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# EASL-ERN Clinical Practice Guidelines on Wilson's disease☆

European Association for the Study of the Liver*

## Summary

Wilson's disease is an autosomal recessive disorder of copper metabolism which affects the liver, brain and other organs. Diagnosis is based on: clinical features; biochemical tests, including plasma ceruloplasmin concentration, 24-h urinary copper excretion, copper content in the liver; and molecular analysis. Leipzig score and additionally relative exchangeable copper determination are recommended for diagnosis. Pharmacological therapy comprises chelating agents (penicillamine, trientine) and zinc salts, while only chelators are recommended for significant liver disease. Monitoring is based on clinical symptoms, liver tests and copper metabolism (urinary copper excretion, exchangeable copper) to detect poor compliance and over/under-treatment. Acute liver failure is challenging as making a diagnosis is difficult and pharmacological therapy may not be sufficient to save life. Liver transplantation has a well-defined role in Wilsonian acute hepatic failure but may also be considered in neurological disease.



## Introduction

Wilson's disease (WD) is an autosomal recessive genetic disorder of copper metabolism which leads to toxic accumulation of copper in the liver, nervous system and other organs.[1,2] Disease-causing mutations on both alleles of *ATP7B* result in WD, in which defective biliary excretion of copper and the absence of holoceruloplasmin complex (five molecules of copper bound to ceruloplasmin) lead to copper accumulation in body organs.[3] Heterozygotes have no disease symptoms. Increased levels of non-protein-bound toxic copper within the hepatocytes lead to hepatitis and cell death, with subsequent release of copper into the circulation. Since the maturation process of ceruloplasmin requires functional intact ATPase 7B, decreased mature ceruloplasmin is secreted into the circulation due to decreased or absent ATPase 7B activity in hepatocytes.[2,4]

The original prevalence estimates for WD of 1:30,000-1:50,000 from 1984 still appear valid according to the recent systematic literature review, at least for the United States, Europe, and Asia.[5] More than 2,700 distinct variants have been described in the *ATP7B* gene, from which over 800 have a confirmed role in disease pathogenesis.[1,2]

Clinical presentation can vary widely, but the key features of WD are liver involvement that can lead to cirrhosis, neurological and psychiatric signs and symptoms, Kayser-Fleischer rings in Desçemet's membrane of the cornea, and acute episodes of haemolysis often in association with acute liver failure (ALF). WD may present at any age, in young children as well as in elderly.[6–8]

The age at presentation, as well as the distribution of presenting symptoms, often depend on the main focus of the institution which collected the data (paediatrics, hepatology, neurology) as well as the region where the data were obtained, except for big national registries. Whether the different genotype distribution has an impact on the phenotypic presentation is unknown. However, the preponderance of typical *ATP7B* mutations varies among different populations. The H1069Q variant is typical for patients with Central- or Eastern European background,[9–11] while R778L (exon 8) occurs mostly in Eastern Asia[12] and C271X (exon 2) in India.[13]

## Methods

The European Association for the Study of the Liver (EASL) and ERN-Rare Liver invited a panel of experts to develop clinical practice guidelines (CPGs) aimed at providing recommendations, based on the best available evidence, for the diagnosis and management of WD for hepatologists, neurologists, general physicians, paediatricians, specialists in training and other healthcare professionals who provide care for this patient population.

P.S. was invited to chair the CPG and a further 11 panellists (including one Governing Board representative [E.T.]) were then selected to comprise the remainder of the CPG panel. The process undertaken is summarised in Fig. 1. The panel initially agreed on the most relevant topics to be addressed in the guideline. The CPG panel drafted 24 clinically relevant ques-

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Clinical Practice Guideline Panel: Chair: Piotr Socha; Secretary to the Chair: Wojciech Jańczyk, Alberto Zanetto. Panel members: Patrizia Burra, Anna Czlonkowska, Dominique Debray, Peter Ferenci†, Uta Merle, Emanuele Nicastro, Aurelia Poujois, Hartmut Schmidt. EASL Governing Board Representative: Emmanuel Tsochatzis.

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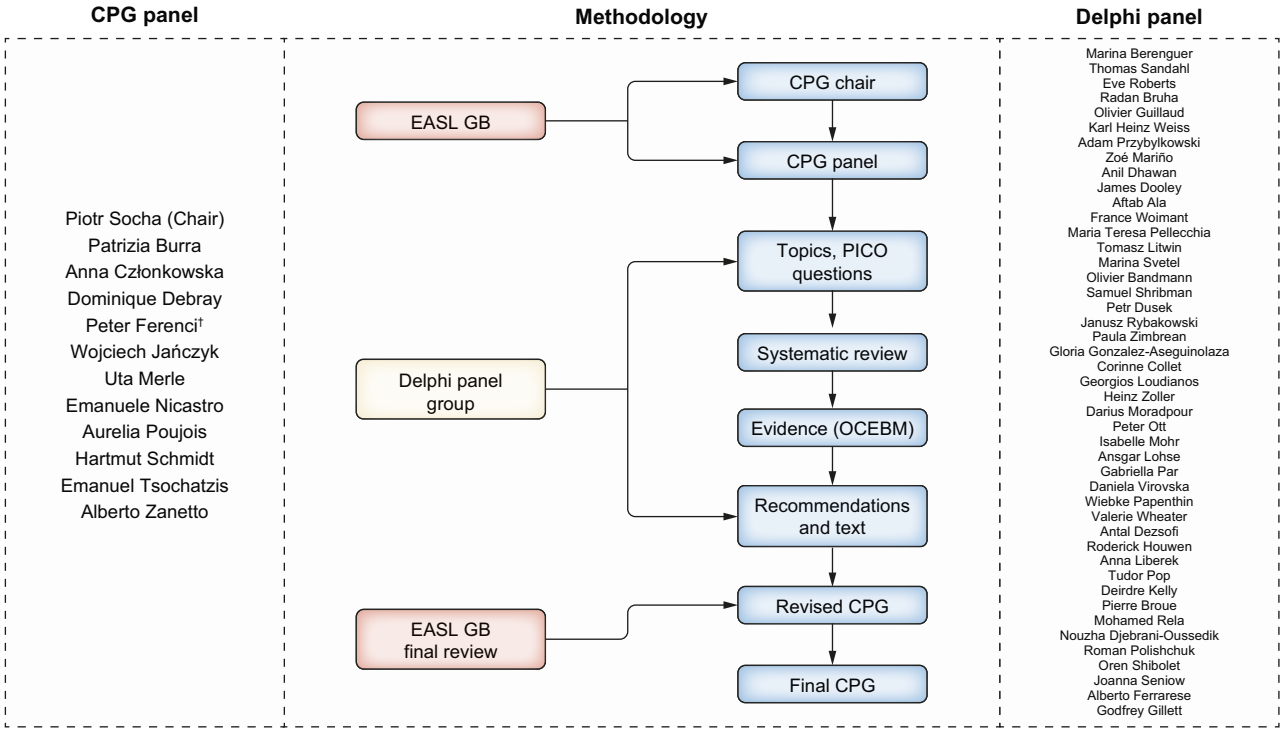


**Fig. 1. Summary of the methods used to prepare the guidelines.**

tions using the PICO (population/patient-intervention-comparison-outcome) format. The PICO format represents a standardised method to address the patient population, intervention, comparisons and outcome and ensures consistency across recent EASL guidelines.

A Delphi panel, jointly nominated by the CPG group as well as the EASL Governing Board, was formulated of 38 academic experts and other stakeholders (Fig. 1) including hepatologists, neurologists, paediatric hepatologists, psychologists, psychiatrists, and patient groups representatives.

A simplified Delphi process was undertaken, and the proposed PICO questions reviewed, with feedback incorporated into a finalised draft. Recommendations were submitted for voting to the Delphi group where the classification of consensus strength was as follows: strong consensus if >95% agreement, consensus if >75-95% agreement, majority agreement if >50-75% agreement, no consensus if <50% agreement.

The CPG panel was divided into subgroups and allocated a proportion of the PICO questions. Each expert took responsibility, made proposals for statements and recommendations for a specific section of the guideline and shared tables of evidence and text with the full panel. Recommendations were drafted for each question following unbiased systematic review of the literature and rated based on the OCEBM (Oxford Centre for Evidence-Based Medicine) guidelines (Tables 1 and 2). The strength of the recommendations was categorised as either 'weak' or 'strong'. The higher the quality of the evidence, the more likely a strong recommendation was made. If no clear evidence was available, recommendations were based on the expert opinion of the panel members.

**Table 2. Grades of recommendation.**

| Grade | Wording | Criteria |
|---|---|---|
| Strong | Shall, should, is recommended. Shall not, should not, is not recommended. | Evidence, consistency of studies, risk-benefit ratio, patient preferences, ethical obligations, feasibility |
| Weak or open | Can, may, is suggested. May not, is not suggested. | |

**Table 1. Level of evidence based on the Oxford Centre for Evidence-based Medicine.**

| Level | Criteria | Simple model for high, intermediate and low evidence |
|---|---|---|
| 1 | Systematic reviews (SR) (with homogeneity) of randomised-controlled trials (RCT) | Further research is unlikely to change our confidence in the estimate of benefit and risk |
| 2 | RCT or observational studies with dramatic effects; SR of lower quality studies (*i.e.* non-randomised, retrospective) | |
| 3 | Non-randomised-controlled cohort/follow-up study/control arm of randomised trial (systematic review is generally better than an individual study) | Further research (if performed) is likely to have an impact on our confidence in the estimate of benefit and risk and may change the estimate |
| 4 | Case-series, case-control, or historically controlled studies (systematic review is generally better than an individual study) | |
| 5 | Expert opinion (mechanism-based reasoning) | Any estimate of effect is uncertain |

Finally, all recommendations were discussed and approved by all participants.

Once the recommendations were drafted and agreed by the CPG panel another Delphi panel review was conducted, and the recommendations were reviewed. Suggested changes were considered in a revised draft that was subsequently sent for review by the EASL Governing Board and external reviewers.

## Clinical presentation

Symptoms are variable (Box 1) and discussed in detail in the text, the frequency is presented in Table 3 and discussed in the text and age of clinical presentation is discussed in the text.

The most common presentations are liver disease and/or neuropsychiatric disturbances. Pre/asymptomatic patients (no clinical symptoms or minor laboratory abnormalities including slightly increased transaminases) are most often detected by family screening. Herein, the term asymptomatic is used to describe patients without clinical symptoms. However, to be more precise in formulating recommendations, asymptomatic patients without signs of liver involvement or those with signs of liver involvement (increased transaminases) were considered separately.

### Age at onset of symptoms

WD may present symptomatically at any age, although the majority of patients present between the ages of 5 and 35. The youngest recorded case of cirrhosis due to WD was 3 years old[14] but hepatomegaly with increased transaminases has been noted as early as 2 years of age.[15] A small minority (3% to 8%) of patients present beyond the fourth decade, either with hepatic or neurologic disease.[6,8,9] The oldest reported patients were two siblings diagnosed in their eighth decade.[16,17]

**Box 1. Major clinical features of WD.**

**Hepatic**
- Hepatomegaly, splenomegaly
- Steatosis
- Increased AST and/or ALT
- Signs/symptoms of portal hypertension: splenomegaly, esophageal/gastric varices, thrombocytopenia, dilated portal vein, splanchnic collaterals
- Symptoms of decompensated liver disease: ascites, hepatic encephalopathy, jaundice

**Neurological**
- Tremor
- Dysarthria
- Ataxia
- Dystonia
- Parkinsonism
- Dysphagia
- Chorea/athetosis
- Cognitive alterations
- Writing difficulties

**Psychiatric**
- Mood disturbance
- Personality changes
- Depression
- Anxiety
- Psychosis

**Other organ manifestations**
- Kayser-Fleischer-rings, sunflower cataracts
- Renal abnormalities
- Cardiomyopathy
- Pancreatitis
- Skeletal anomalies (*e.g.* arthropathy)

### Physical signs

The clinical hallmark of WD is the Kayser-Fleischer ring, which is present in 95% of patients with and slightly over 50% of those without neurological symptoms[18,19] In children presenting with liver disease, Kayser-Fleischer rings are usually absent.[20] Kayser-Fleischer rings represent deposition of copper in the Desçemet's membrane of the cornea. A slit lamp examination by an experienced ophthalmologist is required for their identification. Optical coherence tomography is a more sensitive method to diagnose Kayser-Fleischer rings.[21] Kayser-Fleischer rings are not entirely specific for WD, since they may be found in patients with chronic cholestatic diseases, including children with neonatal cholestasis. Other ophthalmologic changes are rare, and include sunflower cataracts, which represent deposits of copper in the anterior lens capsule.[22] Signs of liver disease are nonspecific, but WD should be ruled out in any liver disease of unknown origin. Neurologic signs are very variable; they most often consist of tremor, dysarthria, ataxia and/or dystonia.

### Liver disease

Any severity of liver disease may be encountered in patients with WD. WD should be considered with any type of liver abnormality and neurological symptoms. Some neurological patients can have normal liver tests.

Clinically evident liver disease may precede neurologic manifestations by as much as 10 years[8,23] and most patients have some degree of liver disease at presentation. Presenting symptoms can be highly variable, ranging from asymptomatic, which can also be associated with only biochemical abnormalities, to overt cirrhosis with complications. WD may also present as fulminant hepatic failure sometimes associated with a Coombs-negative haemolytic anaemia and/or acute renal failure. It is important to note that WD often presents with only slightly increased transaminases.

#### *Acute liver failure due to Wilson's disease*

We define ALF due to WD as a first and acute presentation of liver disease with liver insufficiency indicated by increased international normalised ratio (INR >2 or when encephalopathy occurs INR >1.5), even in the presence of underlying chronic liver disease. WD should be considered in the differential diagnosis of any young patient presenting with acute hepatitis. Its clinical presentation may be indistinguishable from that of acute viral hepatitis, with jaundice and abdominal discomfort. Once a diagnosis is made, lifelong treatment is necessary. On the other hand, rapid deterioration can occur with fulminant liver failure with encephalopathy and renal failure. Acute liver failure due to WD occurs predominantly in young females (female:male ratio 4:1).[18]

**Table 3. Frequency of clinical symptoms in patients with Wilson's disease presenting with liver disease.**

| Author (Country, Ref) | Walshe (UK)[67] | Stremmel/Merle (Ger)[23,68] | Taly (India)[69] | Scott (UK)[70] | Ferenci (Austria)[23,71] |
|---|---|---|---|---|---|
| No. with liver disease (out of) | 87 (>250) | 34/96 (51/163) | 52 (282) | 17* (45) | 30 (64) |
| **Presenting symptom [% of patients presenting with liver disease]** | | | | | |
| Jaundice, anorexia, vomiting (%) | 44 | 27/28 | 40 | 41 | 37 |
| Ascites/oedema (%) | 26 | 21/21 | 12.4 | 24 | 23 |
| Variceal haemorrhage (%) | 6 | | <1 | 6 | 3 |
| Haemorrhagic diathesis (%) | 8 | | 3 | | 3 |
| Haemolysis (%) | 20 | 15/12 | | | 10 |
| Hepatomegaly/splenomegaly (%) | 16 | 74/47 | 39 | 29 | 17 |
| Fulminant hepatic failure (%) | NA | 0/8 | NA | NA | 17 |
| Asymptomatic$ (%) | NA | 18/7.4 | 5 | | 23 |

*Only cases with chronic active hepatitis.
$Elevated alanine aminotransferase at routine testing, or incidental finding of cirrhosis or Kayser-Fleischer rings.

An acute presentation with rapid deterioration may also occur in patients who were previously treated but stopped their medications.[24] Suspicion for acute WD should be particularly high in patients with ALF in combination with severe jaundice, low haemoglobin (haemolysis), low cholinesterase and only mildly increased transaminases.[24] This is usually combined with Coombs-negative haemolysis and relatively high bilirubin levels, but these criteria are not required for the definition used in this guideline.

*Chronic hepatitis and cirrhosis*

Many patients present with evidence of cirrhosis, either compensated or decompensated. Patients may present with isolated splenomegaly due to clinically silent cirrhosis with portal hypertension. The presentation may be indistinguishable from other forms of chronic liver disease, with symptoms including jaundice, malaise, and vague abdominal complaints.

*Haemolysis*

Coombs-negative haemolytic anaemia may be the only initial symptom of Wilson's disease. However marked haemolysis is commonly associated with severe liver disease. Death of liver cells may result in the release of large amounts of stored copper, which further aggravates haemolysis. The more acute the hepatic presentation is, the more likely it is that haemolysis is detectable. In a chronic disease state clinically relevant Coombs-negative haemolysis is usually not present.[25,26] Acute liver disease and haemolysis as a presenting symptom of Wilson's disease can occur during delivery, mimicking HELLP syndrome.[27] Low-grade haemolysis may be associated with Wilson's disease when liver disease is not clinically evident. Some patients presenting with neurological symptoms report that they have experienced transient episodes of jaundice previously, probably due to haemolysis.[28] In one study, 18 of the 26 patients with haemolysis underwent liver biopsy, and 12 had cirrhosis (66.6%). As expected, 38 of the 41 patients with fulminant Wilson's disease underwent urgent liver transplantation, while three died before a graft was available; 35 of the transplanted patients had cirrhosis (92.3%) and three advanced fibrosis.[28]

## Neurologic disease

Wilson's disease can manifest with a wide spectrum of neurological manifestations which may be its first clinical manifestation, or appear simultaneously with hepatic signs, or after a diagnosis is made. Initial neurological presentation occurs in 40–60% of patients,[29] with symptoms typically commencing around 20–30 years of age, a decade after the onset of liver disease.[30] Neurological presentation can be extremely subtle, and intermittent for many years, but may also develop very rapidly leading to complete disability over a few months. The neurological abnormalities can generally be classified into three syndrome types based on predominant signs and symptoms: tremor and ataxia, bradykinesia (parkinsonism-like) and dystonia.[3,30–32] In many cases neurological symptoms are very difficult to classify as patients can have more than one abnormality, each with different severity. Movement disorders are often associated with dysarthria, gait and posture disturbances, drooling and dysphagia. Other neurological symptoms including epilepsy, olfactory dysfunction, autonomic impairment, neuropathy, restless leg syndrome, sleep abnormalities, tics, myoclonus, migraines, pyramidal signs, oculomotor impairment and taste dysfunctions; however, studies describing their frequency at diagnosis and relevance are lacking.[30,33–39] Speech changes and drooling are often very early neurological manifestations so should be carefully examined[40,41]

Because of increasing difficulty in controlling movement or progressive dystonia, patients may become bedridden and unable to care for themselves. In patients presenting with advanced liver disease, neurologic symptoms can be mistaken for signs of hepatic encephalopathy. Although neurological/psychiatric symptoms usually develop in the second or third decade of life, they may occasionally be seen before the age of 10[42,43] and have been reported in 4% to 6% of paediatric cases with hepatic onset.[20,44,45] Kayser-Fleischer rings are present in almost all patients with neurological presentation at WD diagnosis.[46,47]

*Psychiatric symptoms*

In the early years of WD research, cognitive deficit and psychiatric symptoms, such as mood disturbance, abnormal behaviour (*e.g.* increased irritability or disinhibition), anxiety and depression, were considered directly associated with neurological findings, but now it is known that they can present and evolve separately.[48,49] Behavioural and psychiatric symptoms are common and some of them may precede neurological or hepatic signs and symptoms. About one-third of patients initially present with psychiatric abnormalities. In children with WD, declining school performance, personality changes, impulsiveness, labile mood, sexual exhibitionism, and inappropriate behaviour may be observed.[50,51] The initial symptoms are frequently misdiagnosed as behavioural problems associated with puberty. In older persons (>50 years old) psychotic

features resembling paranoia and schizophrenia or depression can be observed but behavioural changes are also common. Severe cognitive deterioration may be observed in advanced neurological cases, but in general cognitive functioning is not markedly impaired.[52] A delay of around 2 years in diagnosing WD for those patients with neuropsychiatric presentations is frequent, with delays as long as 12 years reported.[23] Patients presenting with neuropsychiatric symptoms may have concurrent symptomatic liver disease, but liver disease can only be detected by laboratory evaluations, such as low platelets, imaging or on histology in most patients.[53]

### Other clinical manifestations

Less common manifestations include acromegaly, lunulae, renal abnormalities including aminoaciduria and nephrolithiasis, hypercalciuria and nephrocalcinosis, tubular acidosis,[54,55] cardiomyopathy,[56,57] myopathy,[58] chondrocalcinosis and osteoarthritis,[59] bone demineralization,[60,61] risk of fracture,[62] hypoparathyroidism,[63] pancreatitis,[64] infertility or repeated miscarriages.[65,66]

## Differential diagnosis

A number of liver and neurological diseases were described in the text when discussing symptoms and are summarised in Table 4.

Differential diagnosis of liver presentation should include viral hepatitis, drug-induced liver disease, metabolic-associated steatotic liver disease (MASLD), autoimmune hepatitis, progressive familial intrahepatic cholestasis and metabolic liver diseases.[72] Recently, a number of new diseases presenting with Wilson-like symptoms and/or copper metabolism disturbances have been described – like MEDNIK syndrome,[73] V-ATPase deficiency with liver steatosis[74] and phosphoglucomutase I deficiency[75]– the last two being congenital defects of glycosylation. The main difficulty in differential diagnosis can be related to increased copper accumulation in the liver in cholestatic disorders (primary sclerosing cholangitis, primary biliary cholangitis, progressive familial intrahepatic cholestasis), steatosis as a histological and imaging feature (MASLD, alcohol-related liver disease, lysosomal acid lipase deficiency) or positive autoantibodies (autoimmune hepatitis). Differential diagnosis of WD with neurological presentation includes the different movement disorders, in particular: parkinsonian and parkinsonian-plus syndromes, neurodegeneration with brain iron accumulation, inborn dystonia, as well as multiple sclerosis.[34]

## Diagnosis

***Which stepwise diagnostic approach should be followed in adult patients with suspicion of WD and a predominantly hepatic manifestation?***

### Recommendations

- The first step should be screening for abnormalities in copper metabolism (both serum ceruloplasmin and basal 24-h urinary copper excretion). If available, relative exchangeable copper determination in serum should be performed **(LoE 2, strong recommendation, consensus).**
- In addition, typical extrahepatic features of WD (Kayser-Fleischer rings, neurological symptoms, Coombs-negative haemolysis, brain MRI abnormalities) should be sought **(LoE 3, strong recommendation, strong consensus).**
- Pharmacological treatment should be started once diagnosis is well supported by the Leipzig score **(LoE 2, strong recommendation, consensus).**
- Genetic *ATP7B* analysis should follow to confirm diagnosis, which in turn may enable family screening **(LoE 2, strong recommendation, strong consensus).**
- If diagnosis remains questionable, hepatic parenchymal copper quantification (dry weight) should be performed **(LoE 2, strong recommendation, strong consensus).**

WD is a mosaic diagnosis and the diagnostic algorithm depends on the presenting symptoms and the age at onset (Fig. 2). It should be considered in any adult who presents with chronic liver disease of unknown aetiology irrespective of age. Family history is important to be addressed in the medical history of a patient (*e.g.* consanguinity).

The clinical spectrum of WD is broad and comprises variable features as illustrated in Box 1 and described in the introduction. Steatosis is a frequent finding before cirrhosis develops.[76] Onset of disease may also vary from early childhood (as young as 2 years of age) to as late as >60 years of age.

Increased copper content of the liver is a hallmark of WD (Table 5). More advanced liver failure goes along with impaired synthetic function with reduced albumin secretion, which in turn may result in an underestimated total copper content in plasma. Elevated non-protein-bound serum copper and decreased serum

**Table 4. Differential diagnosis of Wilson's disease.**

| Liver presentation | Neuropsychiatric presentation |
|---|---|
| Steatotic liver diseases (MASLD, ALD, LAL-D) | Essential tremor |
| DILI | Parkinson disease |
| Autoimmune hepatitis | All types of dystonia (focal, segmental or generalized) |
| Viral hepatitis | Specific task dystonia (writer's cramp) |
| Cholestatic liver diseases (PSC, PBC, PFIC) | Functional abnormal movement |
| Hemochromatosis | Spino-cerebellar ataxia |
| Alpha-1-antytrypsin deficiency | Aceruloplasminemia |
| Cystic fibrosis | Niemann Pick type C |
| Congenital defects of glycosylation (V-APTase deficiency, phosphoglucomutase I deficiency) | Manganese transporter disorders |
| MEDNIK syndrome | |

ALD, alcohol-related liver disease; LAL-D, lysosomal acid lipase deficiency; MASLD, metabolic dysfunction-associated steatotic liver disease; PBC, primary biliary cholangitis; PFIC, progressive familial intrahepatic cholestasis; PSC, primary sclerosing cholangitis.

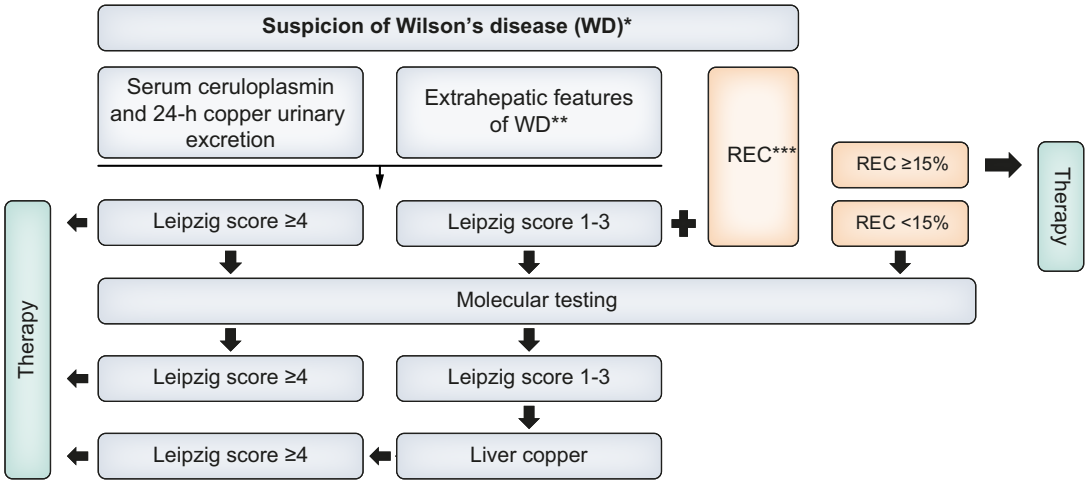


**Fig. 2. Diagnostic algorithm.** REC, relative exchangeable copper. *family screening may be performed by specific pathways including direct molecular testing **including neurological symptoms, Kayser-Fleischer Corneal-rings & Coombs-negative hemolytic anemia ***REC, relative exchangeable copper as percentage of exchangeable to total serum copper.

concentration of ceruloplasmin are therefore typical in untreated patients with WD, though sensitivity is not 100%. A copper challenge test with D-penicillamine can be used for copper mobilisation, which is detected within the urine after exposure to D-penicillamine. This has been validated in children but not in adults.[77] If available, relative exchangeable copper (REC) defined as the ratio of exchangeable copper to total serum copper should be determined (discussed later in this chapter).

Coombs-negative haemolysis may occur in patients with an acute hepatic presentation. Presumably the more acute the liver injury caused by copper excess is, the more likely that haemolysis is detectable.[78] Radiolabelled copper has been used historically and may also serve as a valuable tool; however, this is nowadays rarely available, and experience is limited.

Ceruloplasmin and 24-h urinary copper excretion remain the most common tests used for the diagnosis of WD. The diagnostic value of these tests was analysed in a recent Cochrane review and showed high accuracy.[79] The best WD diagnostic threshold of serum ceruloplasmin was below 14 mg/dl (sensitivity 93% and specificity 100%) in a series of 57 adults and children with WD, with liver dysfunction and/or neurological deficits,[80] and below 20 mg/dl (sensitivity 95% and specificity 84.5%) in a series of 40 clinically asymptomatic children with elevated serum transaminases.[81] On the other hand, up to 20% of children and adults with WD may have normal serum ceruloplasmin levels, as reported in patients carrying bi-allelic missenses mutations of the *ATPB7* gene.[82,83] Notably, misleadingly elevated serum ceruloplasmin levels may be seen when using the immunological-nephelometric assay which also measures the biologically inactive apo-form. This is why the enzymatic assay measuring oxidase activity should be the preferred method but is rarely available in routine practice.[83]

Abnormal ceruloplasmin may also be expected in other diseases with decompensated liver function, malnutrition, protein loss or in aceruloplasminemia.[84]

24-h urinary copper excretion is recommended in all previous guidelines and position papers including the 2023 AASLD guidance. The cut-off values >100 μg/24 h (>1.6 μmol/24 h) are typical for symptomatic patients with WD but sensitivity is not high enough to use this value to exclude WD. 24-h urinary copper excretion may increase in cholestatic liver disease. Sampling error and contamination during urine collection can also influence results.[19,23]

Depending on the presentation, *i.e.* acute *vs.* chronic or hepatic *vs*. neurological, the approach of diagnosing WD may vary. One approach to improve diagnosis is the Leipzig score[85] which is shown in Table 6. The idea of this score is a sum of different parameters and symptoms, which together form the likelihood of diagnosing WD. Thus, although no individual parameters or symptoms are specific for WD, a combination of different parameters is required for diagnosis. Still, ceruloplasmin and 24-h urinary copper excretion remain basic tests. 24-h urinary copper excretion should score 2 points if >100 μg/24 h as indicated in adult patients with significant liver disease.

Slit lamp examination by an experienced ophthalmologist may reveal KFRs, which are characteristic once other cholestatic liver diseases have been excluded.[86] This examination should always be performed for the diagnosis of WD and is an important part of the diagnostic score.

Variable clinical presentation of WD requires a multidisciplinary approach from the very beginning – including a hepatologist, neurologist and ophthalmologist. Once diagnosis is established and the clinical presentation defined – a hepatologist and/or neurologist can take over care in follow-up.

**Table 5. Diagnostic value of copper metabolism parameters.**

| | Normal values | High suspicion of Wilson's disease |
|---|---|---|
| Serum ceruloplasmin | 20–40 mg/dl | <10 mg/dl |
| 24-h urinary copper excretion | <40 μg (<0.65 μmol) in children<br><50 μg (0.8 μmol) in adults | >100 μg (1.6 μmol) |
| Relative exchangeable copper (%) | 3.4-8% | >15% |
| Liver copper content | <50 μg/g dry weight | >250 μg/g dry weight (>4 μmol/g dry weight) |

**Table 6. Diagnostic Leipzig score in Wilson's disease.**

| Score | -1 | 0 | 1 | 2 | 4 |
|---|---|---|---|---|---|
| Kayser-Fleischer rings | | Absent | | Present | |
| Neuropsychiatric symptoms suggestive of Wilson's disease (or typical brain MRI) | | Absent | | Present | |
| Coombs-negative haemolytic anaemia + high serum copper | | Absent | Present | | |
| 24-h urinary copper excretion (in the absence of acute hepatitis) | | Normal | 1-2x ULN | >2x ULN, or normal but >5x ULN during challenge with 2 x 0.5 g D-penicillamine | |
| Liver copper quantitative | Normal | | <5x ULN (<250 μg/g) | >5x ULN (>250 μg/g) | |
| Rhodanine positive hepatocytes (only if quantitative copper 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** | |

ULN, upper limit of normal.

Genetic analysis is part of the diagnostic score but should follow other tests even if diagnosis is confirmed based on clinical/biochemical findings. It enables discovery of disease-causing variants on both alleles in >85% of patients with a typical WD phenotype and in around 60% of those with neurological WD (unpublished data). However, even if disease-causing mutations are not identified on one or both alleles, WD cannot be conclusively excluded. Progress in genetics may enable its use for screening or rapid diagnosis in the future. In addition, a mutational search is a valuable tool for family screening.

The Leipzig score was validated in children for the diagnosis of WD and showed very high accuracy. In a retrospective analysis of 142 children with liver disease in the UK, 53 of whom had WD, the Leipzig score had a high positive and negative predictive value of 95% and 99%, respectively.[87] Similar results were reported from Italy, in 40 children with mild WD and 58 matched patients with other liver diseases, with positive and negative predictive values of 93% and 92%, respectively.[81] Still, validation in adult cohorts has not been conducted.

In recent years several tests have been developed to measure non-ceruloplasmin-bound copper for diagnosis and monitoring of WD. A major diagnostic advance was achieved with the implementation of the direct assay of "free copper", or exchangeable copper.[88,89] The methodology for plasma exchangeable copper measurement by ultrafiltration coupled to atomic absorption spectrometry was reported in 2009 and applied to healthy individuals to set reference value ranges.[90] The REC that corresponds to the ratio between exchangeable copper and total serum copper was shown to enable a diagnosis of WD with high sensitivity and specificity close to 100% when its value is >18.5%.[91] It was also shown to significantly discriminate WD from other liver diseases such as metabolic dysfunction-associated steatohepatitis and autoimmune hepatitis.[92] Finally, REC determination also significantly discriminates heterozygous *ATP7B* carriers and individuals with no *ATP7B* mutations from patients with WD at a cut-off of 15%,[93] and therefore is very useful for family screening of WD. Moreover, exchangeable copper values at diagnosis are a marker of extrahepatic involvement and its severity. A value of >2.08 μmol/L is suggestive of corneal and brain involvement (sensitivity = 86%, specificity $p$ = 94%), and the disease will be more clinically and radiologically severe as values rise.[94] The exchangeable copper assay is available for routine clinical use in France, Spain, Denmark and India, and allows for the calculation of REC. The results from France were confirmed in another study from Spain, where REC values were below 15% in all the control individuals and >14% in all patients with WD.[95] An abnormal REC result indicates the initiation of chelating treatment without delay, pending a definitive confirmation of the diagnosis through a molecular biology study of the *ATP7B* gene. REC can be used as an additional test to the Leipzig scoring system and may help to establish diagnosis.

Additional investigations can help to confirm diagnosis and especially to describe sub-clinical brain involvement. Brain MRI can indirectly detect copper and iron overload using T2/fluid-attenuation inversion recovery (FLAIR) and T2*/susceptibility weighted imaging (SWI) sequence analysis and may in future serve as a standardised non-invasive diagnostic tool for copper overload in organs.[96,97]

***Which stepwise diagnostic approach should be followed in adult patients with suspicion of WD and predominantly neurological or neuropsychiatric manifestations?***

## Recommendations

- Screening for copper metabolism abnormalities (both serum ceruloplasmin and basal 24-h urinary copper excretion) and presence of Kayser-Fleischer rings should be performed. If available, relative exchangeable copper in serum determination should also be performed **(LoE 2, strong recommendation, strong consensus).**
- Brain MRI should be performed in all patients to search for abnormalities especially in basal ganglia, thalamus, brainstem, and cerebellum **(LoE 2, strong recommendation, strong consensus).**
- In addition, testing for any kind of liver involvement should be performed, with liver function tests, liver imaging and non-invasive fibrosis testing **(LoE 2, strong recommendation, strong consensus).**
- Pharmacological treatment should be started once diagnosis is well supported by the Leipzig score **(LoE 2, strong recommendation, consensus).**
- Genetic *ATP7B* analysis should follow to confirm diagnosis, which in turn may enable family screening **(LoE 2, strong recommendation, strong consensus).**

WD should be considered in any adult with neurological or neuropsychiatric anomalies irrespective of the presence of liver disease. Once patients with other neurological or neuropsychiatric diseases (*e.g.* essential tremor, Parkinson disease, all types of dystonia, spino-cerebellar ataxia) do not respond to treatment, differential diagnosis of WD should be re-evaluated.

The localisation of copper deposition within the brain in WD varies, resulting in variable neurological and neuropsychiatric symptoms.[30] Basal ganglia and cerebellum are commonly affected resulting in variable movement disorders and behavioural changes. Therefore, neurological and psychiatric manifestations are manifold (Table 3). Usually, liver disease exists to a variable degree. Since liver disease may not be symptomatic, it may be overlooked. Splenomegaly and/or low platelets may be a sign of cirrhosis and portal hypertension in these patients. Once diagnosis of WD is established, a hepatologist should screen for the presence and severity of liver fibrosis.[98]

The more pronounced the neurological/neuropsychiatric manifestations are, the more likely that Kayser-Fleischer rings are detectable. In some cases, these may be evident even without a slit lamp. MRI of the brain should search for anomalies, especially hyperintensities in —T2-weighted FLAIR images in the basal ganglia, thalamus, midbrain, pontine, and cerebellum. The so-called "face of giant panda" in the midbrain occurs in about 20% of patients with WD with neurological symptoms.[99]

Once WD has been diagnosed, a neuropsychiatric assessment should be performed. The extent of neurological and neuropsychiatric symptoms may be evaluated using the Unified Wilson's Disease Rating Scale (UWDRS) or the Global Assessment for Wilson's Disease.[100] The shorter the duration of neurological symptoms, the greater the chances for a meaningful symptomatic and functional improvement. It should be noted that normal liver tests do not exclude liver involvement in neurological presentations of WD.

***Which stepwise diagnostic approach should be followed in children with suspicion of WD?***

### Recommendations

- The first step should be screening for copper metabolism abnormalities (serum ceruloplasmin and basal 24-h urinary copper excretion). If available, relative exchangeable copper determination in serum should also be performed **(LoE 2, strong recommendation, strong consensus).**
- Typical extrahepatic clinical features of WD (Kayser-Fleischer rings, neurological symptoms, Coombs-negative haemolysis) should be looked for in all children, especially those >10 years of age **(LoE 3, strong recommendation, strong consensus).**
- Pharmacological treatment should be started once diagnosis is well supported by the Leipzig score **(LoE 3, strong recommendation, consensus).**
- Genetic *ATP7B* analysis should follow to confirm diagnosis, which in turn may enable family screening **(LoE 2, strong recommendation, strong consensus).**
- If diagnosis cannot be confirmed or excluded, hepatic parenchymal copper quantification (dry weight) should be performed **(LoE 2, strong recommendation, strong consensus).**
- Especially in older children (>10 years old, even if asymptomatic) brain MRI should be performed at diagnosis to evaluate the extent of disease **(LoE 4, strong recommendation, consensus).**

As in adults, WD in children is a composite diagnosis, however, substantial differences exist in terms of extent of copper accumulation and organ involvement, and consequently in copper metabolism tests.[101] WD can be diagnosed in children >1 year of age upon incidental findings of persistently increased transaminases, hepatomegaly, hyperechogenic liver, acute hepatitis up to ALF, with symptoms rarely occurring before 5 years of age.[44,102–106]

In children and young adults, features of autoimmune hepatitis can be detected in WD, as up to 28% of children with WD exhibit significantly increased (1:160) serum anti-nuclear autoantibodies. In addition, other autoantibodies like smooth muscle, and liver-kidney microsomal autoantibodies and/or increased levels of IgG were also reported.[107–111]

In children with increased transaminases, fatty liver and presence of overweight/obesity, WD should be ruled out before establishing a diagnosis of MASLD.[112]

A high index of suspicion remains the pillar of a correct identification of paediatric liver disease due to WD, while possible competing diagnoses should be challenged. Neurologic symptoms are much less common in children than in adults. However, 4-6% of children with hepatic WD have underlying neurologic involvement at the time of diagnosis, while neurologic issues might remain unrecognised in a proportion of children and emerge later on during childhood and young adulthood.[45,113,114] When present, neurologic symptoms are generally milder and underreported, and mainly manifested by subtle tremor, ataxia, and dysarthria, while frank dystonia occurs rarely.[114] Psychiatric problems – namely mood disorders with depression and anxiety – are described in the paediatric age bracket, but their prevalence is unclear.[115] Poor school attainment, and mild cognitive impairments have been reported in children and young adults with WD, implying special needs in management, rehabilitation, and transition of care.[116]

Neurologic assessment of WD in children is clinical and instrumental. MRI may detect changes in children with WD – even in the absence of neurologic symptoms – and support the diagnosis.[117] On the other hand, MRS (magnetic resonance spectroscopy) has greater sensitivity in detecting changes in neuronal/axonal viability, metabolism, and membrane status even in children with no overt neurologic involvement.[118]

The decision to perform an MRI/MRS for diagnostic purposes should take into account the need for sedation or general anaesthesia, and the expected added value of the exam. Still, sedation may be required only in small children <6 years of age when neurological presentation is not observed or in patients with ALF and encephalopathy, when the decision to perform liver transplantation is based primarily on clinical and laboratory features.

In terms of copper metabolism, the determination of both the serum ceruloplasmin concentration and the 24-h urinary copper excretion are recommended as a first step to the WD diagnosis in children. A ceruloplasmin cut-off of <20 mg/dl is considered acceptable in children,[81] considering that a

proportion of patients bearing biallelic missense mutations may exhibit higher concentrations.[82,83,119]

False positive results may be observed in children with liver failure, and arise from rare conditions such as congenital glycosylation disorders, Menkes disease, MEDNIK syndrome, Huppke-Brendel syndrome, aceruloplasminemia, or alternatively by malabsorption, malnutrition or protein wasting or loss.[81,120–123] 24-h urinary copper excretion mostly reflects age-dependent copper accumulation, and its diagnostic accuracy with the adult cut-off (>100 μg/24 h or >1.6 μmol/24 h) is substantially lower in terms of sensitivity for a first-tier test. In children with mild/asymptomatic liver disease (elevated transaminases and fatty liver, with or without hepatomegaly) a lower cut-off of >40 μg/24 h (>0.65 μmol/24 h) has demonstrated better diagnostic accuracy, with a sensitivity of 78.9% and a specificity of 87.9%.[81]

The D-penicillamine challenge test has poor diagnostic accuracy in asymptomatic children (12% sensitivity and 46% specificity) with the established diagnostic cut-off value of 1,575 μg/24 h (25 μmol/24 h). The alternative cut-off of a 5-fold increase of the upper normal limit for basal urinary copper (200 μg/24 h; 3.2 μmol/24 h) increased the sensitivity to 88% despite a considerable loss in specificity (24.1%). Thus, a D-penicillamine challenge test should not be routinely performed in children with mild liver disease. Ceruloplasmin and 24-h urinary copper excretion are of limited diagnostic value in the setting of paediatric ALF,[124] which will be addressed in a separate paragraph.

The REC determination – currently not widely available – is the ideal complement to ceruloplasmin and urinary copper in investigating children with suspected WD. In two large case-control studies that included children, a REC >18.5% had a sensitivity of 79-100% and a specificity of 100% in discriminating patients with WD from healthy controls and those with non-Wilsonian liver disease, and was unaffected by the low ceruloplasmin levels observed in individuals with cirrhosis.[92,95] In a child with suspected WD and low ceruloplasmin, 24-h urinary copper excretion could provide sufficient proof of the disease to start treatment promptly, while waiting for confirmatory genetic testing. In case the diagnosis remains uncertain after genetic testing, or in case of its unavailability or long turnaround time, or whenever a liver biopsy is performed for clinical reasons, hepatic copper quantification should be performed due to its high sensitivity and specificity.

The Leipzig score is recommended for use in children, as it has shown very high accuracy in two cohorts studied.

### *Which diagnostic approach should be followed to diagnose WD in patients presenting with ALF?*

#### Recommendations

- Screening for WD should be performed in all adult patients and children >4 years of age presenting with ALF **(LoE 3, strong recommendation, consensus).**
- Coombs-negative haemolysis, Kayser-Fleischer rings and neurological symptoms suggestive of WD should be looked for as highly indicative of WD **(LoE 3, strong recommendation, strong consensus).**
- Relative exchangeable copper determination may be performed if available **(LoE 4, weak recommendation, strong consensus).**
- Brain MRI may be performed whenever possible to support diagnosis **(LoE 4, weak recommendation, strong consensus).**
- Genetic *ATP7B* analysis should be performed as soon as possible but is not required for treatment initiation **(LoE 2, strong recommendation, strong consensus).**

The most severe form of hepatic presentation of WD is ALF (formerly 'fulminant WD'). Features indicative of ALF due to WD are Coombs-negative haemolysis, discrepancy between high bilirubin and INR values *vs.* relatively little elevation of alanine aminotransferase (ALT)/aspartate aminotransferase (AST), decreased alkaline phosphatase (ALP) and the presence of Kayser-Fleischer rings.[104,125,126]

Anaemia or disproportionately high bilirubin level is typical for ALF due to WD[125,127–130] and should prompt further haemolysis work-up with reticulocyte count, direct antiglobulin (Coombs) test and haptoglobin level.

While bilirubin is markedly elevated in ALF presentation of WD (WD ALF), serum levels of aminotransferases are only moderately increased (typically less than ten-times normal), and serum concentrations of ALP are normal or extremely low.[125,131]

A low ALP, low ALP to total bilirubin (TB) ratio or high AST to ALT ratio should also raise suspicion of WD. Studies consistently show that the ratios of AST to ALT and of ALP to TB can discriminate ALF due to WD from other aetiologies, but studies differ with respect to optimal cut-offs and diagnostic performance.

The ratio of AST to ALT is typically higher in WD ALF than in non-WD ALF and cut-offs used are AST:ALT ratio >2.2,[125] ≥2.03,[129] and ≥2[128] with sensitivities ranging from 62.5% to 94% and specificities ranging from 69.6% to 87%. Due to typically low serum ALP, the ratio of ALP to TB is typically lower in WD ALF than in non-WD ALF. The cut-off of <4 of ALP:TB yielded a sensitivity of 94% and specificity of 96% for WD ALF,[125] but showed much lower diagnostic performance in other studies (with sensitivities and specificities of 66.7% and 100% at a cut-off of <1.82[128] and 55.6% and 94.8% at a cut-off of ≤8.69.[129] Corresponding to that, in a recent individual patient data meta-analysis of a cohort of paediatric patients with WD ALF, the sensitivity of the amended ratios proposed by Korman *et al.*[125] yielded sensitivities of only 71% (n = 81/114) and 52% (n = 76/146), for the ratios ALP/TB <4.0 and AST/ALT >2.2, respectively.[126] In summary, at least in paediatric patients, the diagnostic performance of these ratios is lower than previously reported.

Despite typical features indicative for WD ALF, WD presenting as ALF is diagnostically challenging as the conventional diagnostic markers of copper metabolism are less sensitive and specific than under non-acute conditions.[125,128,129]

The serum copper level, which represents both ceruloplasmin-bound and non-ceruloplasmin-bound copper, is usually low at the time of diagnosis in non-acute presentations of WD but is markedly elevated (usually >200 μg/dl) in WD ALF due to copper release from hepatocellular injury.[125]

24-h urinary copper excretion is typically greatly elevated.[126] Of note, since urinary copper excretion is known to increase in diseases associated with extensive hepatocellular necrosis, there is a high likelihood of overlap between WD ALF and ALF

of other aetiologies, with slight elevations likely in ALF irrespective of aetiology but greatly elevated levels in WD ALF

Kayser-Fleischer rings are commonly reported to be absent in up to 50% of patients with WD but were recently reported to be detectable in 74% of patients in a large international WD paediatric cohort.[126] Therefore, although slit lamp examination may be challenging in the intensive care setting, it should be considered in any patient with unexplained acute liver injury or failure.

The predictive value of the acute-phase reactant serum ceruloplasmin in ALF is lower than under stable conditions, as it may be only slightly decreased or even low-normal. In addition, ALF of other aetiologies can present with low serum ceruloplasmin levels. Based on prospective registry data including adult and paediatric patients, serum ceruloplasmin in patients with WD ALF was on average only slightly decreased or even low-normal.[125] Due to a wide range of ceruloplasmin levels in WD and non-WD ALF, ceruloplasmin determination had low sensitivity of 56% and low specificity of 63%.[125] In contrast, ceruloplasmin levels were shown to differ significantly between WD ALF and non-WD ALF in a retrospective paediatric cohort study, with significantly lower levels in WD ALF.[129] Accordingly, in a recent individual patient data meta-analysis of a cohort of paediatric patients with WD ALF (n = 256), serum ceruloplasmin was found to be low, at a mean level of 0.11 [IQR 6.7–16.0] g/L.[126] In summary, screening for a diagnosis of WD in the setting of ALF using ceruloplasmin measurements is unreliable but may be more reliable in paediatric patients compared to adult patients, although prospective data on ceruloplasmin test accuracy solely in paediatric patients are missing.

REC determination should be performed if available as it may help to distinguish WD ALF from non-WD ALF. In a retrospective study by Spirea *et al.*[102] in 31 patients diagnosed with ALF (9 patients with confirmed WD, 22 with non-WD ALF), REC had a high diagnostic value with all patients with non-WD ALF having a REC <15% and all WD ALF a REC >15%.

Patients should be evaluated for neurological symptoms as neurologic symptoms or signs can occur in parallel with ALF or emerge while patients are being considered for transplantation. However, it is important to differentiate these from hepatic symptoms due to WD. As brain MRI-features suggestive of WD can be diagnostically helpful, a brain MRI should be performed when possible. Genetic *ATP7B* analysis should follow to confirm diagnosis. Mortality without liver transplantation is high, especially in paediatric patients, with only 11% of paediatric patients achieving spontaneous survival.[104,126]

***Is measurement of copper content and liver histology useful and accurate for the diagnosis of WD in patients with and without neurologic symptoms?***

### Recommendations

- Measurement of hepatic parenchymal copper content in dry weight liver biopsy is recommended if required for diagnostic purposes. The value >250 μg/g is highly suggestive of WD but requires differential diagnosis with cholestatic liver disease **(LoE 2, strong recommendation, strong consensus).**
- Although liver histological evaluation does not provide any definite diagnostic features for WD, it should be carried out whenever a liver biopsy is performed for hepatic copper quantification **(LoE 3, strong recommendation, strong consensus).**
- Histochemical copper staining may be omitted, as it has only minor diagnostic value for WD **(LoE 3, weak recommendation, consensus).**

As hepatic copper accumulation is the hallmark of WD, copper quantification in liver tissue is the method of choice for the diagnosis of WD if a liver biopsy is performed. The normal copper content is 15-55 μg/g liver dry weight.[132] Four studies (1,150 participants, of whom 367 had WD) evaluated the diagnostic value of hepatic copper quantification for the diagnosis of WD.[81,133,134] In most but not all cases of WD, the hepatic copper content was elevated >4 μmol/g or >250 μg/g dry weight. Sensitivity and specificity at this cut-off ranged between 66% to 94% and 52% to 99%, respectively. Lowering the threshold from 4 μmol/g (250 μg/g) dry weight to 1.2 μmol/g (75 μg/g) dry weight improved the sensitivity from 83.3% to 96.5%, while specificity remained acceptable (95.4% *vs*. 98.6%).[135] A prospective study in a Chinese population reported 3.3 μmol/g (209 mg/g) dry weight as the optimal cut-off for diagnosis.[134] In this latter study, 23% of patients without WD had a hepatic copper content >75 μg/g dry weight. Importantly, the hepatic copper content may also be severely increased in long-standing cholestatic disorders. About half of patients with primary biliary cholangitis and primary sclerosing cholangitis in the Chinese study had a hepatic copper content >4 μmol/g (>250 μg/g).[134] However, as the clinical presentation of these patients differs from that of patients with WD, 4 μmol/g (250 μg/g) dry weight is considered as the best biochemical evidence for WD.[79]

Liver biopsies obtained for hepatic copper quantification should be submitted to the analysis centre as so-called “dry biopsies”, which means that the biopsy cylinder is immediately transferred into an empty copper-free container. No additional precautions (like tissue fixation by freezing or chemical solutions) are required until measurement. Due to the uneven copper distribution in liver tissue of patients with WD, the gold standard hepatic copper quantification may give false negative results.[136] To improve the reliability of hepatic copper quantification, at least 1 mg of dry liver tissue should be analysed.[134] Importantly, a second biopsy pass is not associated with an increased risk of complications compared to a single biopsy pass.[137]

As gadolinium is known to interfere with most metal tests, a specimen should not be collected for 96 hours in case a gadolinium-containing contrast medium has been administered.

The liver histology of WD is extremely variable. Thus, WD can be mistaken for other liver disorders. Matching the clinical spectrum, the histopathological changes range from subtle changes over acute hepatic failure to chronic hepatitis with less or more inflammatory activity to the development of cirrhosis. However, there are characteristic histological features, which may support the diagnosis and exclude relevant differential diagnosis. Typical histological findings in WD include features of MASLD like macrovesicular steatosis, glycogenated nuclei, Mallory Denk bodies, portal and lobular mononuclear

inflammation. Additional features include unusual abundant lipofuscin and (in case of haemolysis) Kupffer cell siderosis.[138]

Compared to adults, the features of MASLD (*e.g*. steatosis, glycogenated nuclei, Malloy Denk bodies) are more prevalent in children, while cirrhosis is more frequently seen in adult patients.[139–142]

In general, conventional liver histology alone does not provide sufficient specificity for differentiating WD from relevant differential diagnoses like MASLD.[143]

In paediatric liver biopsies, electron microscopy findings of mitochondrial abnormalities including dilated tips of cristae, pleomorphism, membrane duplication and dense matrix were significantly more frequently observed in patients with WD than in those with MASLD and autoimmune hepatitis,[143] but these findings are neither pathognomonic nor specific for the diagnosis of WD.

Histochemical staining of copper (*e.g.* rhodanine or Timm's sulphide silver staining) and/or copper-associated protein (*e.g.* orcein) is currently used to support the histological evaluation of liver biopsies with suspected WD. Rhodanine is the most used histochemical copper stain, as it is considered the most reliable, reproducible and simple histochemical staining. Nevertheless, especially in early stages of WD, diffuse cytoplasmic localisation of non-protein-bound copper evades histochemical detection, while in later disease stages, copper accumulates in lysosomal complexes and is then more easily stained. However, due to its low sensitivity, ranging from 11–56% depending on disease stage, and very low sensitivity in early stages, rhodanine staining has only a minor value for diagnosing WD and cannot be used to exclude hepatic copper overload.[144,145]

In addition to its low sensitivity, the specificity of histochemical copper detection is also low, as other conditions (*e.g*. chronic biliary diseases) result in hepatic copper accumulation and may give rise to positive staining as well.[146]

Already 50 years ago, metallothionein was described as being upregulated in liver tissue of patients with WD.[147] It represents the major hepatic copper-binding protein[148] and recent, independently validated, data suggest that it is a sensitive, potentially widely available, inexpensive immunohistochemical stain for the diagnosis of WD.[149]

Even in patients without significant fibrosis, the sensitivity of metallothionein immunohistochemistry was reported to be >70%.[145] As the staining pattern is also different between WD and chronic biliary diseases in most patients, the diffuse metallothionein expression typically observed in WD also has a high specificity for the diagnosis of WD.[137,145]

In cases where a liver biopsy has already been performed during the evaluation of unexplained elevated liver enzymes, archived liver biopsy tissue can be used for metallothionein immunohistochemistry.

Liver biopsy is not performed for neurological presentation and therefore is rarely used for diagnostic purposes. Still, once it is performed it can also be used for copper quantification, even if copper cut-offs are not extensively validated in neurological patients.

### *When should molecular-genetic analyses be performed and which approach should be used when WD is suspected?*

#### Recommendations

- Molecular testing is recommended to confirm the diagnosis of WD or to complete diagnosis if clinical and biochemical testing is not decisive **(LoE 2, strong recommendation, strong consensus).**
- A stepwise approach may be applied to reduce costs of testing, starting from most common variants up to whole-exome testing **(LoE 3, weak recommendation, consensus).**
- Screening the full-length sequence of *ATP7B* by next-generation sequencing should be performed in non-conclusive cases **(LoE 2, strong recommendation, strong consensus).**

Direct molecular-genetic diagnosis is difficult, because of the occurrence of more than 2,500 variants; except for a few, each variant is rare.[1,135] Furthermore, most patients are compound heterozygotes (*i.e*. carry two different variants). Over recent decades, genetic testing has improved steadily (for detailed review of the methodologies see[150]). Comprehensive molecular-genetic screening that previously took several months is now more rapid due to advances in DNA sequencing techniques, but still may take weeks in commercial laboratories. This makes this an impractical method in a patient who needs a final diagnosis within a shorter time frame. Nevertheless, it is reasonable to perform molecular analysis of the *ATP7B* gene in any patient who has a provisional diagnosis of WD, both for confirmation purposes and to facilitate the subsequent screening of family members.

Patients with WD present with a spectrum of organ involvement with variability in signs and symptom severity that requires clinical correlation and expertise to interpret genetic findings.

Databases of variants must be used with caution when variant pathogenicity is interpreted. The frequency of misannotation of the *Human Gene Mutation Database* (*HGMD®*) variants and annotation concordance between databases in depth is around 3.5%.[151] Sequencing results or WES reports, which contain information on genetic variants, require clinical correlation. The classification and interpretation of these variants (as pathogenic, likely pathogenic, or variant of uncertain significance [VUS]) reflects the current state of scientific understanding.[152] It should be kept in mind that a VUS corresponds to a genetic alteration for which current information is insufficient to determine pathogenicity; therefore, a VUS should not be used in clinical decision making. Finding an undescribed sequence variation of *ATP7B* is not necessarily sufficient to establish the diagnosis of WD. The availability of new technology does not necessarily mean that disease-causing variants

can be found in all patients.[153,154] Asymptomatic patients with two unknown *ATP7B* variants (homozygous or compound heterozygotes) should undergo complete diagnostic work-up including REC if available, liver biopsy with copper quantitation and imaging of the central nervous system.[155]

However, there are still patients with clinically suspected WD who do not have detectable pathogenic variants, which makes diagnosis difficult and delays treatment. The full-length sequence of *ATP7B* has been screened by next-generation sequencing in such patients. Newly identified synonymous[156] and intronic variants were then identified.[157,158] Pathogenicity of a genetic variant can be tested in cell models, *e.g*. by analysis of RNA transcripts from primary fibroblasts.[159]

Moreover, large deletions in *ATP7B* are rare, but account for a detectable proportion in some patients with WD and may require additional molecular analysis like MLPA (multiplex ligation-dependent probe amplification).[160]

***Which screening approach should be followed in siblings and first-degree relatives (parents, offspring of patients with a confirmed diagnosis of WD)? (whom to screen and with which diagnostic tests, including prenatal screening).***

### Recommendations

- It is recommended to measure serum ceruloplasmin and 24-h urinary copper excretion (and relative exchangeable copper if available), evaluate clinical symptoms and to perform liver tests in siblings and in first-degree relatives (parents and offspring of an index case) **(LoE 3, strong recommendation, strong consensus).**
- Molecular-genetic testing should be performed in siblings to search for the biallelic variants from the index patient **(LoE 2, strong recommendation, strong consensus).**
- Molecular testing should be performed in first-degree relatives with abnormalities of copper metabolism or abnormal liver tests **(LoE 3, strong recommendation, strong consensus).**

It is essential to screen the family of patients presenting with WD[161] because the chance of a sibling having WD is 25%. Parents are at least heterozygotes, and to confirm that the detected variants are biallelic, the father and mother have to be genotyped. It is advisable to extend molecular testing beyond siblings.[162–165] Amongst offspring the likelihood is 0.5% to 4%.[166,167] The probability of nephews and nieces being affected is 1 in 600, and the probability of cousins being affected is 1 in 800,[32] which is significantly higher than that of the general population. Although this risk is low, analysis of the *ATP7B* gene for variants in offspring of an index patient is justified given the potential devastating course of WD.[161] If the child is symptomatic, the other parent needs to be tested, including clinical assessment and copper metabolism.

If the variants on both chromosomes are known in the index patient, it is sufficient to sequence the exons carrying the variant. If the variant(s) of the index case are not detected, pedigree analysis using haplotypes based on polymorphisms surrounding the *ATP7B* gene is available. This analysis requires the identification of an index patient with an unquestionable diagnosis of WD within the family. DNA is required from both parents. The inheritance of the "disease associated" haplotypes make it possible to determine whether siblings are unaffected, heterozygous, or indeed patients. Genetic testing is the most reliable method to separate heterozygote from homozygote siblings.

Based on the Wilson & Jungner criteria,[168] WD may be suitable for mass screening, especially in neonates. However, currently, there are no effective biomarkers or methods suitable for newborn screening for WD.[169]

Ceruloplasmin has been tested for paediatric and newborn screening with limited utility. Newer technologies are needed. Quantification of ATP7B peptide effectively identified 92.1% of patients with known WD and reduced ambiguities resulting from ceruloplasmin and genetic analysis.[170] This method is currently being evaluated for neonatal screening. In the Qingdao area (Province of China), sequencing using multiplex PCR combined with second-generation sequencing of 5,012 dried bloodspots from neonates revealed a carrier frequency of 12 hotspot variants of 1.46%.[171] Therefore, currently family screening is the only way to look for asymptomatic patients with normal liver tests.

***Should children or adults with WD undergo a detailed neurological examination at diagnosis?***

### Recommendations

- A detailed neurological examination should be performed in all adults following a diagnosis of WD **(LoE 3, strong recommendation, strong consensus).**
- A detailed neurological examination should be performed in children following a diagnosis of WD if they have neuropsychiatric symptoms or are >10 years of age **(LoE 3, strong recommendation, strong consensus).**

In many cases, classification of neurological features is challenging as patients with WD can have various signs and more than one abnormality, each with a different level of severity. The clinical course of the disease is also difficult to predict. Neurological symptoms can be subtle and persist for many years, or their onset and progression may be rapid, leading to severe disability within a few months. There may also be substantial fluctuations, with stress, general health conditions and concomitant treatments aggravating neurological symptoms.[40,172,173] To describe the severity of neurological involvement in WD, a detailed neurological evaluation should be performed in all adult patients with a confirmed diagnosis of WD, regardless of presentation. To allow for precise evaluation and follow-up, a validated scale should be used like the UWDRS.174

Children with WD can experience neurological symptoms, but much less frequently than hepatic manifestations.[175–177] In a French study of 182 children with WD, 84.6% had hepatic manifestations, 10.4% had neurological manifestations and 4.9% were asymptomatic at diagnosis.[103] Symptoms among 50 children with neurological WD in Pakistan included dystonia, dysarthria and cognitive decline (92%), drooling (68%), tremors (52%), chorea (24%) and seizures (12%).[175] These symptoms may

represent the more severe end of the clinical spectrum, while other neuropsychiatric symptoms may be more subtle and difficult to distinguish from the behavioural changes of adolescence. Declining school performance, personality changes, labile mood and compulsive behaviours may be observed.[176] If neuropsychiatric symptoms are discovered during the diagnostic work-up, a detailed neurological examination including MRI (see below) should be performed, but teenagers should be examined irrespective of symptoms to detect minor changes for further follow-up and treatment decisions.

***What neurological investigations should be performed at diagnosis in patients with WD?***

**Recommendations**

- Neurological assessment using a validated scale is recommended in adult patients and children >10 years of age with a confirmed diagnosis of WD and at any age if they have neuropsychiatric symptoms **(LoE 2, strong recommendation, consensus).**
- A brain MRI should be performed in all adult patients and children >10 years of age with a confirmed diagnosis of WD **(LoE 2, strong recommendation, consensus).**

Neurological investigations are part of the multidisciplinary approach to WD. The UWDRS neurological subscale is considered a valuable tool for the comprehensive evaluation of neurological signs and symptoms in patients with WD.[178] Developed by the EuroWilson consortium and the German Network of Hereditary Movement Disorders (GeNeMove), this 34-item scale is based on partly modified elements from well-established and validated scales assessing neurological status, such as the Barthel index, the Unified Parkinson's Disease Rating Scale, and the Unified Huntington's Disease Rating Scale.[30,100] Part I of UWDRS concerns consciousness, part II evaluates disability and part III involves a neurological examination using clinical rating scales, *e.g*. for tremor and cerebellar disorders to measure neurological signs. UWDRS part III scores correlate with brain MRI findings,[179] exchangeable copper[180] and optical coherence tomography of the retina,[47] but not serum levels of ceruloplasmin, copper, non-ceruloplasmin-bound copper or liver tests.[34] UWDRS has not been validated in children. Tier 2 of the Global Assessment Scale for Wilson's Disease (GAS for WD) is a shorter 14-item scale that also scores neurological dysfunction[181] and has been suggested as an alternative to UWDRS.[178] In addition, a shorter version of the UWDRS ("minimal UWDRS") that contains only nine patient-reported items has been assessed as a feasible, economical tool for the evaluation of the neurological status in patients with WD, with mild to moderate neurological symptoms.[178] Although not commonly used, with further validation, the minimal UWDRS may be useful as a screening tool in all patients, even children. Currently, brain MRI is the most sensitive neuroimaging method to assess neurological pathology associated with WD.[3,31] More than 90% of patients with WD and neurological symptoms have brain MRI abnormalities.[36,182,183] In addition, neuroimaging abnormalities are present in approximately 40–70% of patients with predominantly hepatic presentation and in 20% of asymptomatic WD cases.[36,184]

Different brain regions appear to have distinct susceptibilities to copper toxicity.[34] The most prominent MRI findings in WD are symmetric hyperintensities in T2-weighted or FLAIR images in the deep grey matter nuclei and white matter predominantly in the brainstem, which presumably reflect oedema, demyelination and gliosis.[184] In addition, signs of diffuse tissue atrophy[185,186] and hypointensities in T2/T2* and SWI in the deep grey matter caused by abnormal iron accumulation (resulting from necrosis) are frequently present.[187,188] So-called pathognomonic neurological signs of WD include the 'face of the giant panda sign', which is present in around 15% of cases and 27% of patients with neurological WD.[179] As the presence of MRI brain changes is observed in patients with neurological, hepatic and presymptomatic WD, MRI seems to be justified in all patients before the initiation of therapy. The evaluation of baseline MRI changes guides treatment and enables monitoring of disease progression and response to treatment.

MRI scoring approaches are needed to quantify the degree of brain parenchyma damage for treatment monitoring and outcome prediction. Recently, a semiquantitative scale for assessing brain MRI abnormalities that scores acute toxicity, chronic damage and atrophy was validated.[97] The acute toxicity score reflects T2/FLAIR hyperintensities in the caudate nucleus, thalamus, putamen, mesencephalon, pons or other areas, and relates to potentially reversible lesions, resulting from oedema, demyelination and gliosis. The chronic damage score reflects the sum of T2/T2*/SWI hypointensities assessed in the putamen, globus pallidus, thalamus, caudate nucleus and dentate nucleus. Together with the atrophy score, which is assessed on T1 sequences, these components represent irreversible damage, resulting from iron accumulation, necrosis and degeneration. Functional impairment and neurological deficits scored using UWDRS part II and III correlated well with acute toxicity, chronic damage and total scores using the MRI scale.[179]

Other neuroimaging methods, such as MRS and transcranial brain ultrasonography,[188–192] may also provide relevant data, although these methodologies are not in routine use. Studies have shown abnormal visual, brainstem auditory and motor evoked potentials in patients with WD,[187,193–195] but currently such investigations may be of more use in the research setting. Retinal and visual pathway abnormalities are also active areas of current research.[47,196] Plasma neurofilament light concentrations have been shown to be a biomarker of neurological involvement[197,198] and, following further validation, may prove a useful adjunct to clinical and neuroimaging disease severity scales.

With regards to abnormal MRI findings in children with WD, a study (n = 50) found that high-signal intensity lesions in the basal ganglia on T1-weighted images reflected hepatic involvement, while high-signal-intensity lesions on T2-weighted images reflected cerebral involvement and showed a good correlation with neurologic symptoms.[117] Following copper-chelating therapy, follow-up of MRI changes was strongly correlated with improvements due to treatment ($p$ <0.001), indicating that MRI may be helpful in assessing clinical response. We suggest that a brain MRI scan should be performed in children with a confirmed diagnosis of WD and neuropsychiatric signs or symptoms or Kayser-Fleischer rings or even without any signs of neuropsychiatric involvement if aged >10 years.

## Treatment

***How should treatment response be defined in patients with WD?***

### Recommendations

- Treatment response should be evaluated by clinical and laboratory/imaging parameters as well as laboratory tests of copper metabolism **(LoE 3, strong recommendation, strong consensus).**
- Treatment response should be defined by resolution of liver symptoms (jaundice, ascites) and/or improvement of liver parameters (ALT, INR, albumin) and/or progressive improvement of neurologic symptoms, disappearance of Kayser-Fleischer rings or at least no deterioration on a validated scale or on brain imaging **(LoE 3, strong recommendation, strong consensus).**

Treatment response should be evaluated according to baseline abnormalities – both clinical and biochemical. The parameters used to define treatment response are variable, depending on the initial clinical presentation. The major parameters to measure clinical response in liver presentation are the resolution of ascites and/or jaundice.[104,199]

In neurological presentation, all abnormal neurological findings should be evaluated and a validated UWDRS scale should be used.[200] Neurological response to chelators may be delayed and is defined by the progressive disappearance or attenuation of symptoms and the decrease or normalisation of the UWDRS score.[174,200] Brain MRI can be used to measure treatment response with a progressive vanishing and disappearance of T2/FLAIR hypersignal.[201]

Liver disease is defined not only by clinical symptoms but also by laboratory liver tests which include mainly ALT, AST, prothrombin time/INR and bilirubin. A complete liver response is indicated by normalisation of all these tests, though some abnormalities such as slightly increased ALT (<1.5x the upper limit of normal) may persist in the long term.[202] Liver biopsy is not used in practice to measure treatment response, however, non-invasive fibrosis assessment can show improvement of fibrosis markers with long-term treatment. Liver copper may drop under therapy but usually remains increased in the long term and is not used for monitoring.[203]

Copper parameters used for diagnosis of WD should be monitored during therapy. Treatment should aim at decreasing urinary copper excretion, non-ceruloplasmin-bound copper and exchangeable copper, but these parameters are strongly related to the choice of pharmacotherapy.[204–207]

***Which pharmacological treatment is recommended in patients with WD to achieve response?***

### Recommendations

- Chelators should be the primary choice in patients with significant liver disease, *e.g.* features of significant fibrosis and cirrhosis, liver failure, and haemolysis **(LoE 3, strong recommendation, strong consensus).**
- Either zinc or chelators should be used in patients with a neurological presentation **(LoE 2, strong recommendation, consensus).**
- A 'start low, go slow' treatment regimen is recommended for chelators, especially in patients with a neurological presentation **(LoE 3, strong recommendation, strong consensus).**
- Either zinc or chelators may be used in asymptomatic patients without signs of significant liver involvement **(LoE 4, weak recommendation, consensus).**

The aim of pharmacological treatment in WD is to remove excess copper via inhibition of intestinal copper absorption (zinc salts) or by using copper-chelating agents such as D-penicillamine and trientine. Treatment should be started immediately after diagnosis in symptomatic children and adults to prevent further progression of liver and/or neurological disease and continued throughout life. Asymptomatic patients diagnosed by family screening should receive treatment after 2-3 years of age. Administration of drugs, especially to very young children is challenging.[15] There is no high-quality evidence for the optimal first-line treatment choice in WD.

**D-penicillamine** chelates copper and enhances its excretion into urine. Additionally, it induces endogenous hepatic metallothionein – a cytosolic metal-binding protein which sequesters copper and protects the liver from its toxic effects. D-penicillamine has been shown to efficiently prevent the progression of disease in children with WD. It improves liver symptoms in over 80% of symptomatic children within a mean time of 16 months[208] including those presenting with liver failure but no hepatic encephalopathy. Adverse effects of D-penicillamine may result in drug withdrawal in 15-30% of cases.[208–210] Worsening of neurologic symptoms may occur in up to 14.3% of patients with WD,[209,211,212] especially in patients with neurological involvement at treatment onset or those treated with dopamine receptor antagonists.[213,214] Early adverse effects include sensitivity reactions, *e.g.* fever, cutaneous eruptions, neutropenia, thrombocytopenia, lymphadenopathy and proteinuria. There are reports on medium- and long-term adverse events such as D-penicillamine-related lupus-like syndrome, bone marrow toxicity with severe thrombocytopenia or aplasia, and skin changes such as *elastosis perforans serpiginosa*, *cutis laxa*, pemphigus, *lichen planus*, and aphthous stomatitis.[215] Iron can be given between the chelator doses orally to prevent iron deficiency, but this is not required for all patients if dietary iron intake is sufficient.

The dose of D-penicillamine should be gradually increased in children to 20 mg/kg/day given in 2 or 3 doses and in adults to 1,000–1,500 mg given in 2 to 3 divided doses (preferably 2 doses) with close follow-up for the occurrence of adverse events mentioned above. Drugs should be administered 1 h before or 2 h after meals (detailed dosing in Table 7). Increases in dose should be progressive and related to neurological severity (*e.g.* prolonged to 8 weeks or longer). In some clinical situations (*e.g.* ALF) the dose has to be increased more rapidly.

**Trientine** (triethylene tetramine hydrochloride) was originally reserved for patients who developed adverse events related to D-penicillamine.[216] Currently two forms of trientine are

**Table 7. Characteristics and description of drug administration for Wilson's disease.**

| | Zinc acetate/sulphate per elemental zinc | D-penicillamine | Trientine |
|---|---|---|---|
| **Dosage** | • Age >16 years and body weight >50 kg: 150 mg/day in 3 divided doses.<br>• Age 6 to 16 years and body weight <50 kg: 75 mg/day in 3 divided doses<br>• Under 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 1,000-1,500 mg in young adults given in 2 or 4 divided doses.<br>• Maintenance dose: 10-20 mg/kg/day up to 750-1,000 mg/day in 2 divided doses | Currently there are two available forms: TN-2HCl and TN-4HCl.<br>• Starting dose for TN-2HCl (250 mg or 200 mg capsules) gradually increasing to about 20 mg/kg/day: 500-750 mg/day in children and 750-1,600 mg/day in adults in 2-4 divided doses.<br>• Maintenance dose for TN-2HCl is 10-15 mg/kg per day, maximum 1,500 mg/day in children and 750-1,500 mg/day in adults divided in 2-4 doses.<br>• Starting dose for TN-4HCl (150 mg capsules) gradually increasing to 225-600 mg/day in children and 600-975 mg/day in adults in 2-4 divided doses<br>• Maintenance dose: 225-600 mg/day in children and 450-975 mg/day in adults divided in 2-4 doses. |
| **Administration** | 1 h before meal or 2 h after meal | 1 h before meal or 2 h after meal | 1 h before meal or 2 h after meal |
| **Adequacy of treatment parameters** | • 24-h urinary copper excretion: 30-75 μg (0.5–1.2 μmol)/24 h on maintenance treatment<br>• Serum zinc level >125 μg/dl<br>• Urinary zinc >2 mg/24 h on maintenance treatment | • 24-h urinary copper excretion: 200-500 μg (3-8 μmol)/24 h on maintenance treatment | • 24-h urinary copper excretion: 150-500 μg (3-8 μmol)/24 h on maintenance treatment |
| **Liver test improvement** | ALT normalisation up to 1 year | Up to 6 months, INR normalisation to 1 year | Up to 6 months, INR normalisation to 1 year |
| **Indication for a drug change** | • Persistent ALT >3x upper limit of normal and/or INR >1.5<br>• Poor tolerance or side effects, *e.g.* abdominal pain | Poor tolerance or side effects | Poor tolerance or side effects |

ALT, alanine aminotransferase; INR, international normalised ratio; TN-2HCl, trientine dihydrochloride; TN-4HCl, trientine tetrahydrochloride.

available: trientine dihydrochloride (trientine-2HCl) and trientine tetrahydrochloride (trientine-4HCl). Adverse effects on trientine seem to be less frequent than on D-penicillamine but still may include allergic reactions, arthralgias, muscle cramps, and sideroblastic anaemia in cases of overtreatment.[217] The therapeutic efficacy of trientine-2HCl is similar to that of D-penicillamine, which was shown in a cohort of adults with liver symptoms.[218] In one study, trientine-2HCl was associated with a higher risk of neurologic worsening than D-penicillamine in patients with a neurologic manifestation of WD. In a paediatric study, trientine-2HCl, used as second-line therapy after D-penicillamine intolerance, improved liver function but did not alleviate accompanying neurological or psychiatric symptoms.[217] In a recent randomised, open label study, 4HCl-trientine as maintenance therapy was non-inferior to D-penicillamine and was well tolerated in adults with WD.[219]

The dose of trientine should be gradually increased, similarly to D-penicillamine, to avoid neurologic deterioration. The dose of trientine-2HCl in children is 20 mg/kg/day given in 2-3 doses. In adults, the dose is 750-1,600 mg/day in 2-4 divided doses (preferably 2 doses) for trientine-2HCl, or 600-975 mg/day in 2-4 divided doses (preferably 2 doses) for trientine-4HCl. During therapy patients should avoid concomitant oral iron supplementation. Tablets must be given on an empty stomach for optimal absorption (for details see Table 7). In many countries, trientine is a second-line option after D-penicillamine because of its high cost.

**Zinc** induces metallothionein in enterocytes and subsequently copper is sequestered in enterocytes, which – at the end of their life cycle – carry copper into the lumen. Zinc also has an impact on hepatocyte metallothionein and may have additional copper-detoxifying effects. Zinc salts are usually used for the first-line treatment of asymptomatic patients and for maintenance therapy after initial de-coppering with D-penicillamine or trientine. Zinc monotherapy in symptomatic patients with liver disease remains controversial.[220]

Zinc as first-line monotherapy showed a better tolerance profile than D-penicillamine in various presentations of WD.[207,209,221,222] However, treatment failure was reported in symptomatic children with liver disease. Furthermore, patients who relapsed on zinc improved after reintroduction of a chelating agent.[207,223] Patients receiving zinc salts can experience neurological deterioration, though the risk appears lower than for D-penicillamine or trientine.[222]

There are several formulations of zinc salts available: zinc sulphate, zinc acetate and zinc gluconate. Zinc sulphate is associated with gastrointestinal problems, such as nausea, vomiting, epigastric pain, gastric/duodenal mucosal ulceration that may lead to poor adherence both in children and adults.[224] Such symptoms seem to be observed less often with zinc acetate.[224,225] Other adverse reactions include anaemia and increased serum amylase and lipase levels without clinical or radiological features of pancreatitis. The recommended dose of zinc is 25 mg of elemental zinc in children under 5 years of age, 75 mg/day in older children (<50 kg of body weight) or 150 mg/day in adults and children with body weight >50 kg, in 2-3 divided doses. Zinc should not be taken with food because it interferes with its absorption (1 h before a meal or 2 h after a meal) (Table 7). Some centres use combined zinc and chelator therapy, which is generally not recommended. Still, if such a combination is used, the drugs should be given at least 3 h apart.[84]

In the publications reporting treatment of WD, asymptomatic patients were inconsistently described either as healthy patients picked up by family screening or as patients with asymptomatic alterations in liver function or neurological status.

Both chelators and zinc were shown to be effective in the treatment of asymptomatic patients.[209,210,224–226] Although chelators were reported to be used efficiently for treatment of significant liver disease, we still do not have the same evidence for zinc.[207,208,210,217,218,222,227] Both zinc and chelators were shown to be effective in the treatment of patients with a neurological presentation.[209]

The studies performed to date have used mainly clinical and basic laboratory parameter endpoints. Most of the studies did not compare different therapies head-to-head and only one proper randomised-controlled trial on the described therapies has been reported.[219] Some new drugs have been tested and described without further registration.[228] Long-term effects of therapy are mainly dependent on patient adherence to treatment. There are several reasons for poor compliance. Insufficient knowledge of the disease, lack of family support, poor monitoring of copper metabolism by treating physicians, inadequate transition programmes and neuropsychiatric symptoms are the key factors.[229,230] Even if WD is a genetic disorder with favourable treatment outcomes in almost 85% of cases, the problems with irreversible neurological deteriorations (up to 12%), adverse drug reactions (in up to 30%), non-compliance with anti-copper treatment (3 times daily, before or after meals, administration of zinc without milk in food) or persistence of neurological symptoms (up to 50% patients) exist.[33,101,173,231]

New therapies with a better safety profile, greater efficacy, and easier administration (*e.g.*, once daily or with food) are needed. The current investigations focus on: 1) new pharmacological treatment possibilities[232]; 2) cell/gene therapies which aim to restore the function of ATP7B.[231]

***In patients with WD, should a low-copper diet be advised?***

### Recommendations

- Avoiding frequent dietary intake of food containing high concentrations of copper is suggested in symptomatic patients with WD until remission/stabilisation of signs and symptoms, especially in the first year of treatment **(LoE 4, weak recommendation, strong consensus).**
- Further low-copper dietetic restrictions may be evaluated with regard to the effects of therapy and quality of life **(LoE 4, weak recommendation, consensus).**

There is no high-quality evidence for the efficacy of a low-copper diet in the management of WD. It is known that copper restriction is important, but it does not prevent copper accumulation.[233,234] Therefore, it cannot be recommended as the only therapy.[235] Common copper-rich foods are shellfish, nuts, black chocolate, cocoa powder, mushrooms, liver and organ meats. Sometimes high concentrations of copper may be found in water, especially when the household is supplied by copper pipes. Avoiding copper is advised until remission of symptoms and improvement of biochemical abnormalities, usually in the first year of treatment.[235] After that, restrictions on copper intake are modified based on the response to therapy, treatment used (chelators *vs*. zinc) and quality of life. Dietary support can be considered in all patients with WD.

***Once treatment response is achieved, should initial therapy (dose and type of drug) be changed?***

### Recommendation

- Once treatment response is achieved, a change of treatment (lowering chelator dose, switching to zinc) can be considered for medium and long-term safety reasons **(LoE 4, weak recommendation, strong consensus).**

Changing therapy is justified by several factors like efficacy and side effects but also patient's preference, compliance and copper balance. This question is not discussed in publications so we cannot directly describe how dose changes during therapy. Different treatment scenarios are presented in clinical practice. Still, the major issue is copper balance and usually it improves with time due to de-coppering. Therefore, we suggest adjusting the dose of chelators or zinc to copper balance. This problem was carefully discussed in a longitudinal study by Jan Pfeiffenberger *et al.*[206]

Still, even this study did not present changing dose over time when compared with copper balance. However, long-term studies have shown that over time an increasing number of patients are being treated with zinc or trientine *vs*. D-penicillamine.[23]

Once clinical and biochemical response is achieved (as described above), usually in about 6-12 months, patients may still be treated with maintenance dosages of chelators or switched to zinc.[236] Long-term treatment with zinc can be considered as more selective for de-coppering than chelators and related to milder side effects,[237] but is not recommended in cirrhosis. On the other hand, it has recently been shown that trientine was equally efficient and well tolerated as D-penicillamine for the maintenance treatment of WD.[219] The initiative to change treatment may come from the patients or parents and should be discussed with the physician. However, there is no solid scientific evidence regarding when to change treatment in patients with either hepatic or neurological presentations of WD.[238]

***What is the preferred therapeutic strategy in patients with WD who do not achieve sufficient treatment response or develop paradoxical neurological worsening or side effects on first-line therapy?***

### Recommendations

- When patients do not achieve sufficient treatment response, adherence should be checked in detail based on copper balance, laboratory investigations and clinical symptoms **(LoE 2, strong recommendation, strong consensus).**
- In patients with WD who do not achieve sufficient treatment response on first-line therapy despite a good adherence to treatment and a 24-h urinary copper excretion in the target range, or side effects, switching treatment should be considered (D-penicillamine to trientine and vice versa or zinc to chelators) **(LoE 2, strong recommendation, strong consensus).**

- In patients with WD who develop paradoxical neurological worsening on first-line therapy, decreasing the dose of chelators and slowing the increase of doses or changing the WD treatment should be considered (chelators to zinc or zinc to chelators) **(LoE 2, strong recommendation, consensus).**
- LT should be considered on a case-to-case basis in patients with a continuous worsening of neurological symptoms despite at least 6 months of optimised medical treatment **(LoE 2, strong recommendation, consensus).**
- LT should be considered in patients with decompensated cirrhosis despite adequate medical treatment **(LoE 2, strong recommendation, strong consensus).**

If the diagnosis is made early, before the development of advanced liver or brain disease, and patients adhere well to pharmacological treatment, a favourable treatment outcome is observed in almost 85% of cases, and prolonged survival has become the norm.[239–241] Markers of liver dysfunction improve in over 90% of patients, usually within 2–6 months, while clinical neurological improvement is observed in approximately 50–60% of patients over a longer time course of 1–3 years.[3,46,242] A recent meta-analysis of 16 cohort studies exploring the efficacy of D-penicillamine or zinc revealed that the pooled improvement rate in all symptomatic patients with WD is 78.0% (95% CI 70.8%–85.2%). In patients with symptomatic hepatic WD and neurological WD, the pooled improvement rates are 76.0% (95% CI 59.0%–92.0%) and 74.0% (95% CI 66.0%–81.0%), respectively.[222]

Despite the good overall outcome, first-line therapy may lead, in some patients, to an insufficient treatment response with liver decompensation and worsening of neurologic symptoms (14.3%),[211,212,243] especially in patients with neurological involvement at treatment onset or those treated with dopamine receptor antagonists, or adverse drug reactions (up to 30%).[46,213,214] An approach to overcome this problem is the careful and systematic assessment of biochemical response patterns and the quantitative monitoring of symptoms using validated rating scales.

When patients do not achieve a sufficient treatment response, adherence should be examined in detail, as poor adherence to treatment is present in up to 50% of patients with WD,[230,244,245] and is a frequent cause of worsening or inadequate response.[230,246] The reasons for poor compliance with treatment are multiple: insufficient knowledge of the disease, psychological difficulties, the burden of taking medication 2 or 3 times a day outside of meals, side effects of medication, lack of family support, and infrequent monitoring of copper levels by physicians. Close follow-up with monitoring of treatment, copper metabolism,[206] adverse events, and involving the patient in the treatment process, along with psychological support and/or educational programmes, may improve adherence.[230,244] To improve adherence to lifelong therapy, the treatment scheme should be as simple as possible. Simplifying maintenance therapy by using a single daily dose could be a good option but further studies are required to confirm similar effectiveness.[247–249]

The presence of side effects is also a potential reason for poor adherence and may lead to clinical aggravation. D-penicillamine efficiently prevents disease progression in children and adults with WD, but intolerance and serious side effects as previously described may result in drug withdrawal in 15% to 30% of cases in both children and adults.[208–210] There is evidence that D-penicillamine could perturb $H_2O_2$ redox homeostasis (through transient but recurring catalase inactivation) and induce oxidative stress, which may, in part, explain some of the deleterious effects observed with this therapeutic agent.[211,250] Trientine or zinc are effective in preventing the effects of interrupting D-penicillamine therapy.[251–253] Trientine has a better tolerance profile than D-penicillamine, but some side effects (nausea, skin rash, colitis, anaemia, etc.) may lead to proposing a switch of treatment. Zinc as a first-line monotherapy showed a better tolerance profile than D-penicillamine in various presentations of WD.[207,209,221,251,254] The main side effects are gastrointestinal, including nausea, vomiting, and abdominal pain.[224,254–256]

To date, no randomised-controlled trials have been conducted on monotherapies for first- and second-line WD treatments. However, current efforts are underway to design clinical trials in WD to compare the efficacy and safety of various treatments.[257] Regardless of the reason for moving to second-line treatment (insufficient treatment response, development of neurological worsening, or side effects on first-line therapy), the choice of therapy should be based on the patient's phenotype. Owing to the distinct mechanisms of action between copper chelators and zinc salts, transitioning requires a period of overlap and increased monitoring. No large studies have investigated the optimal transition strategies between agents.

In patients with hepatic disease, with or without the presence of acute haemolytic anaemia, the severity of liver disease determines the treatment approach. Validated scores guide physicians in assessing whether the timeframe for another medical intervention is sufficiently broad or if urgent liver transplantation (LT) is warranted.[104] LT may be considered in WD cases at the stage of ALF or when there is a progression of liver dysfunction despite drug therapy.[46] If LT is not indicated, the preferential use of an alternative chelating agent appears reasonable.[218,219,258–261] Chelators establish a negative copper balance more rapidly than zinc salts, and zinc monotherapy may prove inadequate for controlling hepatic disease in a subset of these patients. Moreover, individuals who experienced relapses on zinc demonstrated improvement upon reintroduction of chelating agents.[207,223] In a paediatric study, trientine, used as a second-line therapy after D-penicillamine intolerance, was as efficacious as D-penicillamine, and small population studies indicate an improved side effect profile.[217] That said, zinc monotherapy was reported to be effective as an alternative treatment option for WD-related decompensated liver disease in a recent case report.[262] Furthermore, a recent meta-analysis comparing the effects of D-penicillamine and zinc demonstrated that these two treatment options exhibit similar efficacy in managing symptomatic hepatic WD (relative risk 0.98, 95% CI 0.86–1.12; $p = 0.765$). It is important to note that first- and second-line therapies were merged in the analysis.[222]

A recent meta-analysis of 32 retrospective studies (217 cases) showed that early neurological worsening on first-line therapy – corresponding to a worsening up to 6 months after the initiation of anti-copper treatment – occurred in 14.3% of patients with WD and mainly in those with neurological disease. It involved 21.8% of patients with initial neurological symptoms.[212] Risk factors included severe neurological involvement at baseline (especially dystonia), brainstem and thalamic lesions on MRI, younger age of onset and concurrent antipsychotic drug use.[213,263] Most neurological deterioration occurred in patients treated with D-penicillamine (70.5%), and much less frequently with trientine (14.2%) or zinc salts (6.9%); based on the data it was not possible to determine if the risk of deterioration differed with therapy.[212] Studies concentrating on second-line therapy for patients experiencing neurological deterioration despite initial treatments are limited. Retrospective analyses involving children and adults with WD who exhibited neurological deterioration while on D-penicillamine therapy have suggested that effective management and positive outcomes can be achieved with trientine or zinc. Additionally, small-scale population studies have indicated a lower incidence of side effects.[217,252] A recent meta-analysis comparing the effectiveness of D-penicillamine and zinc salt treatments for patients with a neurological presentation, but where first- and second-line therapies were combined, showed that the response rate to chelation therapy was in the same range as that reported for zinc monotherapy (relative risk 0.83, 95% CI 0.40%–1.75%; $p$ = 0.632). The pooled improvement rate in five studies reporting effectiveness data for patients with neurological WD treated with D-penicillamine was 56.3% (95% CI 37.5%–75.1%). In contrast, the pooled improvement rate in three studies reporting zinc salt treatment for patients with neurological WD was 80.2% (95% CI 67.2%–93.2%). Consequently, zinc salts appear to have superior effectiveness to D-penicillamine in the first- or second-line treatment of patients with neurological WD.[222] For patients experiencing worsening neurological symptoms on first-line therapy, the initial recommendation should involve reducing the chelator dosage and adopting a gradual dose escalation approach ("start low and go slow"), along with discontinuing dopamine receptor antagonists.[46,212] If ineffective, the recommendation is to consider switching WD treatment (between chelators and from chelators to zinc), despite the absence of clear evidence from head-to-head treatment studies comparing the effects of D-penicillamine, trientine, and zinc in patients with neurological symptoms. There are indications that zinc and trientine are associated with fewer side effects and a lower treatment discontinuation rate than D-penicillamine therapy while being similarly effective.[211,251,252,264] Consequently, zinc or trientine may also be employed as second-line therapy for patients experiencing neurological deterioration despite first-line treatment.

As a last option, LT may be considered in the case of continuous worsening of neurological symptoms or an intractable neurological situation under active chelation therapy[265] (see 2.10). Objective clinical and radiological scores, such as the UWDRS and the semiquantitative brain MRI scale, are recommended to assess the severity of the disease and its evolution.[97,174,178] The combination of D-penicillamine and zinc salts is effective in treating liver and neurological symptoms but increases adherence difficulties. This combination has not been studied as a second-line therapy.[266]

CRISPR/Cas9-mediated correction of *ATP7B* point mutations is feasible and may have the potential to be transferred to the clinic.[267–269]

***Is a defined period of medical treatment (chelators or zinc) indicated in patients with WD and decompensated cirrhosis before they are referred for LT?***

**Recommendation**

- Patients with decompensated cirrhosis in WD may respond to medical therapy, usually after >3 months of treatment, but they should be concomitantly evaluated for LT **(LoE 3, strong recommendation, strong consensus).**

Liver function in patients with WD and decompensated cirrhosis may improve with chelation treatment.[46] However, the probability of treatment response is affected by a variety of factors such as patient age, tolerance to therapy, and degree of liver dysfunction.[23,270] Patients with WD and decompensated cirrhosis typically present with hypoalbuminemia and coagulopathy, complications of portal hypertension such as ascites or hepatic encephalopathy, and jaundice.[271] These patients are usually older by 10–20 years than those with ALF,[238] thus increasing the risk of treatment nonresponse. In decompensated patients receiving medical therapy, close follow-up of liver function and monitoring for development of further decompensation are mandatory and could be better performed in tertiary care liver units with immediate access to LT.[272] Recently, "combination" therapy with either D-penicillamine or trientine plus zinc has been proposed as an intensive regimen for patients with decompensated liver disease.[84] However, further studies are required to better understand the potential clinical benefit of this practice. Essentially, all patients with WD and decompensated chronic liver disease who fail to respond to or tolerate medical therapy should be considered promptly for transplantation.[273]

Prognostic scoring systems such as the new Wilson index (NWI) may help identify these patients.[104] This score assigns points to serum total bilirubin, AST, INR, white blood cell count, and serum albumin. The points assigned for each of these five parameters are summed to calculate the score. A score of ≥11 is a strong predictor of mortality without LT. Importantly, the NWI had a higher diagnostic accuracy and lower false negativity rate than the Nazer and MELD (model for end-stage liver disease) scores.[274] Prospective assessment of NWI in patients receiving therapy may improve prediction of disease trajectory and need for transplantation.[84]

Case series and small observational studies suggest that dialysis, plasmapheresis, albumin dialysis and high-volume plasma exchange can be considered as bridging therapies to LT in patients with WD ALF, especially once excess copper is detectable within the plasma.[275,276] Indications for such therapies in patients with decompensated cirrhosis should be discussed in a multidisciplinary setting and on an individual basis, and ultimately depend on local availability and experience. It should be highlighted, however, that the availability of such therapies should not preclude or slow down LT evaluation or the access to the waiting list.

***Which treatment strategy is recommended in patients with WD during pregnancy and breastfeeding?***

### Recommendation

- Any anti-copper therapy should be maintained during pregnancy and breastfeeding **(LoE 4, weak recommendation, consensus).**

Reproductive health is a major need for women with childbearing potential living with WD. Untreated WD is associated with infertility, miscarriage, premature birth and perinatal mortality.[66] Of more than 800 reported pregnancies from around 450 women affected by WD, 21.7% resulted in spontaneous abortions, and almost 70% of these cases occurred in untreated patients.[277] Undiagnosed women have a 2.8-fold higher risk of miscarriage compared to treated patients with an established WD diagnosis.[278] Also, maternal health status can be affected by pregnancy. While a limited and transient elevation in liver enzymes can occur in pregnant women with stable disease, severe hepatic deterioration has been observed almost exclusively in those with uncontrolled copper status, either naïve to anti-copper drugs[279,280] or following treatment discontinuation.[280] Neurologic deterioration only occurs in 1% of pregnancies but can be irreversible.[278,281] The benefit of anti-copper treatment during pregnancy clearly outweighs the risks to the foetus of potential teratogenicity or drug-induced copper deficiency. The overall proportion of stillbirths and birth defects in WD pregnancies is comparable to that expected in non-WD pregnancies. Evidence for the potential teratogenicity of D-penicillamine related to copper deficiency comes from animal studies,[282] and reports of birth defects in humans (*e.g.*, connective tissue defects) are related with the highest dosage.[283–285] Similarly, trientine teratogenicity in rats is mediated by the low foetal copper status,[286] but there are no safety concerns in pregnant women under standard dosage.[277,287] The speculative risk of over chelation affecting foetal outcomes has led to the conservative recommendation to reduce the dose of copper-chelating agents during the first trimester.[46,173,277,278,287] Zinc is usually considered safe in pregnancy, although birth defects in zinc-treated women have been reported.[288,289]

Women with WD willing to conceive or who are pregnant should be carefully followed and supported to start or maintain anti-copper drug treatment. Intrauterine devices should be avoided.

Limited information indicates that D-penicillamine and trientine have no substantial passage in breast milk.[290] Neither copper-chelating agents nor zinc substantially affect the copper content of breast milk.[291] Thus, there is no evidence to contraindicate breastfeeding in mothers treated with anti-copper drugs.

***Which symptomatic treatment is recommended in patients with WD and neurological and/or neuropsychiatric manifestations?***

### Recommendations

- Specific treatment for WD (chelators and zinc salts) enables improvement of neurological and neuropsychiatric symptoms but may be insufficient to control symptoms, in which case symptomatic treatments should be considered **(LoE 2, strong recommendation, strong consensus).**
- Symptomatic treatments of neurological symptoms should be based on pharmacotherapy, botulinum toxin injections, physiotherapy, speech therapy and rarely neurosurgery **(LoE 2, strong recommendation, strong consensus).**
- Neuropsychiatric symptoms can be treated by psychotropic medications (mood stabilisers, antidepressants, anxiolytics) and/or psychotherapy. Neuroleptics should be avoided (except quetiapine or clozapine) as they could worsen neurological symptoms **(LoE 2, strong recommendation, strong consensus).**

In addition to anti-copper therapy, symptomatic treatments are crucial at any stage of the disease for the long-term management of patients with WD who present neurological or psychiatric symptoms.[40,115,292–295]

The symptomatic treatment of neurological symptoms depends mainly on the predominant symptoms and includes pharmacotherapy, toxin botulinum injections, physiotherapy, and speech therapy. In rare situations, neurosurgical procedures may also be considered.[292] Symptomatic treatments need to be regularly adjusted to address the evolving nature of symptoms throughout the progression of the disease. Factors such as stress, concurrent medication use, trauma, or infections may exacerbate neuropsychiatric symptoms, displaying classical daily fluctuations, and should be taken into consideration.

Table 8 summarises the main therapy proposed for each symptom. The majority of these treatment proposals come from case reports.

#### Tremors

In cases of action/postural tremor, the most effective pharmacological treatment option is propranolol (20–240 mg/day, divided into two or three doses), followed by primidone (25 mg/day up to 750 mg daily in three divided doses).[296,297] If these treatments prove ineffective, benzodiazepines (alprazolam 0.75–1.5 mg/day) or clonazepam (0.5–4 mg/day) may offer some relief.[297] High dose zolpidem was effective in "wing beating" tremor in a case report.[298] For voice tremors, the optimal treatment involves the use of botulinum toxin A (BTX) with laryngeal electromyography-guided injections. BTX injections are also the preferred first-line treatment for dystonic tremors affecting the head, jaw, or voice.[299] Dystonic hand tremors should initially be addressed with anticholinergics or beta-blockers. In the event of treatment failure, second-line medications include benzodiazepines, primidone, or tetrabenazine. Intention, rubral or resting tremor are rare in WD and typically unresponsive to pharmacotherapy. In the case of severe disability due to tremor, and after long-term anti-copper treatment, deep brain stimulation (DBS) of the subthalamic regions or thalamus or thalamotomy, should be considered in light of the promising outcomes from several single case reports, but more studies are needed.[300–304]

#### Dystonia

Dystonia is one of the most disabling symptoms of WD and is often refractory to anti-copper treatment, with an unfavourable prognosis.[305] Focal dystonias are usually effectively treated with BTX injections[306–310] and segmental or generalized dystonias are treated with oral drugs alone or in combination with

**Table 8. Summary of symptomatic treatments of neurological and psychiatric symptoms of WD.**

| Psychiatric symptoms | Class/drug or procedure |
|---|---|
| Tremors (pseudo essential tremor, dystonic tremor, resting tremor, voice tremor) | • Beta-blockers/propranolol 20-240 mg/day (divided into 2-3) first-line treatment for action/postural tremor<br>• Barbiturates/primidone (25-750 mg/day divided into 3 doses) first-line treatment for action/postural tremor<br>• Benzodiazepines/alprazolam 0.75-1.5 mg/day or clonazepam 0.5-4 mg/day<br>• Zolpidem (20 mg twice daily)<br>• BTX injections, first-line treatment for dystonic head, jaw and voice tremor<br>• Anticholinergics/trihexyphenidyl 8-30 mg or biperiden 6-16 mg, with low starting doses, first-line treatment for all types of tremor<br>• Dopamine depleting drugs/tetrabenazine 50-75 mg/day with initial dose 12.5 mg – for dystonic tremor<br>• Levodopa (300-1,200 mg) or dopamine agonists, first-line treatment for rubral or parkinsonian tremor<br>• Antiepileptics drugs/levetiracetam<br>• Neurosurgical treatment – DBS of thalamic nucleus or thalamotomy, ultimate treatment |
| Dystonia | • BTX injections, first-line treatment for focal dystonia<br>• Anticholinergics/trihexyphenidyl 8-30 mg, first-line treatment<br>• Presynaptic gamma-aminobutyric acid agonists/baclofen 60-120 mg/day<br>• Benzodiazepines/alprazolam 0.75-1.5 mg/day or clonazepam 0.5-4 mg/day<br>• Levodopa (300-1,200 mg) or dopamine agonists<br>• Dopamine depleting drugs/tetrabenazine 50-75 mg/day with initial dose 12.5 mg<br>• Antiepileptics drugs/oxcarbazepine up to 300 mg/day, gabapentin 900 mg/day<br>• Repetitive transcranial magnetic stimulation (rTMS)<br>• Neurosurgical treatment – DBS of GPi, pallidotomy or thalamotomy, ultimate treatment |
| Parkinsonism | • Levodopa dopamine agonists to be tried as a therapeutic test<br>• Neurosurgical treatment – DBS or neuroablative lesions of GPi or STN; ultimate treatment |
| Chorea/choreoathetosis | • Dopamine depleting drugs/tetrabenazine 50-75 mg/day with initial dose 12.5 mg<br>• Avoid neuroleptic drugs or dopamine antagonists |
| Dysarthria | • Speech therapy<br>• Zolpidem (low doses for dystonic dysarthria)<br>• BTX for voice tremor or spasmodic dysphonia<br>• Augmentative communications devices |
| Dysphagia | • Dietary modifications<br>• Stopping the drugs influencing arousal<br>• Neuromuscular electrical stimulation<br>• Tube feeding (may increase dystonic features)<br>• Percutaneous gastrostomy |
| Drooling | • Chewing gum or sucking candies<br>• Anticholinergics as sublingual 1% atropine drops or trihexyphenidyl 8-30 mg, or transdermal scopolamine<br>• Adrenergic alfa-2 receptor agonists/clonidine 0.15 mg/day<br>• BTX (injection in parotid and/or sublingual glands) |
| Cognitive deficit | • No data on pharmacological agents<br>• Neuropsychological training<br>• Avoid agents that worsen cognition (benzodiazepines, anticholinergics …). |
| Sleep disturbances | • RLS: dopaminergic substances, gabapentin (600 mg/day)<br>• Insomnia: cognitive behavioural therapy, hypnotics or melatonin to try<br>• RBD: melatonin or clonazepam to try<br>• Treat pain, dysautonomia, depression and anxiety |
| **Psychiatric symptoms** | **Class/drug or procedure** |
| Depression | • SSRI/citalopram 20-40 mg/day or escitalopram 10-20 mg/day or sertraline 50-200 mg/g in first line<br>• TCA/nortriptyline 50-150 mg/day or desipramine 50-150 mg/day second line<br>• SNRI/venlafaxine 75-225 mg/day second line<br>• SSRI/paroxetine 20-60 mg/day or mirtazapine 15-45 mg second line<br>• ECT if resistance to pharmacological treatment |
| Psychosis/hallucinations | • Second-generation antipsychotics/olanzapine 10–20 mg; quetiapine 300–800 mg; aripiprazole 15–30 mg in first line<br>• Clozapine only for treatment-resistant cases (leukopenia and seizures risk)<br>• Antipsychotic/amisulpride 200–800 mg; sulpiride 200–800 mg, second line<br>• Avoid haloperidol and high-potency antidopaminergic agents<br>• Avoid long-acting antipsychotics |
| Behavioural troubles | • Behavioural therapy, first line<br>• SSRI/citalopram, escitalopram, sertraline, first line<br>• Antiepileptic drugs/carbamazepine, lamotrigine, gabapentin, pregabaline, first line<br>• Benzodiazepines short-term/lorazepam, oxazepam, temazepam, first line<br>• Adrenergic beta-blockers/propranolol 20–60 mg, first line<br>• Second-generation antipsychotics/quetiapine 50–300 mg, second line |
| Obsessive-compulsive behaviours | • SSRI/escitalopram 10–20 mg; sertraline 50–200 mg, first line<br>• SSRI/fluvoxamine 150–250 mg; paroxetine 20–60 mg, second line<br>• Cognitive behavioural therapy (exposure and response prevention)<br>• Avoid clomipramine |
| Mania/bipolar disorder | • Mood stabilisers/lithium carbonate in first line (serum target 0.6-1 mmol/L)<br>• Mood stabilisers/valproate 500-1,000 mg/day and carbamazepine, second line (hepatotoxicity)<br>• Second-generation antipsychotics/quetiapine 300-800 mg/day, olanzapine 5-20 mg/day, aripiprazole 10–30 mg, second line<br>• Benzodiazepines/alprazolam, clonazepam for psychomotor agitation and anxiety<br>• Avoid haloperidol and high-potency antidopaminergic agents |

(*continued on next page*)

**Table 8.** (*continued*)

| Psychiatric symptoms | Class/drug or procedure |
|---|---|
| Catatonia | • Benzodiazepines/lorazepam, first line<br>• ECT, second line<br>• Second-generation antipsychotics/quetiapine 300-800 mg/day, olanzapine 5-20 mg/day, third line<br>• Avoid haloperidol and high-potency antidopaminergic agents<br>• Avoid long-acting antipsychotics |

BTX, botulinum toxin A; ECT, electroconvulsive therapy; RBD, REM sleep behaviour disorder; RLS, restless legs syndrome; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

BTX injected into the most affected muscles. Only a few case and series reports have provided data about the effectiveness of oral treatments for dystonia. Anticholinergic drugs show moderate efficacy with well-known side effects to watch for (confusion, urinary retention, blurred vision, etc.) (trihexyphenidyl with a starting dose of 2 mg, slowly increased up to a maximum of 30 mg/day, or biperiden with a starting dose of 6 mg/day in three doses, slowly increased up to 16 mg/day).[292,311] Other pharmacological agents include (a) baclofen (ranging between 60 and 120 mg/day),[292] (b) benzodiazepines[294] (c) levodopa or dopamine agonists,[312–316] (d) tetrabenazine (starting dose 12.5 mg, increased up to 50–75 mg/day),[294] and (e) carbamazepine (up to 900 mg/day) or oxcarbazepine (up to 300 mg/day).[317–319] More anecdotally, a single case report described the efficacy of cannabis in reducing dystonic symptoms.[320] More recently, two trials investigating the efficacy of repetitive transcranial magnetic stimulation over the somatosensory or the motor cortex in limb dystonia found some improvements.[321–323] Results of exceptional surgical procedures such as DBS or thalamotomy in cases of severe generalized dystonia refractory to long-term anti-copper treatment and symptomatic pharmacological treatment are not convincing.[302,303,305,324] Severe structural changes of basal ganglia and thalami should be absent as the efficacy of DBS with electrodes placed in damaged targets is unpredictable and often limited.[292]

### Parkinsonism

The majority of reports indicate no significant effect of dopaminergic drugs on Parkinsonian symptoms in WD. Nevertheless, considering the established alteration in dopaminergic neurotransmission among patients with WD[325] and the low prevalence of adverse reactions to dopaminergic treatment, a trial of dopaminergic treatment should be considered for patients with WD to address dystonia and parkinsonism.[297,313,314,326–328]

### Chorea and choreoathetosis

Treatment of chorea and choreoathetosis are poorly studied in WD. Only one case reported good efficacy of tetrabenazine in treating chorea in WD.[297] Neuroleptic drugs and dopamine antagonists should not be used in WD due to a high risk of neurological deterioration.[213]

### Dysarthria

Speech therapy is the primary treatment for this highly prevalent and debilitating symptom associated with social challenges due to reduced communication. Speech rehabilitation is tailored to the specific type of dysarthria, incorporating targeted training on relaxation techniques for the spastic form, methods to modify speech rate and prosody in cases of ataxic disturbances, and intensive voice treatment, such as the Lee Silverman voice treatment, to enhance loudness and improve articulation in the hypokinetic form.[329] In instances of dystonic dysarthria, the use of zolpidem (2x 10 mg and 5x 5 mg orally) has been reported to yield positive effects without sedative side effects.[330] For spasmodic dysphonia or voice tremor, injections of BTX have been identified as a viable treatment option in isolated cases.[307,331] In cases of severe dysarthria with limited or poor vocalisation, the recommendation is to utilise alternative and augmentative communication devices, such as computer systems, tablets, or smartphone applications.

### Dysphagia

Objective methods, such as videofluoroscopy and fibre optic endoscopic evaluation, should be employed to assess swallowing and determine the severity of dysphagia for the purpose of tailoring treatment.[292] Initial interventions should encompass discontinuation of sedatives and drugs that may affect arousal, as well as anticholinergic drugs contributing to mouth dryness, thereby exacerbating swallowing difficulties. In addition to specific behavioural therapies aiming to enhance food bolus preparation and ingestion (including optimising position, maintaining concentration on the task, and swallowing before the next bite), dietary modifications are recommended. These modifications involve avoiding dry and sticky foods and opting for cold liquids or those with gas. Neuromuscular electrical stimulation, explored in dysphagia rehabilitation for improving swallowing, holds significant promise.[332,333] In cases of severe dysphagia accompanied by weight loss, tube feeding with direct delivery of food into the stomach may be contemplated to prevent food aspiration, address malnutrition, and facilitate anti-copper therapy. However, this procedure may exacerbate dystonia, necessitating prompt consideration of percutaneous endoscopic gastrostomy.[334] Both solutions may be implemented temporarily and discontinued upon neurological improvement and recovery from dysphagia.

### Drooling/hypersialorrhea

The severity of drooling should be assessed using objective tools such as the drooling severity and frequency scale and objective assessment of saliva secretion.[335,336] Factors contributing to drooling (saliva hypersecretion, salivary stasis, swallowing dysfunction, extrapyramidal postural abnormalities, oro-facial dystonia, sensitive alterations, cognitive, and behavioural impairment) must be considered. Chewing gum or sucking candies, which reduces salivation by triggering automatic swallowing and reduces saliva volume in the mouth, should be tried.[337] As no therapeutic study exists in WD, pharmacological options used for drooling in other neurological conditions should be considered, including anticholinergics (*e.g.* benzatropine, trihexyphenidyl, transdermal scopolamine, sublingual 1% atropine drops), adrenergic alpha-2 receptor agonists (clonidine 0.15 mg/day), or BTX injection in parotid and/or sublingual glands or to treat oro-mandibular dystonia.[336–338]

### Cognitive deficit

There are currently no pharmacological agents used for cognitive disturbances in WD, and no published studies describing the efficacy and safety of cholinesterase inhibitors or memantine in WD. Neuropsychological training is usually proposed and agents that worsen cognition should be avoided (*e.g.* benzodiazepines, anticholinergics).

### Sleep disturbances

Insomnia, restless legs syndrome, daytime sleepiness, and REM sleep behaviour disorder are present in WD and should be explored with video polysomnography and multiple sleep latency test. Pain, motor symptoms, psychiatric disorders, dysautonomia and drugs are involved in the mechanisms of sleep abnormalities and should be taken into consideration and decreased.[339–341] In case of significant restless legs syndrome, treatment with dopaminergic substances[39] or gabapentin (600 mg/day)[340] may be considered. No specific study exists but cognitive behavioural therapy, hypnotics or melatonin should be discussed in insomnia, and melatonin or clonazepam can be used in REM sleep behaviour disorder.[340]

### Depression

There are no randomised trials evaluating the efficacy and safety of antidepressant treatment in WD but tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors, as well as electroconvulsive therapy, have been successfully used in the treatment of depression in WD and could be recommended.[49,115,312,342–346] The choice of SSRIs to treat depression in WD aligns with evidence of altered serotonergic neurotransmission in WD and SSRIs appear to be a reasonable choice as a first-line treatment.[115] Caution is advised when using imipramine, amitriptyline, duloxetine, and bupropion with a higher risk of hepatic injury. Psychotherapy or cognitive behavioural therapy can be considered for treatment of mild depression in patients with WD; however, there is currently no data documenting the efficacy of these interventions.

### Mania/bipolar disorder

Lithium is the recommended first-line treatment for mania and hypomania in WD because it is renally excreted and not metabolised by the liver.[347–350] However, lithium may worsen tremor and impair cognition. Other mood stabilisers, such as valproate and carbamazepine, carry a risk of hepatotoxicity, which would necessitate strict monitoring. Case studies reported that second-generation antipsychotics (quetiapine, olanzapine, aripiprazole) can successfully treat mania in WD[49,115,346,351] with relative low risk of side effects. First-generation neuroleptics should be avoided as they could induce neurological deterioration. Benzodiazepines have been used for the short-term treatment of agitation in WD.[115] Alprazolam improves psychomotor agitation and anxiety, and clonazepam decreases insomnia in mania. Lorazepam, oxazepam, or temazepam, should be preferred as they are metabolised in the liver by glucuronidation rather than oxidative metabolism by the cytochrome $P_{450}$ enzymes.[347]

### Psychosis/hallucinations

Patients with WD are especially sensitive to the adverse effects of neuroleptics,[342] and are more likely to develop parkinsonian symptoms or tardive dyskinesia. Quetiapine and clozapine are neuroleptics associated with low risk of extrapyramidal symptoms, as well as low hepatic risk, and could be recommended as the first-line treatment for psychosis. However, clozapine should be reserved for the most severe and treatment-resistant cases due to increased risk of leukopenia. Haloperidol and risperidone should be used as a last resort as there have been reports of irreversible neurological deterioration and neuroleptic malignant syndrome. Long-acting antipsychotics should be used in patients with WD only with great caution.

### Behavioural disorders

Behavioural and personality disorders are mostly characterised by irritability, aggression, personality changes, antisocial behaviour and may lead to non-compliance with anti-copper treatment, as well as other medical recommendations. Therapeutic recommendations are based on general psychiatry recommendations and include behavioural therapy when possible and SSRIs (citalopram, escitalopram or sertraline) to reduce irritability. Antiepileptic medications may also have some anti-aggressive and mood-stabilising effects, and promising results have been obtained with carbamazepine, lamotrigine, gabapentin, oxcarbamazepine and valproate. Second-generation antipsychotics (clozapine or quetiapine) can be used for severe symptoms, their use being restricted to the shortest effective time course with the lowest effective dosages. Benzodiazepines are a safe option for short-term acute management of aggression in patients with WD.[115]

***What are the indications for LT in patients with ALF due to WD and how should they be managed?***

#### Recommendations

- All patients with ALF due to WD should be referred to LT centres **(LoE 2, strong recommendation, strong consensus).**
- Patients with ALF and encephalopathy should be immediately listed for LT **(LoE 2, strong recommendation, strong consensus).**
- Patients with ALF due to WD should be evaluated according to the modified King's College prognostic score at each biochemical evaluation but at least every 24 h; scores ≥11, even without encephalopathy, are an indication for LT **(LoE 3, strong recommendation, strong consensus).**
- Pharmacotherapy with chelators (rapidly increased to full dose) should be started immediately in all patients with ALF due to WD and those listed for LT, to be continued until LT **(LoE 3, strong recommendation, consensus).**
- High-volume plasma exchange should be considered as a bridge to LT. Albumin dialysis might also be considered if available **(LoE 3, strong recommendation for high-volume plasma exchange, weak recommendation for albumin dialysis, strong consensus).**
- Patients on a waiting list for LT should be monitored closely and possibly withdrawn from the waiting list when improvement is noted **(LoE 3, strong recommendation, strong consensus).**

Indications for LT are rare (<1%), including patients with ALF or those with progression of liver dysfunction to liver failure despite drug therapy. Excellent post-LT outcomes are reported.[238,352] Actual patient survival rates were 87% at 5, 10, and 15 years in a French series of 75 adults and 46 children (median age: 14 years, range 7 to 17 years) transplanted between 1985 and 2009 for ALF (53%), decompensated cirrhosis (41%), or severe neurological disease (6%). In another study analysing the United Network for Organ Sharing database, including 515 adults and 156 children with WD who underwent LT between 1987 and 2016, 3-, 5- and 10-year survival rates were 87.5%, 85.4%, and 80.5% for adults, and 90.5%, 89.7%, and 86.5% for children, respectively. In both studies, patients transplanted for end-stage chronic liver disease had better long-term survival than patients transplanted for ALF.

Paediatric LTs were also evaluated using data from the European Liver Transplant Registry, showing good results from after the year 2000, with risk factors for poor outcomes being treatment in an intensive care unit, dialysis and partial graft transplantations.[353] Most of the centres reported on cadaveric donor LT but there are also reports on living related donor LT from the left or the right lobe depending on the size of the recipient.[354,355]

Patients presenting with decompensated cirrhosis but no hepatic encephalopathy can often be rescued with chelation therapy. Response to medical treatment may take time, with improvement of prothrombin time after a minimum of 1 month and normalisation between 3 months and 1 year or more.[199] Close follow-up and monitoring for hepatic encephalopathy, ascites, sepsis and liver function tests are required in specialised units to enable timely listing of patients for LT, a decision that is extremely challenging. In 1986, Nazer *et al.* devised a scoring system to predict the outcome of patients, including adults and children, with hepatic decompensation in the setting of WD.[356] In 2005, the score was re-examined in the paediatric population by Dhawan *et al.* who proposed a new scoring system (NWI) that had a better positive predictive value for mortality without transplantation (Table 9)[104,357,357357 357357 358] The NWI is reported to be 93% sensitive and 98% specific, with a positive predictive value of 93%.[104] All patients with encephalopathy and WD died. The NWI was also tested in adult cohorts with fulminant liver failure and decompensated cirrhosis due to WD, showing higher accuracy and lower false negativity compared to the Nazer and MELD scores[274].

Dialysis, plasmapheresis, albumin dialysis and plasma exchange are considered as bridges to LT, but they are also discussed as rescue therapies in ALF. The argument to use high-volume plasma exchange as a rescue therapy comes from one publication from India comparing two groups of children with WD ALF on high-volume plasma exchange (90-day survival in 9/19) *vs.* standard medical therapy (90-day survival 3/18), but the patients were not randomised.[358]

When patients with WD present with ALF, the diagnosis is not established at presentation. The general recommendation is to treat and diagnose ALF in liver specialised units that can directly refer to or transplant patients. The diagnostic approach is demanding for many reasons: it should be done very quickly, access to advanced laboratory methods is necessary and patient monitoring usually requires intensive care units, access to dialysis and transplant surgery.

The definition of ALF, fulminant liver failure or end-stage liver disease with liver failure is not well defined and described in the literature. Most of the papers report on LT from mixed groups with different courses of liver failure. We decided to define ALF as a first and acute presentation of liver disease, even if this is chronic (see Introduction). This is usually combined with Coombs-negative haemolysis and relatively high bilirubin levels, but these criteria were not required for the definition used in our guideline.

ALF has been reported in children, predominantly teenagers but also younger children, and in young adults, with significant female predominance from puberty onwards. Very few patients have been described and transplanted at an age >40 years.[359]

**Table 9. Wilson's disease scoring system to predict outcomes in children with hepatic decompensation without encephalopathy (King's College Wilson index) by Dhawan *et al.***

| Score | Bilirubin (μmol/L) | INR | AST | Leukocytes ($10^9$/L) | Albumin (g/L) |
|---|---|---|---|---|---|
| 0 | 0-100 | 0-1.29 | 0-100 | 0-6.7 | >45 |
| 1 | 101-150 | 1.3-1.6 | 101-150 | 6,8-8.3 | 34-44 |
| 2 | 151-200 | 1,7-1.9 | 151-200 | 8.4-10.3 | 25-33 |
| 3 | 201-300 | 2.0-2.4 | 201-300 | 10.4-15.3 | 21-24 |
| 4 | >300 | >2.5 | >300 | >15.3 | 0-20 |

AST, aspartate aminotransferase; INR, international normalised ratio.
if 11 and over, then urgent listing for liver transplantation.

**Table 10. Treatment and monitoring.**

| | Zinc salts | D-penicillamine | Trientine |
|---|---|---|---|
| Adequacy of treatment parameters | • 24-h urinary copper excretion: 30-75 μg (0.5–1.2 μmol)/24 h on maintenance treatment<br>• Serum zinc level >125 μg/dl<br>• Urinary zinc >2 mg/24 h on maintenance treatment | • 24-h urinary copper excretion: 200-500 μg (3-8 μmol)/24 h on maintenance treatment | 24-h urinary copper excretion: 150-500 μg (3-8 μmol)/24 h on maintenance treatment |

***Should LT be considered in patients with WD and severe neurologic symptoms?***

### Recommendations

- LT should not be contraindicated in patients with WD and neurological symptoms who need to be transplanted for decompensated cirrhosis **(LoE 2, strong recommendation, strong consensus).**
- LT may be considered a "brain indication" on a case-to-case basis in patients with severe neurological WD who do not respond to anti-copper treatment **(LoE 2, weak recommendation, consensus).**

When started early in the course of the disease and appropriately taken, copper chelators and zinc therapy are effective treatments in most patients with WD: clinical improvement is observed in almost 85% of treated patients[218,239,360] and patient survival is similar to that of age-matched populations,[361] with an amelioration of survival in the last decades.[240]

However, the neurological situation remains difficult to control with confidence as early deterioration is observed in 14.3% of patients with an initial neuropsychiatric presentation,[212,213,261] and may lead to irreversible cerebral lesions in 44% of such patients, resulting in severe disability or even death despite optimal therapy.[51,68,213,362] This neurological worsening can be "primary" in *de novo* neurological patients in whom treatment is newly started but also "secondary" in patients with known WD who experience neurological symptoms after discontinuation of their treatment and in whom treatment is reintroduced.[214]

Inefficacy of intracerebral chelation or excessive copper mobilisation by the chelating agents leading to oxidative stress and an accentuation of brain tissue damage are the classical hypotheses proposed to explain this paradoxical worsening.[180,363]

In the absence of comparative studies, it is difficult to know which treatment causes the most neurological worsening; however, neurological worsening seems to be more frequently associated with chelators than zinc.[40,207,209,210,213,364–366] So far, the only consensual recommendations to reduce the risk of neurological deterioration are to start at a low dose and to slowly increase the dose of chelators over a period of 3 to 6 months.[46,84] Unfortunately, this proposal may be insufficient to prevent neurological deterioration.

LT is the recommended therapeutic option in WD with ALF or end-stage cirrhosis, but since the first report of good neurological outcomes after LT in 1973,[367,368] the place of this therapeutic option for patients with significant neurological symptoms has been questioned.[265,369–376]

In the last five decades, data on 383 patients with WD and neurological symptoms who underwent LT were reported through retrospective and prospective cohorts[218,222,352,354,355,377–404] or case reports and case series;[36,367,368,405–434] 68 patients (17.8%) were transplanted solely for neurological deterioration, and 319 underwent LT for a liver indication.

The cumulative survival rate of patients with neurological symptoms was 92.5% at 1 year and 89.1% at 5 years, with a clear trend toward better results of LT in more recent studies compared with older studies, which may be due to improvements in LT techniques as well as improved candidate selection. Sepsis was the main cause of death (65.8%).

Among patients with neurological and/or psychiatric symptoms transplanted for a liver indication, major improvement or complete neurological recovery was reported in 76% of patients, stability in 6.4% and worsening in 7.4% of patients, mainly due to previous brain necrosis in the basal ganglia. 8.8% of patients developed new neurological symptoms. Most of the neurological symptoms occurring early after LT were related to immunosuppressive drugs, but metabolic disturbances[435] leading to central or extrapontine myelinolysis were reported in 5 to 10% of cases.[404,436]

Among patients with neurological and/or psychiatric symptoms transplanted for a brain indication, 55/68 patients (80.9%) presented with moderate to major improvement of their neurological symptoms, and eight patients (11.8%) had a stabilisation of their symptoms. Even in bedridden patients with extremely severe neurological symptoms, amelioration was possible with some patients being able to gain full autonomy. Improvement was reported to take up to 3–10 years[390] and positive effects were maintained in the long term.[377,396] Appearance of new symptoms secondary to immunosuppression or side effects of LT were not reported. Eleven patients died (16.1%), mainly from sepsis.[377,390,396] In the largest series reported, of 14 highly dependent LT recipients (median modified Rankin scale score 5) with severe neurological symptoms (median UWDRS score 105), mRS and UWDRS scores improved significantly after LT ($p$ <0.0001 and $p$ = 0.0003 respectively)".[396]

Evaluating psychiatric outcomes is difficult due to the complexity of the presenting signs and the variety of factors potentially influencing clinical outcomes, such as immunosuppressive therapy, WD itself, and major surgery. However, 101 patients with psychiatric symptoms were studied before and after LT with description of psychiatric symptoms or use of dedicated questionnaires. No significant changes after LT were reported, suggesting that LT neither improves nor impairs psychiatric symptoms in patients with WD. Close collaboration with psychiatrists is essential for an accurate decision and follow-up.[377,381,387,388,394–396,404,406,412,414–416,418,423,424,426–428,430,432,433] LT had a positive effect on brain MRI lesions in the large majority of 26 studies (71%), with the T2/FLAIR hypersignal vanishing after a mean post-LT follow-up of 3 years.[377,381,387,388,394–396,404,406,412,414–416,418,423,424,426–428,430,432,433] Lesions remained stable in 26.1%. Only two patients presented a worsening of the brain images with extension of the necrosis.[424,433] It was shown that transplantation attenuates (11.4%) and even leads to complete disappearance of Kayser-Fleischer rings in 70.9% of patients after a mean follow-up of 3.7 years.[36,354,355,368,382,388,394,396,398,399,405,413,418,422,428,437]

***Should living donor LT be considered in paediatric patients with WD and indications for transplantation?***

### Recommendation

- Living donor related LT from the left or the right lobe, depending on size of the recipient, should be considered if WD is excluded in the donor **(LoE 3, strong recommendation, strong consensus).**

Several papers describe living donor related LT (LRLT) for both fulminant liver failure and decompensated cirrhosis in the course of WD. The Chinese experience showed good results in two patients with fulminant hepatic failure and 32 patients with chronic

advanced liver disease, including 13 patients with Wilsonian neurologic manifestations.[380] On the other hand, living donation in the European database was associated with poor patient and graft survival, but living donor related LT was also related to longer waiting list time and more pretransplant complications.[353] Again, a group from Japan reported good results from their country, the indication for LT was chronic liver failure in 42 children and fulminant hepatic failure in 17 children with WD. The 1-, 5-, 10-, and 15-year patient and graft survival rates were 98.4%, 96.6%, 94.7% 77.5%, and 96.6%, 94.7%, 90.1%, 62.9%, respectively.[438] While the techniques used and the age of patients undergoing living donor related LT varies, the experience of the transplant team is extremely important to decide when and whom to transplant.

***In patients with WD who undergo LT, should anti-copper therapy be resumed after LT?***

### Recommendation

- Anti-copper therapy is not indicated after LT **(LoE 4, strong recommendation, strong consensus).**

LT corrects the hepatic metabolic defects of WD and permits normalisation of extrahepatic copper disposition without WD treatment.[84,273] Therefore, medical treatment specific for WD is unnecessary after LT. Some authors have proposed that patients continue at least low-copper dietary control and zinc monotherapy[424] or chelators after LT[396] to improve long-term prognosis especially if urinary copper excretion remains elevated after LT. Data are too scarce to confirm the positive effect of this procedure. If anti-copper therapy is maintained after LT, a regular control of serum copper and urinary copper excretion is recommended to avoid copper deficiency.

## Treatment monitoring

***With which parameters and examinations, other than copper metabolism markers, and how often should patients with WD be monitored depending on their clinical status?***

### Recommendations

- Patients with WD who are stable on treatment should be monitored every 6 to 12 months **(LoE 4, weak recommendation, consensus).**
- Patients who have recently started treatment, have decompensated cirrhosis, significant neurological disability or suspected non-adherence should be followed up more frequently **(LoE 4, strong recommendation, consensus).**
- Monitoring should include history on symptoms and adherence, physical examination, measurement of body weight and vital signs, ophthalmologic examination if Kayser-Fleischer rings were present at baseline or if concerns about adherence, laboratory investigations (full blood count, liver profile, renal profile and a coagulation profile if the patient has cirrhosis) and abdominal ultrasound **(LoE 3, strong recommendation, consensus).**
- Patients with WD and cirrhosis should be screened for complications of portal hypertension and hepatocellular carcinoma **(LoE 3, strong recommendation, consensus).**

Patients with WD should be monitored at least every 6 months. More frequent monitoring might be required in patients who have recently started treatment, and in those with decompensated cirrhosis, significant neurological disability or suspected non-adherence to treatment. For patients who have been stable on treatment for many years, with no cirrhosis or neurological manifestations at baseline, monitoring can be performed every 12 months. The goals of monitoring are to assess the response to treatment, to identify potential side effects and to ensure the adherence to the prescribed medication.

Monitoring should consist of history, to include any new symptoms and the adherence to the prescribed medication both in terms of dose and taking the medication in a fasting state. A physical examination should look for symptoms of liver disease, neurological manifestations and skin changes if the patient is taking penicillamine. Body weight should be measured and alcohol intake should be recorded. Patients should be counselled to maintain a normal body weight, abstain from alcohol if they have cirrhosis and otherwise only drink alcohol within the recommended limits. Kayser-Fleischer rings should be checked periodically if present at baseline or if there are concerns about adherence.

Laboratory investigations should include a full blood count, liver profile, renal profile, bone profile and a coagulation profile if the patient has cirrhosis.

Patients with cirrhosis at baseline might require 6-monthly liver ultrasounds for hepatocellular carcinoma surveillance, particularly in the presence of co-factors such as obesity or increased alcohol intake.[439–441]

***Which copper parameters should be used in the monitoring of patients with WD?***

### Recommendations

- Adequacy of treatment with D-penicillamine or trientine should be monitored during all stages of treatment by measuring 24-h urinary copper excretion and serum non-ceruloplasmin-bound copper or serum exchangeable copper whenever available **(LoE 3, strong recommendation, consensus).**
- Adequacy of treatment with zinc salts should be monitored during all stages of treatment by measuring 24-h urinary copper excretion and serum non-ceruloplasmin-bound copper or serum exchangeable copper whenever available **(LoE 3, strong recommendation, consensus).**
- Monitoring serum exchangeable copper is advised when available and its value should decrease progressively in response to treatment **(LoE 3, weak recommendation, consensus).**
- Medication adherence can be assessed based on monitoring serum non-ceruloplasmin-bound copper levels, serum exchangeable copper, 24-h urinary copper excretion at baseline and 48 hours after cessation of chelators **(LoE 3, weak recommendation, consensus).**

Treatment strategies aim at decreasing copper overload in the body. Therefore, in addition to evaluating the clinical signs

and symptoms of the disease, appropriate monitoring of copper balance is essential to assess efficacy of treatment and avoid undertreatment that may result from non-adherence, and overtreatment that may result in copper deficiency.[442] Moreover, monitoring becomes a real challenge in patients who have persistently increased serum transaminases but deny non-adherence.

Currently, WD treatment monitoring lacks reliable and fully validated bioanalytical methods. For many decades, monitoring of copper metabolism in WD has been assessed with serum ceruloplasmin concentrations, total serum copper concentration, and 24-h urinary copper excretion, as described in recent international guidelines.[46,84,219,243,443] (Table 10). As recommended in these guidelines, 24-h urinary copper excretion values should be monitored and remain between 150 and 500 μg/24 h (3–8 μmol/24 h) on maintenance therapy with chelators.[46,84,101,219,443,444] Values of 24-h urinary copper excretion of >500 μg/24 h in treated patients previously excreting 200–500 μg/24 h suggest insufficient drug action (non-adherence to medication, poor drug absorption, inadvertently low dosing), or excessive intake of dietary copper. 24-h urinary copper excretion <100 μg/24 h (<1.6 μmol/24 h) on chelator treatment may signal overtreatment following excessive copper removal or, occasionally, non-adherence. With overtreatment, serum copper and exchangeable copper are very low, as is the calculated non-ceruloplasmin-bound copper (typically <5 μg/dl) although the estimated value may not accurately reflect this. In contrast, when low urinary copper excretion accompanies non-adherence, serum copper and exchangeable copper increase, and non-ceruloplasmin-bound copper may be elevated (>25 μg/dl). The previous European WD guidelines recommend the cessation of chelator therapy 2 days before determination of 24-h urinary copper excretion, while the American guidelines recommend it as an alternative.[46,84,206] During long-term treatment with chelating agents, a 2-day interruption of the treatment should result in normal 24-h urinary copper concentrations (<50 μg/dl), and appears as a reliable method for confirming patient compliance.[205] Under zinc salts, 24-h urinary copper excretion <20 μg/24 h (<0.3 μmol/24 h) suggests overtreatment, while values higher than target (≥100 μg/24 h) suggest poor adherence, insufficient dosing or increased dietary copper intake. A reasonable goal in children is to maintain 24-h urinary copper excretion between 1 and 3 μg/kg/day.[445] Urinary excretion of zinc, with target values of >1–2 mg/24 h may be measured to check adherence. Urinary zinc content correlates positively with the patient's total daily dosage of zinc[225] and serum zinc levels may be informative and should be >125 mg/dl.

The main limitation is that 24-h urine collection is cumbersome, especially in young children and results show large individual patient variability making this biomarker a less than ideal parameter to monitor therapy in isolation for treatment recommendations.[206,219,446,447]

To *et al.* aimed to examine patterns of ALT and AST elevation in treated adult patients for a mean duration of 21 years.[447] Having normal to low 24-h urine copper did not directly correlate with normalisation of ALT and AST for the different treatment regimens (trientine or D-penicillamine or zinc or combination therapy). Similarly, higher levels of urinary copper excretion failed to show a linear correlation with ALT and AST.

Monitoring non-ceruloplasmin-bound copper has long been recommended as it theoretically reflects the toxic fraction of copper, *i.e.* so-called free copper, especially in patients treated with copper chelators, which mobilise tissue copper, contributing to a non-bioavailable pool of circulating copper. In adequately treated patients, serum non-ceruloplasmin-bound copper is in the range of 5–15 μg/dl. Just after anti-copper treatment initiation, non-ceruloplasmin-bound copper is usually >15 μg/dl, decreases afterwards and shows normalisation with effective treatment. However, non-ceruloplasmin-bound copper is estimated using a calculated method assuming a ceruloplasmin-copper/ceruloplasmin ratio of 6:1 that could yield negative values, which are biologically implausible. Moreover, although non-ceruloplasmin-bound copper values tend to decline over time under treatment, a higher variation of results than that observed for urinary copper excretion rate has been reported.[206]

Measurement of exchangeable copper is routinely monitored nowadays in treated patients in France, Spain, Denmark, and India, and is under evaluation in other countries.[448] To date, it has not been included in clinical recommendations apart from in France[449] nor in clinical studies, but was recently shown to be an accurate tool for the follow-up of WD.[270] The authors reported the long-term changes in exchangeable copper levels compared to urinary copper excretion levels in symptomatic children with WD under chelation therapy. Of 36 children (median age of 10.5 [8.4-13.1] years), predominantly with a hepatic form of WD (n = 31), the median (IQR) exchangeable copper value was 1.01 (0.60-1.52) μmol/L at diagnosis and decreased significantly during the first year of chelation, then stabilised with values at 0.43 (0.31-0.54) μmol/L after 5 years of chelation. Similarly, there was a significant decrease in 24-h urinary copper excretion during the first year of chelation treatment that then stabilised, suggesting the usefulness of both biomarkers in clinical practice for monitoring treatment.

Other methods to measure direct non-ceruloplasmin-bound copper in plasma (dNCC) are very promising and have been developed for therapeutic controlled trials. A non-ceruloplasmin-bound copper assay using liquid chromatography and ICP mass spectroscopy (NCC-Sp) was developed for a multicentre controlled trial (NCT03539952), the CHELATE trial (trientine-4HCl *vs.* D-penicillamine), in which 53 adults with stable WD were randomly allocated after a 12-week baseline observation period to either D-penicillamine or trientine-4HCl for 24 weeks.[450] Paired samples for NCC-Sp and 24-h urinary copper excretion were compared pre- and 24 weeks post-randomisation. Validation studies for NCC-Sp included 50 healthy adults, identifying a range (2.5% to 97.5%) of 40–150 μg/L used as reference target range for the study population.[451,452] The recommended therapeutic range for 24-h urinary copper excretion was 200–500 μg/24 h. NCC-Sp was in the reference range at randomisation *vs.* study end in 86% *vs.* 84% of individuals, respectively, while 24-h urinary

copper excretion was in the recommended therapeutic range in only 41% *vs.* 37% respectively. Agreement when both NCC-Sp and 24-h urinary copper excretion were in range at randomisation/study end was 17/49 (35%) and 17/51 (33%), respectively. NCC-Sp had less intra-patient variability than urinary copper excretion, suggesting that NCC-Sp is a more reliable biomarker for monitoring chelation therapy in WD.[451] Following these data, a small study aimed to determine if dNCC is a useful biomarker for treatment monitoring based on data from a multicentre, multinational WD patient registry (data coordinating centre and biorepository at Yale). dNCC was determined in serum from patients on zinc (n = 13) or trientine (n = 8) therapy, using a previously described novel assay based on copper protein speciation and inductively coupled plasma mass spectroscopy.[453] dNCC ranged from 0.22 to 1.66 μmol/L, with the average for zinc treatment being significantly lower at 0.74 ± 0.29 *vs*. 1.21 ± 0.37 μmol/L for those on trientine ($p$ = 0.009). For reference, the dNCC range for a non-WD population was determined to be 1.17 to 3.87 μmol/L. 24-h urinary copper excretion showed a poor correlation with dNCC though average values were in expected ranges for most patients on long-term treatment.[446]

Another direct and fast liquid chromatography inductively coupled plasma mass spectroscopy method was developed to assess copper metabolism during treatment with ALXN-1840 (bis-choline tetrathiomolybdate).[454] The assay utilises immunocapture of ceruloplasmin, followed by chelation and filtration to isolate different copper fractions, including ceruloplasmin-protein, ceruloplasmin-Cu, dNCC, and labile bound copper in human plasma. Finally, a fluorometric assay to determine labile copper (II) ions in serum was also recently developed and may prove useful for monitoring treatment progress.[455]

Finally, cerebrospinal fluid copper concentrations in patients with neurological symptoms have been shown to decrease slowly over the years, as clinical symptoms improve, and may increase in non-adherent patients, suggesting that they may reflect the accumulation of copper in the brain and may be useful to monitor in very specific clinical situations.[200,456,457]

The minimum recommended frequency of monitoring is twice annually. More frequent monitoring is required during treatment initiation, for those experiencing worsening of symptoms or medication side effects, and in individuals suspected of non-adherence.

A survey was conducted in Germany to investigate monitoring of WD and included 63 departments.[458] Forty-eight reported adherence to the previous European recommendations for chelator cessation before measuring 24-h urinary copper excretion. The proportion of departments that paused chelator treatment before urinary copper excretion was low in paediatrics (15%) and high in departments of neurology and gastroenterology (taken together 70%). Most patients with WD were seen at least every 3 (45%) to 6 months (38%). The procedures performed during check-up varied between the departments. Total serum copper (71%), ceruloplasmin (75%) and 24-h urinary copper excretion (69%) were determined by most departments at least twice a year.

## Transition from paediatric to adult care

***How should paediatric patients with WD be transitioned to adult care?***

### Recommendations

- Transition planning should be initiated by the paediatric team in early adolescence (between 12-14 years of age) to ensure the progressive development of competencies regarding self-care, before moving to adult healthcare **(LoE 4, strong recommendation, strong consensus).**
- There can be a specific programme for transition and transfer of adolescents and young adults with WD that allows them to become autonomous, independent, and responsible in their healthcare **(LoE 4, weak recommendation, strong consensus).**
- The minimum core team involved in transition to adult care may include a physician and a specialist nurse; additionally, a psychologist and social worker might be involved **(LoE 4, weak recommendation, consensus).**
- Joint or alternate clinical appointments with a paediatrician and adult hepatologist and/or neurologist, preferably in the presence of a specialist nurse, are advised during transition **(LoE 4, weak recommendation, strong consensus).**

There is an increased risk of medical complications and morbidity following transfer from paediatric to adult health care services in patients with childhood-onset chronic illness. Unlike most paediatric rare liver diseases, WD is a well-known disease among adult hepatologists and neurologists, but a poor training in adolescent medicine and at-risk behaviours may become a barrier to transition at the level of the adult provider.

Patients with WD have unique challenges, as some may have neurologic or psychiatric involvement leading to impaired executive functioning. Moreover, there is also evidence of impaired cognition in treated patients despite the absence of neurological symptoms and normal cerebral MRI scan results, which should be taken into account when beginning the healthcare transition process.[116,459–461]

In the recent study from Day *et al.*[116] involving 69 children and young adults with WD (37.8% who presented with ALF, 48.6% with chronic liver disease and 13.5% after family screening), the most frequently reported cognitive concerns were memory difficulties with specific learning difficulties together with poor school performance in 14.5% of patients. Mental health concerns (depression, anxiety, rage, and/or psychosis with hallucinations) were recorded in 49.3% and were more common in young patients who presented with acute liver disease/liver failure (70.8%) but also reported in those with chronic liver disease (40%) and those asymptomatic with familial screening (30%). Four patients (5.4% of the cohort) were diagnosed with an autism spectrum condition prior to the diagnosis of WD. Deliberate self-harm and suicidal ideation/attempts were noted in 3 (4%) cases.[116]

General management principles do not differ substantially between pre-adolescents and adults. Patients who are leaving the paediatric age group continue to have substantial medical problems, which are complicated by individual behavioural, social, and educational difficulties. A new subspecialty – transitional medicine – is slowly developing; it is faced with the difficult task of offering a similar level of medical care with very different individual responsibilities.

Older pre-adolescent patients should be educated, and active participation in their care should be promoted by paediatric hepatologists as they approach adolescence. The adult hepatologists taking over the formerly paediatric patients should be clearly identified. The main challenge is treatment and follow-up adherence. The relationship between non-adherence and significant morbidity and mortality has been well described in particular during adolescence.[462] Non-adherence to medication was mentioned in half (50.7%) of the WD children and young patients reported by Day *et al*.[116] Type of WD treatment, gender, phenotypic presentation, adverse events and duration of treatment have not been related to treatment adherence in most studies in adolescents (or adults).[116,229,230]

Higher or upper/post-secondary education and a supportive family attitude towards treatment were the most important factors related to adherence.[229,230] Despite this inherent risk, there has been no formal, standardised approach to transition planning for children with WD. Young patients with WD require a multidisciplinary approach and follow-up as some may have chronic liver disease, others neurological disease, or some both. The goal of a transition programme is to help facilitate the process of changing from a paediatric to an adult model of health care and optimise the likelihood of sustained well-being in young adults by fostering their ability to achieve physical, social, and psychosocial potential. To reach such a goal, a dedicated team involving the paediatrician, a specialist nurse as the coordinator of the healthcare transition process, a psychologist, a social worker working in collaboration with the parents and the adult care services is warranted.[463–465] Transition planning should be initiated by the paediatric team in early adolescence.[243] The transition process does not end at the time of transfer but must continue throughout early adulthood. Transfer of care is just an event, *i.e*. the planned movement of a patient from paediatric to adult health care facilities.

Ineffective transition increases the risk of non-adherence to medication, and irreversible hepatic or neurological deterioration.

Ideally, a joint transition liver-neurology clinic for young people with WD (12 to 25 years) involving hepatologists and neurologists, with input from psychiatrists, social workers, liaison nurses, and clinical psychologists/neuropsychology, should be provided to ensure subtle symptoms are identified early and addressed appropriately. This also includes patients who are diagnosed through family screening and are apparently "asymptomatic."

Continued multidisciplinary efforts in adult practice are essential for long-term success, including the involvement of social workers and a geneticist for genetic counselling. Patient associations could also get involved in this process.

## Unmet needs and future research

The Leipzig diagnostic score still needs validating in adult patients and in ALF. Rapid molecular testing should be further developed, mainly for quick diagnosis in ALF. Currently no screening tests have been validated for whole population screening.

Even if current therapies are effective, further development of new drugs is expected and strong chelators could improve treatment of ALF and severe neurological disease. Gene therapy can improve efficacy, mainly in those with poor compliance, and ongoing clinical trials will allow recommendations to be formulated in the near future. The role of LT warrants further evaluation, particularly in patients with neurological presentations. Monitoring of pharmacotherapy requires validated biomarkers both for copper metabolism and liver and brain injury. Transition programmes need to be developed and assessed.

## Appendix. Delphi round agreement on the recommendations of the present clinical practice guidelines.

| Recommendation | Consensus |
|---|---|
| The first step should be screening for abnormalities in copper metabolism (both serum ceruloplasmin and basal 24-h urinary copper excretion). If available, relative exchangeable copper determination in serum should be performed **(LoE 2, strong recommendation).** | 94% |
| In addition, typical extrahepatic features of WD (Kayser-Fleischer rings, neurological symptoms, Coombs-negative haemolysis, brain MRI abnormalities) should be sought **(LoE 3, strong recommendation).** | 100% |
| Pharmacological treatment should be started once diagnosis is well supported by the Leipzig score **(LoE 2, strong recommendation).** | 88% |
| Genetic *ATP7B* analysis should follow to confirm diagnosis, which in turn may enable family screening **(LoE 2, strong recommendation).** | 100% |
| If diagnosis remains questionable, hepatic parenchymal copper quantification (dry weight) should be performed **(LoE 2, strong recommendation).** | 97% |
| Screening for copper metabolism abnormalities (both serum ceruloplasmin and basal 24-h urinary copper excretion) and presence of Kayser-Fleischer rings should be performed. If available, relative exchangeable copper in serum determination should also be performed **(LoE 2, strong recommendation).** | 97% |
| Brain MRI should be performed in all patients to search for abnormalities especially in basal ganglia, thalamus, brainstem, and cerebellum **(LoE 2, strong recommendation).** | 97% |
| In addition, testing for any kind of liver involvement should be performed, with liver function tests, liver imaging and non-invasive fibrosis testing **(LoE 2, strong recommendation).** | 97% |
| Pharmacological treatment should be started once diagnosis is well supported by the Leipzig score **(LoE 2, strong recommendation).** | 94% |

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(*continued*)

| Recommendation | Consensus |
|---|---|
| Genetic *ATP7B* analysis should follow to confirm diagnosis, which in turn may enable family screening **(LoE 2, strong recommendation).** | 100% |
| The first step should be screening for copper metabolism abnormalities (serum ceruloplasmin and basal 24-h urinary copper excretion). If available, relative exchangeable copper determination in serum should also be performed **(LoE 2, strong recommendation).** | 97% |
| Typical extrahepatic clinical features of WD (Kayser-Fleischer rings, neurological symptoms, Coombs-negative haemolysis) should be looked for in all children, especially those >10 years of age **(LoE 3, strong recommendation).** | 97% |
| Pharmacological treatment should be started once diagnosis is well supported by the Leipzig score **(LoE 3, strong recommendation).** | 91% |
| Genetic *ATP7B* analysis should follow to confirm diagnosis, which in turn may enable family screening **(LoE 2, strong recommendation).** | 100% |
| If diagnosis cannot be confirmed or excluded, hepatic parenchymal copper quantification (dry weight) should be performed **(LoE 2, strong recommendation).** | 97% |
| Especially in older children (>10 years old, even if asymptomatic) brain MRI should be performed at diagnosis to evaluate the extent of disease **(LoE 4, strong recommendation).** | 93% |
| Screening for WD should be performed in all adult patients and children >4 years of age presenting with ALF **(LoE 3, strong recommendation).** | 94% |
| Coombs-negative haemolysis, Kayser-Fleischer rings and neurological symptoms suggestive of WD should be looked for as highly indicative of WD **(LoE 3, strong recommendation).** | 100% |
| Relative exchangeable copper determination may be performed if available **(LoE 4, weak recommendation).** | 96% |
| Brain MRI may be performed whenever possible to support diagnosis **(LoE 4, weak recommendation).** | 96% |
| Genetic *ATP7B* analysis should be performed as soon as possible but is not required for treatment initiation **(LoE 2, strong recommendation).** | 97% |
| Measurement of hepatic parenchymal copper content in dry weight liver biopsy is recommended if required for diagnostic purposes. The value >250 μg/g is highly suggestive of WD but requires differential diagnosis with cholestatic liver disease **(LoE 2, strong recommendation).** | 97% |
| Although liver histological evaluation does not provide any definite diagnostic features for WD, it should be carried out whenever a liver biopsy is performed for hepatic copper quantification **(LoE 3, strong recommendation).** | 93% |
| Histochemical copper staining may be omitted, as it has only minor diagnostic value for WD **(LoE 3, weak recommendation).** | 88% |
| Molecular testing is recommended to confirm the diagnosis of WD or to complete diagnosis if clinical and biochemical testing is not decisive **(LoE 2, strong recommendation).** | 97% |
| A stepwise approach may be applied to reduce costs of testing, starting from most common variants up to whole-exome testing **(LoE 3, weak recommendation).** | 86% |
| Screening the full-length sequence of *ATP7B* by next-generation sequencing should be performed in non-conclusive cases **(LoE 2, strong recommendation).** | 97% |
| It is recommended to measure serum ceruloplasmin and 24-h urinary copper excretion (and relative exchangeable copper if available), evaluate clinical symptoms and to perform liver tests in siblings and in first-degree relatives (parents and offspring of an index case) **(LoE 3, strong recommendation).** | 100% |
| Molecular-genetic testing should be performed in siblings to search for the biallelic variants from the index patient **(LoE 2, strong recommendation).** | 100% |
| Molecular testing should be performed in first-degree relatives with abnormalities of copper metabolism or abnormal liver tests **(LoE 3, strong recommendation).** | 97% |
| A detailed neurological examination should be performed in all adults following a diagnosis of WD **(LoE 3, strong recommendation).** | 97% |
| A detailed neurological examination should be performed in children following a diagnosis of WD if they have neuropsychiatric symptoms or are >10 years of age **(LoE 3, strong recommendation).** | 97% |
| Neurological assessment using a validated scale is recommended in adult patients and children >10 years of age with a confirmed diagnosis of WD and at any age if they have neuropsychiatric symptoms **(LoE 2, strong recommendation).** | 94% |
| A brain MRI should be performed in all adult patients and children >10 years of age with a confirmed diagnosis of WD **(LoE 2, strong recommendation).** | 93% |
| Treatment response should be evaluated by clinical and laboratory/imaging parameters as well as laboratory tests of copper metabolism **(LoE 3, strong recommendation).** | 97% |
| Treatment response should be defined by resolution of liver symptoms (jaundice, ascites) and/or improvement of liver parameters (ALT, INR, albumin) and/or progressive improvement of neurologic symptoms, disappearance of Kayser-Fleischer rings or at least no deterioration on a validated scale or on brain imaging **(LoE 3, strong recommendation).** | 100% |
| Chelators should be the primary choice in patients with significant liver disease, *e.g.* features of significant fibrosis and cirrhosis, liver failure, and haemolysis **(LoE 3, strong recommendation).** | 97% |
| Either zinc or chelators should be used in patients with a neurological presentation **(LoE 2, strong recommendation).** | 80% |
| A 'start low, go slow' treatment regimen is recommended for chelators, especially in patients with a neurological presentation **(LoE 3, strong recommendation** | 100% |
| Either zinc or chelators may be used in asymptomatic patients without signs of significant liver involvement **(LoE 4, weak recommendation** | 86% |
| Avoiding frequent dietary intake of food containing high concentrations of copper is suggested in symptomatic patients with WD until remission/stabilisation of signs and symptoms, especially in the first year of treatment **(LoE 4, weak recommendation).** | 97% |
| Further low-copper dietetic restrictions may be evaluated with regard to the effects of therapy and quality of life **(LoE 4, weak recommendation).** | 90% |
| Once treatment response is achieved, a change of treatment (lowering chelator dose, switching to zinc) can be considered for medium and long-term safety reasons **(LoE 4, weak recommendation).** | 97% |
| When patients do not achieve sufficient treatment response, adherence should be checked in detail based on copper balance, laboratory investigations and clinical symptoms **(LoE 2, strong recommendation).** | 100% |

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| Recommendation | Consensus |
|---|---|
| In patients with WD who do not achieve sufficient treatment response on first-line therapy despite a good adherence to treatment and a 24-h urinary copper excretion in the target range, or side effects, switching treatment should be considered (D-penicillamine to trientine and vice versa or zinc to chelators) **(LoE 2, strong recommendation).** | 100% |
| In patients with WD who develop paradoxical neurological worsening on first-line therapy, decreasing the dose of chelators and slowing the increase of doses or changing the WD treatment should be considered (chelators to zinc or zinc to chelators) **(LoE 2, strong recommendation).** | 91% |
| LT should be considered on a case-to-case basis in patients with a continuous worsening of neurological symptoms despite at least 6 months of optimised medical treatment **(LoE 2, strong recommendation).** | 86% |
| LT should be considered in patients with decompensated cirrhosis despite adequate medical treatment **(LoE 2, strong recommendation).** | 100% |
| Patients with decompensated cirrhosis in WD may respond to medical therapy, usually after >3 months of treatment, but they should be concomitantly evaluated for LT **(LoE 3, strong recommendation).** | 100% |
| Any anti-copper therapy should be maintained during pregnancy and breastfeeding **(LoE 4, weak recommendation).** | 91% |
| Specific treatment for WD (chelators and zinc salts) enables improvement of neurological and neuropsychiatric symptoms but may be insufficient to control symptoms, in which case symptomatic treatments should be considered **(LoE 2, strong recommendation).** | 97% |
| Symptomatic treatments of neurological symptoms should be based on pharmacotherapy, botulinum toxin injections, physiotherapy, speech therapy and rarely neurosurgery **(LoE 2, strong recommendation).** | 100% |
| Neuropsychiatric symptoms can be treated by psychotropic medications (mood stabilisers, antidepressants, anxiolytics) and/or psychotherapy. Neuroleptics should be avoided (except quetiapine or clozapine) as they could worsen neurological symptoms **(LoE 2, strong recommendation).** | 97% |
| All patients with ALF due to WD should be referred to LT centres **(LoE 2, strong recommendation).** | 100% |
| Patients with ALF and encephalopathy should be immediately listed for LT **(LoE 2, strong recommendation).** | 97% |
| Patients with ALF due to WD should be evaluated according to the modified King's College prognostic score at each biochemical evaluation but at least every 24 h; scores ≥11, even without encephalopathy, are an indication for LT **(LoE 3, strong recommendation).** | 97% |
| Pharmacotherapy with chelators (rapidly increased to full dose) should be started immediately in all patients with ALF due to WD and those listed for LT, to be continued until LT **(LoE 3, strong recommendation** | 93% |
| High-volume plasma exchange should be considered as a bridge to LT. Albumin dialysis might also be considered if available **(LoE 3, strong recommendation for high-volume plasma exchange, weak recommendation for albumin dialysis).** | 100% |
| Patients on a waiting list for LT should be monitored closely and possibly withdrawn from the waiting list when improvement is noted **(LoE 3, strong recommendation).** | 100% |
| LT should not be contraindicated in patients with WD and neurological symptoms who need to be transplanted for decompensated cirrhosis **(LoE 2, strong recommendation).** | 100% |
| LT may be considered a "brain indication" on a case-to-case basis in patients with severe neurological WD who do not respond to anti-copper treatment **(LoE 2, weak recommendation).** | 93% |
| Living donor related LT from the left or the right lobe, depending on size of the recipient, should be considered ifWD is excluded in the donor **(LoE 3, strong recommendation).** | 100% |
| Anti-copper therapy is not indicated after LT **(LoE 4, strong recommendation).** | 97% |
| Patients with WD who are stable on treatment should be monitored every 6 to 12 months **(LoE 4, weak recommendation).** | 91% |
| Patients who have recently started treatment, have decompensated cirrhosis, significant neurological disability or suspected non-adherence should be followed up more frequently **(LoE 4, strong recommendation).** | 100% |
| Monitoring should include history on symptoms and adherence, physical examination, measurement of body weight and vital signs, ophthalmologic examination if Kayser-Fleischer rings were present at baseline or if concerns about adherence, laboratory investigations (full blood count, liver profile, renal profile and a coagulation profile if the patient has cirrhosis) and abdominal ultrasound **(LoE 3, strong recommendation).** | 94% |
| Patients with WD and cirrhosis should be screened for complications of portal hypertension and hepatocellular carcinoma **(LoE 3, strong recommendation).** | 94% |
| Adequacy of treatment with D-penicillamine or trientine should be monitored during all stages of treatment by measuring 24-h urinary copper excretion and serum non-ceruloplasmin-bound copper or serum exchangeable copper whenever available **(LoE 3, strong recommendation).** | 91% |
| Adequacy of treatment with zinc salts should be monitored during all stages of treatment by measuring 24-h urinary copper excretion and serum non-ceruloplasmin-bound copper or serum exchangeable copper whenever available **(LoE 3, strong recommendation).** | 91% |
| Monitoring serum exchangeable copper is advised when available and its value should decrease progressively in response to treatment **(LoE 3, weak recommendation).** | 86% |
| Medication adherence can be assessed based on monitoring serum non-ceruloplasmin-bound copper levels, serum exchangeable copper, 24-h urinary copper excretion at baseline and 48 hours after cessation of chelators **(LoE 3, weak recommendation).** | 90% |
| Transition planning should be initiated by the paediatric team in early adolescence (between 12-14 years of age) to ensure the progressive development of competencies regarding self-care, before moving to adult healthcare **(LoE 4, strong recommendation).** | 100% |
| There can be a specific programme for transition and transfer of adolescents and young adults with WD that allows them to become autonomous, independent, and responsible in their healthcare **(LoE 4, weak recommendation).** | 100% |
| The minimum core team involved in transition to adult care may include a physician and a specialist nurse; additionally, a psychologist and social worker might be involved **(LoE 4, weak recommendation).** | 78% |
| Joint or alternate clinical appointments with a paediatrician and adult hepatologist and/or neurologist, preferably in the presence of a specialist nurse, are advised during transition **(LoE 4, weak recommendation).** | 96% |

## Abbreviations

ALF, acute liver failure; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BTX, botulinum toxin A; CPG, clinical practice guidelines; DBS, deep brain stimulation; dNCC, direct non-ceruloplasmin-bound copper; EASL, European Association for the Study of the Liver; FLAIR, fluid-attenuation inversion recovery; INR, international normalised ratio; LT, liver transplantation; MASLD, metabolic-associated steatotic liver disease; MRS, magnetic resonance spectroscopy; NCC-Sp, non-ceruloplasmin-bound copper assay using liquid chromatography and ICP mass spectroscopy; NWI, new Wilson index; REC, relative exchangeable copper; SSRIs, selective serotonin reuptake inhibitors; SWI, susceptibility weighted imaging; TB, total bilirubin; UWDRS, Unified Wilson's Disease Rating Scale; VUS, variant of uncertain significance; WD, Wilson's disease.

## Conflict of interest

Please refer to the accompanying ICMJE disclosure forms for further details.


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## Supplementary data

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