should be measured within the first 2 months to confirm an adequate copper excretion	4

Ferrarese et al. Liver Transpl 2020

Shribman et al. Lancet Gastroenterol Hepatol 2022

Schilsky et al. Hepatology 2022

Conclusiones

¿Qué nos llevamos a casa?

CONCLUSIONES

- La **enfermedad de Wilson** es una enfermedad rara con **múltiples manifestaciones**.
- El **fenotipo neurológico** es más frecuente en **adultos**, mientras que la **presentación hepática** es más frecuente en **niños**.
- Se deben seguir los **criterios de Leipzig** para la confirmación del **diagnóstico, aunque** existen **falsos positivos y negativos** en algunas pruebas.
- El **tratamiento** actual consiste en quelantes de cobre (**penicilamina y trientina**) y **sales de zinc,** y debe ser mantenido **de forma indefinida**.
- La **trientina 4HCL** tiene **mayor biodisponibilidad** que la trientina 2HCL, y ha demostrado **no ser inferior a penicilamina** como tratamiento de mantenimiento.

GRACIAS

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