

Investigation and management of Wilson’s disease: practical guidance from the British Association for the Study of the Liver

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Key words:

Wilson's disease; copper; chelation therapy; movement disorder; cirrhosis; acute liver failure

Abbreviations:

ABN	Association of British Neurologists
AIH	Autoimmune hepatitis
ALF	Acute liver failure
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BASL	British Association for the Study of the Liver
BSG	British Society of Gastroenterology
DBS	Deep brain stimulation
FLAIR	Fluid attenuation inversion recovery
HCC	Hepatocellular carcinoma
INR	International normalised ratio
KF	Kayser-Fleischer
LT	Liver transplantation
MLPA	Multiplex ligation-dependent probe amplification
MMSE	Mini-mental state examination
MoCA	Montreal cognitive assessment
MRI	Magnetic resonance imaging
NWI	New Wilson index
PALF	Paediatric acute liver failure
PT	Prothrombin time
TE	Transient elastography
WD	Wilson's disease

SUMMARY

Wilson's disease is an autosomal-recessive disorder of copper metabolism with hepatic, neurological, psychiatric, ophthalmological, haematological, renal, and rheumatological manifestations. Making a diagnosis can be challenging given no single test can confirm or exclude the disease and diagnostic delays are common. Treatment protocols vary and adverse effects, including paradoxical neurological worsening, can occur. Here, we provide a practical guide to the workup of Wilson's disease. We include recommendations on indications for testing, how to interpret results, and when additional investigations are required. We also cover treatment initiation, ideally under the guidance of a specialist centre for Wilson's disease, and the principles behind long term management. This guidance was developed by a multi-disciplinary group of Wilson's disease experts formed through the British Association for the Study of the Liver. It has been endorsed by the British Society of Gastroenterology and approved by the Association of British Neurologists.

INTRODUCTION

Wilson's disease (WD) is an autosomal recessive disorder of copper metabolism with an estimated disease prevalence of 2 per 100,000 in the UK.¹ ATP7B mutations lead to impaired biliary excretion and subsequent accumulation of copper in multiple organ systems. The majority of patients present between the age of 3 and 40 years with liver disease, a movement disorder, or psychiatric features. However, ophthalmological, haematological, renal, and rheumatological manifestations can also occur,^{2,3} and presentations in older adults, including septuagenarians, are described.^{4,5} Clinical presentations are thus highly variable, often mimicking more common diseases, and diagnoses are frequently missed or delayed.⁶ Whilst routine investigations can be suggestive of WD, specialised tests are required to confirm the diagnosis.

Here, we clarify the indications for specific investigations and how they should be interpreted. We also discuss common pitfalls in diagnosis and management, and make consensus recommendations for both paediatric and adult physicians. Compared to previous guidelines, this document offers a more practical guide to the investigation and management of WD for the non-expert that includes advice on how to screen for neurological involvement at the bedside, which investigations are indicated in specific clinical scenarios, how these should be prioritised and when and how to proceed with initiating treatment, in addition to incorporating recent changes in clinical practice.⁷⁻¹⁰

BACKGROUND AND METHODS

This guidance document was commissioned by the British Association for the Study of the Liver (BASL) Rare Diseases Special Interest Group (SIG) to provide advice for general physicians regarding the initial investigation and management of WD and to promote interdisciplinary working. The working party was chaired by OB and included experts in adult hepatology (TM, AA, GA, JD, WG), paediatric hepatology (AS, SV, AD, DK), adult neurology (SS, TTW, OB), genetics (AM), clinical chemistry (GTG) alongside patient representation (VW). The major subject areas were agreed by the working party and allocated to individuals responsible for searching the literature and synthesising the evidence (SS, TM, AS, SV). The writing group (SS, TM, AS, SV, GA, AD, GTG, DK, TTW, WG, OB) then had a series of six interval virtual meetings to evaluate the evidence and agree on a set of provisional consensus recommendations. The guidance document and recommendations were then circulated to the entire BASL Rare Diseases SIG, as well as expert members of the British Society of Gastroenterology (BSG), Association of British Neurologists (ABN), and Wilson’s Disease Support Group UK (WDSG-UK). After addressing reviewer comments, all societies formally approved the guidance and recommendations. The level of supporting evidence for the recommendations was assessed using the Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence.¹¹ This process took place over a total of 10 months between January and October 2021.

SEARCH STRATEGY AND SELECTION CRITERIA

The published literature (up until 1st May 2021) was searched using PubMed, Cochrane, and Google Scholar. Studies were identified using keywords, including “Wilson’s disease” and “Wilson disease”. These searches were combined with the set operator “AND” with additional terms including: “chelation”, “penicillamine”, “trientine”, “zinc”, “cirrhosis”, “movement disorder”, and “acute liver failure” to identify relevant studies. Additionally, abstracts from conference proceedings from the European Association for the Study of the Liver and the American Association for the study of Liver Diseases (2017-2020) were manually searched to identify potentially eligible studies in abstract form. Reference lists from identified articles were also assessed for relevance. ClinicalTrials.gov was searched using the terms “Wilson’s disease” and “Wilson disease” to screen for relevant ongoing interventional studies. The final reference list was generated on the basis of applicability to the broad scope of this guidance document.

CLINICAL PRESENTATION AND INDICATIONS FOR TESTING

The most striking reason to suspect WD is the combination of liver disease with a movement disorder or psychiatric features.¹² Patients with hepatic disease tend to present at a younger age than those with

neurologic manifestations.^{6,13} Irrespective of the initial presentation, a family history of liver disease or a movement disorder in a sibling should immediately raise suspicion for WD, noting that presentation can vary considerably within families.¹⁴

We advocate for a pragmatic approach to WD diagnosis where *routine investigations* are performed in cases where there is a lower index of suspicion, and a *wider screen* reserved for cases with additional clinical features suggestive of WD. A number of *additional tests* may be required in specific circumstances. These categories of investigations are presented in **Figure 1**, which provides an overview of the major learning points and consensus recommendations in this guidance document. Typical presentations of WD and specific recommendations on indications for the different categories of investigations are discussed in greater detail below.

Patients presenting with suspected liver disease

Virtually all patterns of liver disease have been described in WD in both paediatric and adult populations. This includes asymptomatic derangements in liver biochemistry, hepatic steatosis on imaging, hepatomegaly, acute hepatitis, cirrhosis, and acute liver failure (ALF).¹⁵⁻¹⁹ When faced with any of these clinical presentations WD should form part of the differential diagnosis and *routine investigations* should be arranged. The index of suspicion should be higher in children and a *wider screen* should be performed at initial presentation to a paediatrician. In adults, most presentations with liver disease will be secondary to common insults such as alcohol, non-alcoholic fatty liver disease and viral hepatitis. Therefore, a *wider screen* should be performed where an alternative aetiology for liver disease cannot be identified or there are additional features of WD such as a movement disorder or unexplained haemolytic anaemia or the serum caeruloplasmin is low.

WD can mimic or co-exist with other liver pathology. Hepatic steatosis identified on imaging or biopsy is common in WD and can be misattributed to alcohol or non-alcoholic steatohepatitis. Similarly, histological features of WD on liver biopsy may resemble autoimmune hepatitis (AIH) and clinicians should keep an open mind for WD in those labelled with AIH who fail to respond to immunosuppressive medication.²⁰ Left untreated, WD progresses to cirrhosis, which is present in 25-54% of patients at diagnosis and may ultimately become decompensated with jaundice, ascites, variceal haemorrhage, hepatic encephalopathy, and susceptibility to infection.²¹⁻²⁴

Recommendation: *All children presenting with liver disease should have routine investigations and a wider screen for WD (level 3).*

Recommendation: All adults presenting with liver disease should have routine investigations for WD (level 3).

Recommendation: All adults with unexplained liver disease despite investigation with laboratory tests, liver imaging, and histology should have a wider screen for WD (level 3).

Recommendation: All adults with liver disease in combination with a movement disorder or an unexplained haemolytic anaemia should have routine investigations and a wider screen for WD (level 4).

Acute Liver Failure

Up to 20% of WD patients with hepatic presentations have acute hepatic WD, formerly ‘fulminant’ WD,²⁵ with a higher frequency in paediatric cohorts.²⁶ This severe acute liver injury can rapidly progress to ALF defined in adults by the presence of jaundice, coagulopathy, and encephalopathy.^{27,28} Coagulopathy is an independent risk factor for death in children in whom mental status is more difficult to assess. Paediatric ALF (PALF) is therefore defined as an acute liver injury with prothrombin time (PT) >15 seconds or international normalised ratio (INR) >1.5 not corrected by vitamin K in the presence of encephalopathy, or a PT >20 seconds or INR >2.0 regardless of the presence or absence of encephalopathy.²⁹ Definitions of ALF and PALF traditionally require the absence of chronic liver disease, however, an exception is made in WD where most patients will have underlying cirrhosis at initial presentation.³⁰

The typical presentation is a young patient presenting with moderately elevated transaminases and a high bilirubin to alkaline phosphatase ratio who develops a Coombs-negative haemolytic anaemia and encephalopathy. Acute hepatic WD is more common in females than males (4:1) and often presents *de novo* and without warning, although there may be a concurrent viral trigger.²⁶ It may also occur in patients with an established diagnosis of WD with non-adherence to medication.

Patients presenting with neurological symptoms

Slurred speech is the most common neurological symptom of WD and reported in 52% of children and 74-91% of adults with neurological presentations.^{6,31} A postural tremor of the upper limbs is the most common movement disorder. It is usually irregular or jerky and can easily be examined by asking patients to hold out their arms. However, other movement disorders including dystonia, parkinsonism, ataxia, and, less commonly, chorea can occur (**Panel 1**).^{6,31,32} Patients may refer to shaking, clumsiness, or loss of balance. Handwriting is often affected and should be specifically assessed, particularly in

children.⁶ Some patients also have a characteristic grimacing facial expression (risus sardonicus) and seizures occur in around 10% of children with neurological presentations.^{6,33}

Several clinical features can help differentiate movement disorders in WD from other aetiologies. Firstly, while symptoms are often chronic and slowly progressive, some patients with WD have a subacute onset with progression over months; this is unusual in other movement disorders and should prompt urgent investigation. Secondly, movement disorders in WD often occur in combination as mixed movement disorders with dystonic tremor or dystonia-parkinsonism syndromes. Thirdly, early bulbar involvement, which may include dysphagia and/or drooling in addition to dysarthria, is common in WD but unusual in other causes of movement disorders.

Neuropsychiatric features

Executive function may be impaired but this can be subtle and easily missed in a brief consultation.³⁴⁻³⁶ Processing speed, memory, and social cognition can also be affected.³⁷ Asking about difficulties at school, university, or work may be a useful screen for cognitive impairment in WD. Commonly used bedside tests such as the Mini-Mental State Examination (MMSE) or Montreal Cognitive Assessment (MoCA) are less sensitive for mild cognitive impairment and more detailed assessments with the Addenbrooke's Cognitive Examination or formal neuropsychometry may be required.³⁸

Behavioural or personality changes (incongruous behaviour, irritability, aggression, and disinhibition), mood disorders (hypomania or depression), and anxiety are common.^{39,40} Psychosis can also occur, typically with paranoid delusions.⁴¹ Psychiatric features often go unnoticed, particularly in the paediatric population where changes in behaviour or mood may be attributed to adolescence.⁴² In a large retrospective study of patients with WD from the UK, 51% had psychiatric symptoms at the time of diagnosis and 20% had previously seen a psychiatrist.⁴⁰ While the yield from screening patients with isolated psychiatric symptoms is low,⁴³ psychiatrists should be aware of hepatic and neurological features and urgently arrange initial investigations and onward referral if WD is suspected.

Recommendation: All patients between the age of 5 and 50 years who develop a progressive postural tremor, dystonia, or parkinsonism, except those with isolated cervical dystonia or blepharospasm, should have routine investigations for WD (level 4).

Recommendation: All patients who develop a mixed movement disorder with any red flags (subacute onset/progression, early bulbar involvement, executive dysfunction, behavioural/personality changes, or suspected liver disease) should have routine investigations and a wider screen for WD, in addition to neuroimaging (level 4).

Haemolysis

A Coombs-negative haemolytic anaemia occurs in 4-10% of cases and is more common in presentations during childhood or adolescence.^{23,44,45} When associated with unexplained liver disease or movement disorders, it is highly suggestive of WD. The clinical course may be with an acute haemolytic syndrome or insidious with previous episodes of unexplained jaundice. In a retrospective analysis of 321 patients, haemolysis was the initial presentation in 22 cases and the diagnosis of WD was frequently delayed with subsequent progressive liver injury and/or neurologic deterioration.⁴⁶

Recommendation: *All patients with an unexplained Coombs-negative haemolytic anaemia should have routine investigations and a wider screen for WD.*

INTERPRETING INITIAL INVESTIGATIONS

Liver function tests

Abnormal liver biochemistry is a well-recognised but non-specific feature of WD. Crucially, normal liver function tests do not exclude the diagnosis of WD: Elevated transaminases (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]), typically ranging between 50-200 U/L,²³ are only found in 60% of patients with hepatic presentations and 30% of patients with neurological presentations.²² Hyperbilirubinaemia, which is present in 20-50% of cases, may reflect liver injury, Coombs-negative haemolysis, or a combination of these in patients with WD.^{22,23} Measuring the relative proportions of conjugated and unconjugated bilirubin is helpful when haemolysis is suspected.

Full blood count and clotting profile

Haematological abnormalities are common in WD occurring in a third of patients at diagnosis.²¹ Thrombocytopenia and, less commonly, leukopenia, occur in the setting of portal hypertension. Elevated prothrombin time (PT) and international normalised ratio (INR) can occur in parallel with hepatic dysfunction but are not features of WD *per se*.⁴⁹ Patients with haemolysis will typically have a macrocytic anaemia associated with a reticulocytosis.

Serum caeruloplasmin

A very low serum caeruloplasmin (<0.10 g/L) is characteristic of WD.⁴⁷ However, patients often have intermediate levels (0.10-0.20 g/L) and up to 15% of those with neurological presentations and 40% of those with hepatic presentations have levels in the normal range (>0.20 g/L).^{21,48} Systemic inflammation and the effect of oestrogens during pregnancy or oral contraceptive pill use can increase caeruloplasmin levels into the normal range in patients with WD.⁴⁹ Conversely, reduced levels between 0.10-0.20 g/L can be found in end-stage liver disease of any aetiology, in addition to copper deficiency due to

gastrointestinal malabsorption or dietary zinc supplementation. Up to 30% of heterozygous *ATP7B* carriers have a serum caeruloplasmin 0.15-0.19 g/L and variants in the caeruloplasmin (*CP*) gene can also cause reduced or undetectable levels.⁵⁰ Patients with bi-allelic *CP* mutations develop acaeruloplasminemia, a very rare neurodegenerative disease associated with abnormal iron metabolism, anaemia, and diabetes.⁵¹ In light of all of these limitations, the positive predictive value of serum caeruloplasmin <0.20 g/L for the diagnosis of WD among adults being investigated for liver disease is only 6%.⁵²

Recommendation: Serum caeruloplasmin <0.10 g/L is highly suggestive of WD but a wider screen for WD is usually required to make a diagnosis (level 2).

Recommendation: Serum caeruloplasmin 0.10-0.20 g/L has numerous causes and a wider screen for WD is indicated (level 2).

Recommendation: Serum caeruloplasmin >0.20 g/L does not exclude diagnosis of WD but reduces the likelihood (level 2).

24-hour urinary copper output

Urinary copper output varies throughout the day and 24-hour urine collections are required. Written instructions should be provided (**Panel 2**). Whilst laboratories often insist on using acid-washed containers this has recently been shown to be unnecessary.⁵³ With a cut-off of 0.64 $\mu\text{mol}/24$ hours (40 $\mu\text{g}/24$ hours), the sensitivity and specificity for diagnosing WD in children are 79% and 88%, respectively.⁴⁷ Data confirming an appropriate cut-off in adults are limited,⁴⁷ but mean copper output was 0.34 $\mu\text{mol}/24$ hours (21 $\mu\text{g}/24$ hours) in a study of 111 healthy adults from the UK,⁵⁴ and most clinical biochemists would consider a copper output >0.64 $\mu\text{mol}/24$ hours (40 $\mu\text{g}/24$ hours) to be abnormal in an adult as well. Cholestasis prevents the biliary excretion of copper and can lead to systemic copper overload with markedly elevated urinary copper output, particularly in children.⁵⁵ Other causes of increased urinary copper output include autoimmune hepatitis and non-alcoholic fatty liver disease.⁵⁶

Recommendation: Patients should be offered written instructions for 24-hour urine collections and provided with non-acid washed containers (level 3).

Recommendation: Copper output >0.64 $\mu\text{mol}/24$ hours (40 $\mu\text{g}/24$ hours) is suggestive of WD but further investigations are required to make a diagnosis (level 2).

Slit lamp examination

Copper deposits within Descemet's membrane, known as Kayser-Fleischer (KF) rings, are characteristic of WD and seen on slit lamp examination in 90% of neurological presentations and 47% of hepatic presentations.^{48,57} They can also occur with systemic copper overload due to cholestasis, and, very rarely, alcoholic hepatitis and multiple myeloma.^{58,59} They are often visible with the naked eye as a yellowish-green or golden-brown discoloration at the periphery of each cornea, which on close inspection, is distinct from the underlying iris. A tentative diagnosis of WD based on the presence of KF rings can therefore take place at the bedside before being confirmed with slit lamp examination by an experienced Ophthalmologist.

Recommendation: *The presence of KF rings on slit lamp examination is highly suggestive of WD (level 2).*

Have I made the diagnosis yet?

The diagnosis of WD is relatively straightforward when there is a low serum caeruloplasmin (<0.20 g/L), high urinary copper output (>0.64 µmol/24 hours or 40 µg/24 hours) and KF rings.⁶⁰ A typical neurological presentation with either a very low serum caeruloplasmin (<0.1 g/L) or KF rings is also considered diagnostic of WD. Otherwise, a number of additional investigations may need to be considered, as described below. The Leipzig scoring system (see **supplementary material**) may be helpful here but we recommend this is used in conjunction with discussion with a clinician experienced in managing WD given some additional investigations are invasive and/or time-consuming and may delay the initiation of treatment unnecessarily.⁶¹ Consolidating expertise in hepatology and movement disorders into paediatric and adult centres for WD can help with diagnosis and management and has been successfully implemented in England (see **supplementary material** for contact details). This also provides patients with opportunities to participate in clinical research and trials.

How urgent is the situation?

A suspected diagnosis of WD should be taken seriously. Both neurological and hepatic complications can rapidly develop, even after many years of subclinical disease. These complications can be fatal, particularly in the context of ALF, or lead to irreversible neurological disability. Clinicians in primary and secondary care should have a low threshold for urgent discussion with a specialist centre and all newly diagnosed cases must be discussed prior to or soon after treatment initiation. Patients should also be encouraged to contact a patient advocacy service such as the WDSG-UK (www.wilsonsdisease.org.uk), which offers support for people living with WD and their families.

Recommendation: *Initial investigations should be performed as soon as possible given the risk of hepatic and neurological deterioration (level 4).*

Recommendation: *Patients suspected to have WD should be urgently discussed with a specialist centre (level 4).*

ADDITIONAL INVESTIGATIONS

Additional investigations may be indicated in a patient with suspected WD. Here, we clarify when these investigations should be performed and how they should be interpreted.

Serum copper

The serum copper concentration reflects copper incorporated into caeruloplasmin and non-caeruloplasmin-bound copper. Patients with a low serum caeruloplasmin usually have a low serum copper, irrespective of the underlying cause, and so serum copper should not be used to confirm or exclude WD in isolation.⁶² In patients with WD, a normal copper with a low serum caeruloplasmin indicates a very high non-caeruloplasmin-bound concentration, which is often associated with severe acute liver injury and haemolysis.^{46,63} The non-caeruloplasmin-bound copper can be calculated in $\mu\text{mol/L}$ by subtracting the serum caeruloplasmin in g/L multiplied by 47 from the serum copper in $\mu\text{mol/L}$.⁶⁴ A factor of 3.15 is used with serum copper in $\mu\text{g/dL}$ and caeruloplasmin in mg/dL .⁶⁵ The non-caeruloplasmin-bound copper is useful for monitoring treatment response but variation in the sensitivity and specificity of caeruloplasmin assays between laboratories makes deriving a universal cut-off value for diagnostic purposes problematic.⁶⁴

Recommendation: *Serum copper should not routinely be used alone to confirm or exclude a diagnosis of WD (level 3)*

Recommendation: *Clinicians should not delay initiation of treatment while serum copper is pending (level 4).*

Genetic testing

More than 700 pathogenic mutations in *ATP7B* have been described. In a genetic study of 181 patients from the UK, two mutations were identified in 98% of participants when using a combination of Sanger sequencing (including coding regions, splice sites and promoter region) and multiplex ligation-dependent probe amplification (MLPA, for identifying deletions and duplications).⁶⁶ However, data on the pathogenicity of some variants is based on individual case reports and several common variants

appear to exhibit reduced clinical penetrance.⁶⁷ Genetic testing is also relatively expensive and time consuming.

Despite these limitations, *ATP7B* sequencing has an important role in confirming the clinical diagnosis and is helpful when initial investigations are inconclusive and for family screening. Clinicians should be aware of several important caveats when requesting this investigation: A genetic diagnosis of WD should always be corroborated with clinical and biochemical findings, the absence of two pathogenic mutations does not exclude a diagnosis of WD and awaited genetic testing should not delay initiation of chelation therapy when other features are diagnostic.

Recommendation: *Genetic testing is required in all patients suspected to have WD on clinical and biochemical grounds but should not delay the initiation of treatment (level 3).*

Liver imaging and transient elastography

Ultrasound has an important role in staging liver disease severity and should be requested in any patient with suspected WD. Hepatic steatosis is the most common finding, seen in in 35-88% of patients.^{68,69} Cirrhosis may be suggested by an irregular liver edge, reversed portal vein flow, increased spleen size, and the presence of ascites. Computed tomography or magnetic resonance imaging may also demonstrate intra-abdominal collaterals or varices suggestive of elevated portal pressure. Even patients with exclusively neurological features have a high rate of liver abnormalities on imaging.²² Multiple hyper- and hypoechoic nodular lesions, a perihepatic fat layer, and the absence of caudate lobe hypertrophy in a cirrhotic liver have been suggested to be specific for WD. However, these have only been demonstrated in small series and should not be considered diagnostic.^{68,70}

Liver stiffness measurement (LSM) by transient elastography (TE) may be used as an additional tool for non-invasive fibrosis staging in WD. A LSM cut-off of ≥ 9.9 kPa has good accuracy in identifying cirrhosis in newly-diagnosed adults.⁷¹ LSM remains stable over time in the majority of chronically-treated patients and routine monitoring may be unnecessary unless there are concerns about non-adherence or disease progression.⁷¹ Studies evaluating the performance of LSM in children with WD are lacking.

Recommendation: *All patients with suspected WD should have a liver ultrasound scan irrespective of their clinical presentation (level 2).*

Recommendation: *Liver stiffness measurement by transient elastography should be performed in all adults without overt cirrhosis at the point of WD diagnosis (level 2).*

Neuroimaging

Hyperintense signal abnormalities in the basal ganglia, thalamus, and/or brainstem are seen on T2-weighted or fluid attenuated inversion recovery (FLAIR) sequences of 90% of patients with neurological presentations but may also be found in patients without neurological or psychiatric symptoms (**Figure 2**).⁷²⁻⁷⁴ When seen in the posterior midbrain, pons, or simultaneously involving the basal ganglia and brainstem, these appear to be highly specific for WD.⁷⁵ The pathognomonic 'face of the giant panda' sign is present in only 12% of cases.⁷⁴ WD can rarely cause confluent white matter abnormalities.^{76,77} Brain atrophy and susceptibility-weighted imaging abnormalities are also common at diagnosis and correlate with neurological severity at diagnosis.⁷⁸ T1-weighted hyperintensities in the basal ganglia, which likely represent manganese deposition and can occur with cirrhosis of any cause, may also be seen.⁷⁹⁻⁸¹

Recommendation: MRI brain is indicated in any patient with suspected WD who has neurological or psychiatric manifestations (level 2).

Recommendation: WD should be considered in patients with an unexplained movement disorder and signal abnormalities in basal ganglia, thalamus, or brainstem (level 3).

Recommendation: All patients with a confirmed diagnosis of WD should have an MRI brain, irrespective of their initial presentation (level 2).

Liver biopsy

Liver biopsy has an important role in the workup for WD when the diagnosis remains unclear or to establish the presence or absence of cirrhosis. A percutaneous approach is preferable unless there is a concern regarding bleeding risk or ascites, when a transjugular biopsy can be considered. Steatosis may be the only histological feature in the early stages of WD, although this is often seen alongside portal inflammation and fibrosis.²⁴ Copper and copper-associated proteins may be identified by histochemical stains (e.g. rhodamine or orcein). However, these are also seen in heterozygous *ATP7B* carriers and in a range of cholestatic liver diseases, and copper staining is absent in some patients with WD. Histological appearances cannot rule out WD. Measurement of hepatic parenchymal copper concentration is more useful. The normal copper content of the liver is <50 µg/g of dry weight and ≥250 µg/g has traditionally been regarded as diagnostic of WD.²⁴ However, a large prospective study has shown that, in the absence of cholestatic liver disease, a cut-off of 209 µg/g has sensitivity 99% and specificity 96%.⁸² A practical guide to the processing of liver tissue, including common pitfalls, is presented in **Panel 3**.

Recommendation: A liver biopsy with hepatic dry weight parenchymal copper may help with the diagnosis of WD when other non-invasive tests have proved inconclusive (level 2).

Recommendation: A liver biopsy may be considered in patients with a confirmed diagnosis of WD when there is clinical uncertainty about the presence or absence of cirrhosis (level 2).

Recommendation: Liver biopsy is not indicated in patients with a confirmed diagnosis of WD who have no evidence of liver involvement (level 4).

Recommendation: In the absence of cholestatic liver disease, a hepatic parenchymal copper content $>209 \mu\text{g/g}$ dry weight tissue is highly suggestive of WD (level 2).

Copper-65 absorption test

This test involves administering an oral solution of a non-radioactive isotope of copper (^{65}Cu) and measuring the $^{65}\text{Cu}/^{63}\text{Cu}$ ratio in serum samples over 72 hours. Patients with WD have a characteristic pronounced early peak before a gradual decline as they fail to incorporate ^{65}Cu into caeruloplasmin whereas healthy controls and heterozygote carriers have a gradual increase in the ratio as ^{65}Cu is incorporated into caeruloplasmin. This test has been validated in a cohort of 13 WD patients, 12 heterozygote carriers and 10 healthy controls from the UK.⁸³ Some experts on the panel have found this test invaluable in difficult cases and suggest that it should be more widely used. A radioactive copper incorporation test is available in some other countries.⁸⁴

Recommendation: A Copper-65 test can be performed in specialist centres when other tests are inconclusive and clinical suspicion remains (level 3).

Penicillamine challenge test

Historically, urinary copper excretion was measured following the administration of penicillamine as part of the diagnostic work-up of WD. However, results have proved unreliable and this test is no longer recommended for symptomatic or asymptomatic patients with suspected WD.

INITIAL MANAGEMENT

Acute liver failure

ALF is a medical emergency which requires early recognition, rapid diagnostic work-up, prompt supportive management, and referral to a transplant centre (see **supplementary material** for contact details for paediatric and adult transplant centres in the UK). All patients require urgent imaging to

examine liver texture and vasculature. KF rings are present in half of patients with WD in ALF and urinary copper is usually markedly elevated. Slit-lamp examination and 24-hour urine collection should therefore be attempted in patients with ALF where the underlying aetiology is not immediately apparent, even in the emergency setting. Transjugular liver biopsy with copper staining can be useful for providing urgent histological support for a diagnosis of WD with later validation through quantification of parenchymal copper content.

Patients with acute hepatic WD who develop encephalopathy should be listed for super-urgent liver transplantation (LT). Decisions to transplant patients who are not encephalopathic can be difficult. The new Wilson index (NWI) is accurate in predicting mortality with listing for LT recommended for patients with a score ≥ 11 (**supplementary material**).^{26,85} Plasmapheresis, renal replacement therapy (RRT), exchange transfusion, and artificial liver support systems have been used as bridging therapy for patients with WD awaiting LT with mixed results.⁸⁶⁻⁸⁹ Medical treatment with chelation therapy (with or without zinc salts) should be used in patients with acute hepatic WD without encephalopathy in an attempt to avoid LT.²⁶

Recommendation: *All children with PALF or decompensated liver disease should be urgently referred to a paediatric liver transplant centre (level 2).*

Recommendation: *Liver transplantation is indicated in children who have decompensated liver disease with encephalopathy (level 2).*

Recommendation: *The new Wilson index (NWI) should be used for prognosis and to facilitate decision making for liver transplantation in children (level 3).*

Recommendation: *Adults with ALF should be urgently referred to a liver transplant centre (level 2).*

Recommendation: *Liver transplantation should be considered in all adults with ALF (level 2).*

Chelation therapy

Chelating agents mobilise intracellular copper into the circulation and enhance urinary excretion of copper. They are used initially to ‘de-copper’ patients and then continued as lifelong maintenance therapy, often at lower doses. The primary treatment goals are to induce an adequate urinary copper excretion, arrest the disease process, and reduce symptom burden whilst minimising adverse effects. After a period of sustained clinical and/or biochemical response, typically at least two years, the aim is to prevent disease progression with the lowest effective dose, ensuring adherence is maintained at all

times. Chelation therapy is not required in patients who have been successfully treated with liver transplantation.

The most commonly used chelating agents are penicillamine and trientine. There are no randomised controlled trials comparing their efficacy and data from retrospective studies are conflicting. Clinicians in the UK tend to have more experience with penicillamine which is significantly cheaper than trientine but adverse effects leading to drug discontinuation are more frequent.^{90,91} Because of the increase in cost of trientine, NHS England published a clinical commissioning policy in 2018 stating that trientine can only be initiated through specialist centres for WD and in patients either intolerant of penicillamine or with an increased risk of adverse effects including past history of autoimmune diseases, severe thrombocytopenia or renal disease and allergy to penicillin.⁹² Specific examples of penicillamine intolerance outlined in the document are listed in the **supplementary material**. We are aware that trientine is considered first-line in some other countries.

Importantly, the dose of trientine in previous guidelines refers to the trientine dihydrochloride salt. However, an alternative formulation, trientine tetrahydrochloride, has become available and European Medicines Agency (EMA) approval now requires trientine dihydrochloride and trientine tetrahydrochloride to be labelled with respect to the trientine base. Trientine dihydrochloride labelled according to the salt content remains available in the UK and other countries and so clinicians should always check whether doses refer to the base or salt when prescribing trientine. In addition, the bioavailability of the trientine base differs between trientine dihydrochloride and trientine tetrahydrochloride and so doses are not equivalent even when referring to the trientine base.⁹³

There are no universally accepted dosing schedules for penicillamine or trientine and most adverse effects are dose-dependent (**Table 1**). The general rule is to “start low and go slow” in children and in adults presenting with neurological or psychiatric symptoms, aiming to reach the initial target dose over 4-6 weeks. Doses may need to be escalated more rapidly in patients with features of advanced liver disease. Patients do not necessarily need to be admitted to initiate treatment but do need close monitoring for adverse effects. They should be offered clear information on the risks, monitoring, and outcomes associated with these treatments at the outset and given a point of contact from a specialist centre if starting treatment in the community. We recommend reviewing the checklist in **Panel 4** for all patients starting chelation therapy.

Recommendation: *Penicillamine monotherapy is the first-line treatment for children and adults in the UK and should be introduced in consultation with a specialist centre for WD (level 3).*

Recommendation: *Penicillamine should be introduced gradually with dose increments of 125-250 mg per week in children (level 4).*

Recommendation: *Penicillamine should be introduced gradually with dose increments of 125-250 mg per week in adults with neurological or psychiatric symptoms (level 4).*

Recommendation: *Penicillamine can be introduced more quickly in adults presenting with decompensated liver disease in the absence of neurological symptoms or neuroimaging abnormalities (level 4).*

Recommendation: *Trientine dihydrochloride or tetrahydrochloride can be used in children and adults intolerant to penicillamine or at increased risk of adverse effects (level 3).*

Some clinicians offer pyridoxine (vitamin B6) supplementation to patients being treated with penicillamine on the basis that high doses have been shown to disrupt pyridoxine metabolism. The evidence to support this is limited.⁹⁴ Prophylactic supplementation with 50 mg once daily may be warranted in patients requiring doses higher than 40 mg/kg and those at increased risk of vitamin B6 deficiency through pregnancy, breastfeeding or malabsorption.

Zinc salts

Zinc salts inhibit the absorption of dietary copper by increasing metallothionein expression in enterocytes. Their role in the treatment of WD remains controversial given that monotherapy prevents disease progression of liver disease in some cohorts but not others.⁹⁵⁻⁹⁷ Chelation therapy is preferred by adult physicians in the UK. However, we recognise that zinc salts are commonly used in other countries where chelating agents are unavailable or not deemed cost effective. They are also a valid alternative if other treatments are contraindicated and may have a role as first-line treatment in carefully selected paediatric cases.

Recommendation: *We cannot make a strong recommendation for the use of zinc salts in children because of inadequate data. Zinc salts have been used by paediatric hepatologists in children identified through family screening, or as maintenance therapy with or without chelators.*

Recommendation: *Zinc salts are considered a third-line treatment for adults in the UK and should only be initiated by specialist centres. They are not recommended as monotherapy in patients with cirrhosis unless other treatments are unavailable or contraindicated (level 3).*

Dietary copper restriction

A low copper diet has long been considered an important aspect of the management of WD. However, there are no randomised controlled trials supporting this strategy. Most clinicians in Europe advise dietary copper restriction for at least the first year of treatment or until liver function tests normalize.⁹⁸ The literature mentions avoiding chocolate, nuts, liver (and other offal), shellfish, and mushrooms.^{7,8} The WDSG-UK has published a table outlining the approximate copper content in specific foods to aid patients and their families (<https://www.wilsonsdisease.org.uk/Site/Pages/diet>). Referral to a dietician may be helpful for patients requiring additional support.

Recommendation: *Dietary copper intake should be restricted in the first year of treatment. Decisions to continue this after one year should consider response to treatment, adherence and impact on quality of life (level 4).*

Paradoxical neurological worsening

Between 11-30% of patients with neurological or psychiatric symptoms at presentation develop paradoxical neurological worsening, which may be irreversible, in the first six months after initiation of treatment.⁹⁹⁻¹⁰¹ It can occur with penicillamine, trientine, and zinc salts and data on the risk of worsening with each treatment are conflicting.^{90,102} The pathophysiological basis for this phenomenon is unclear but risk factors may include severe neurological involvement at baseline, brainstem/thalamic lesions on MRI and concurrent anti-psychotic use.⁹⁹ It can also be difficult to differentiate between underlying disease progression (i.e. undertreatment) or paradoxical worsening when patients deteriorate soon after treatment initiation.

There is a consensus among experts that rapidly escalating doses may provoke or exacerbate worsening but there is limited data to guide how clinicians should respond when patients deteriorate. Clinicians may need to consider the disease course prior to treatment initiation, the current dose relative to the target dose, the severity of the deterioration and the risk of hepatic decompensation when deciding whether to continue, decrease or increase the dose, switch treatments or consider other options with anecdotal evidence such as a course of intramuscular dimercaprol.¹⁰³ It is unclear whether liver transplantation should be used to treat patients with paradoxical neurological worsening or severe neurological worsening resistant to active chelation therapy.¹⁰⁴

Response to treatment

Chelation therapy is usually effective for managing liver disease but neurological outcomes are less predictable.¹⁰⁵ The delay between treatment initiation and clinical response is variable but liver function

tests and neurological symptoms usually begin to improve within six months. It can take several years before neurological recovery reaches a plateau.¹⁰⁶

The 24-hour urinary copper output and non-caeruloplasmin-bound ('free') copper can be used to monitor the biochemical response to treatment. Chelation therapy induces a marked increase in urinary copper excretion (cupriuresis) in the first few months which typically peaks at around six months with penicillamine and 18 months with trientine.¹⁰⁷ The urinary copper output can either be measured while continuing medication ('on treatment') or after 48 hours of treatment cessation ('off treatment').¹⁰⁸ An 'on treatment' collection (or spot urine copper) can be useful for confirming that there is an adequate cupriuresis. The 'on treatment' copper output is usually above 8 μmol (500 μg) per 24 hours after reaching the target dose of penicillamine. The 'off treatment' copper output, which is thought to indicate the residual copper load, decreases over the first and second year of treatment for patients on penicillamine but takes longer for patients on trientine.¹⁰⁷ It is not usually helpful to measure this in the first six months of treatment. The non-caeruloplasmin-bound ('free') copper should gradually decrease with treatment.

Recommendation: A full blood count, liver function tests, renal profile, and urine dipstick should be performed to monitor for adverse effects prior to starting penicillamine, after one week of treatment and then every two weeks for three months (level 4).

Recommendation: Patients with neurological symptoms should have regular follow up with a movement disorders specialist for a minimum of 12 months after treatment initiation (level 4).

Recommendation: 24-hour urinary copper output while continuing medication ('on treatment') should be measured within the first two months to confirm an adequate copper excretion (level 4).

LONG TERM MANAGEMENT

Follow up

Patients established on treatment should be followed up every 6-12 months. Those with decompensated liver disease, significant neurological disability or non-adherence may require more frequent monitoring. Follow up should include clinical assessment, measurement of body weight, urine dipstick, and blood tests, including a full blood count, liver function tests, coagulation profile, renal function, bone profile, serum caeruloplasmin, and serum copper. It may be helpful to video-record the neurological examination and/or use the Unified Wilson's Disease Rating Scale to monitor the neurological response to treatment. Adherence and any wider concerns about medications should be addressed given non-adherence leads to progression of liver disease and neurological symptoms and is

the second most common cause of death in patients with WD after diagnostic failure.¹⁰⁹⁻¹¹⁴ 24-hour urine copper output should be measured on at least an annual basis to confirm compliance and adjust dose if required. The presence of KF rings should be re-examined at the bedside to document whether and when they resolve and vitamin D supplementation should be encouraged given metabolic bone disease is common in WD.

Copper indices

Clinicians vary in whether they recommend ‘on treatment’ or ‘off treatment’ collections during maintenance therapy. Results from ‘on treatment’ collections can be misleading if patients are non-adherent around the time of the collection. An ‘off treatment’ collection should be performed when the urinary copper output is unexpectedly high or low in an ‘on treatment’ collection and may therefore be preferable in the first instance. There is limited evidence to guide treatment targets for either approach. A safe copper output for one patient may be harmful for another and the overall trend may be more important. Nonetheless, values above the targets in the following recommendations may indicate undertreatment or non-adherence.

Recommendation: *24-hour urinary copper output while continuing medications (‘on treatment’) should be 3-8 $\mu\text{mol}/24$ hours (200-500 $\mu\text{g}/24$ hours) with chelating agents and 0.5-1.2 $\mu\text{mol}/24$ hours (30-75 $\mu\text{g}/24$ hours) with zinc salts (level 4).*

Recommendation: *24-hour urinary copper output after 48 hours of treatment cessation (‘off treatment’) should be 0.2-0.6 $\mu\text{mol}/24$ hours (12-40 $\mu\text{g}/24$ hours) for patients treated with chelating agents (level 4).*

Recommendation: *Non-caeruloplasmin-bound copper should be $< 2.4 \mu\text{mol}/\text{L}$ (15 $\mu\text{g}/\text{dL}$; level 4).*

Some patients require high doses of chelating agents and are then at risk of dose-dependent long term adverse effects. For example, patients taking higher doses of penicillamine are at risk of elastosis perforans serpiginosa and cutis laxa. Iatrogenic copper deficiency manifesting with pancytopenia and/or myelopathy has also been reported.¹¹⁵ An ‘off treatment’ urinary copper output $< 0.2 \mu\text{mol}/24$ hours (12 $\mu\text{g}/24$ hours) may indicate overtreatment and patients should be carefully monitored if doses are reduced.

Multi-disciplinary team

WD patients, including those treated with liver transplantation, need to be followed up in a dedicated multi-disciplinary team clinic typically consisting of hepatologists, neurologists, and experts in inherited metabolic disease. Some patients will have particularly complex needs which require the input

of additional services including psychiatry, clinical psychology, speech and language therapy, physiotherapy, occupational therapy, and dietetics services. Clear care pathways should be established locally to ensure reliable and timely access to professionals in these associated specialties.

Neurological and psychiatric symptoms

Some medications commonly used to treat neurological and psychiatric symptoms, such as benzodiazepines, tricyclic antidepressants and valproate, are metabolised by the liver, and should be used with caution in patients with cirrhosis and other medications, such as anti-psychotics, can exacerbate movement disorders. Clinicians should also be aware that some neurological symptoms, particularly tremor,¹¹¹ are more likely to improve with chelation therapy than others. Deep brain stimulation surgery (DBS) may be appropriate for a small minority of carefully selected patients with persistent, disabling tremor and/or dystonia despite symptomatic treatments and several years of intensive chelation therapy.¹¹⁶⁻¹¹⁸ Patients with neurological symptoms that impede safe driving should be advised to contact their licensing authority.

Hepatocellular carcinoma screening

Hepatocellular carcinoma (HCC) is a major complication of cirrhosis. However, the specific risk of HCC in WD is widely regarded as being low compared to other causes of chronic liver disease.^{25,105,119} Nonetheless, HCC remains a well-recognised complication of WD, occurring nearly exclusively in those with cirrhosis,¹²⁰ and UK electronic health record data have identified HCC as the underlying cause of death in 3/52 (6%) WD patients between 2008-2018 (not peer reviewed; available as abstract only). We therefore suggest HCC screening is appropriate in patients with WD and established cirrhosis particularly in the presence of additional co-factors such as alcohol or features of metabolic syndrome. This should be performed using 6-monthly ultrasound in line with international guidelines for HCC screening in cirrhosis.¹²¹

Recommendation: *HCC screening should be considered in patients with cirrhosis using 6-monthly ultrasound (level 4).*

Family planning and pregnancy

Preparation for pregnancy in patients with WD should include careful optimization of copper status. Whilst historically there have been some concerns about teratogenicity of chelation therapy, particularly with penicillamine, this has not been clearly demonstrated in published series.¹²²⁻¹²⁵ Conversely, drug discontinuation during pregnancy has been associated with acute liver failure.^{124,126} Therefore, the benefits of continuing chelation therapy throughout pregnancy currently outweigh the theoretical risks. There is currently no evidence that breast feeding while taking chelation therapy is harmful.¹²⁷

Recommendation: Chelation therapy should be continued throughout pregnancy (level 3).

Recommendation: Women on chelation therapy should not be advised against breastfeeding (level 4).

FAMILY SCREENING

Each sibling of an affected patient has a 25% chance of having WD and should be offered screening for WD. Diagnoses across multiple generations with pseudo-dominant inheritance have been described and screening is therefore usually extended to other first-degree relatives, including parents and offspring. Up to 69% of patients diagnosed through family screening have clinical features of liver or neurological disease.¹⁴ Some require urgent investigations and initiation of treatment. We therefore recommend clinical assessment and *routine investigations* for WD (**Figure 1**) in parallel with genetic testing in all first-degree relatives. Slit lamp examination and 24-hour urine collection for copper should also be considered, especially in siblings of index cases.

Genetic screening for WD should be arranged through a clinical genetics service and follow standard practice for autosomal recessive conditions. Genetic testing can be helpful to confirm that both parents are heterozygous carriers and hence that variants identified in the index case are *in trans* (on separate chromosomes), in addition to diagnosing WD in siblings and other first-degree relatives. The parents should then be asked to contact their own siblings to make them aware that they have a chance of being a WD carrier and that they should be referred for family screening. Risks to relatives outside of the nuclear family are likely to be low unless there is a history of consanguinity. Partners of index patients or heterozygous carriers may wish to undergo genetic screening when planning a family. These individuals should also be referred to a clinical genetics service. It may be appropriate to discuss reproductive medicine options for couples who are carriers of *ATP7B* variants.

Recommendation: Clinical assessment, routine investigations, and genetic screening should be offered to all first-degree relatives of patients diagnosed with WD (level 2).

Recommendation: Treatment of asymptomatic patients should only be initiated by specialist centres (level 4).

FUTURE DIRECTIONS

Recent advances in the diagnosis and management of WD may influence mainstream practice in the near future. Direct measurement of *ATP7B* peptides using dried blood spot samples has been shown to

differentiate patients with WD from healthy controls with high sensitivity and specificity and may have a role in initial screening or confirmatory testing for WD.¹²⁸ Anterior segment ocular coherence tomography appears to be more sensitive than slit lamp examination for the detection of KF rings but is not yet widely available.¹²⁹ Wet (fluid) and imaging biomarkers for neurological involvement are in development and could be used to guide treatment decisions or as end-points in clinical trials.¹³⁰ Finally, drug therapies are being tested: a phase III trial comparing bis-choline tetrathiomolybdate to standard of care has recently been completed (NCT03403205) and an open-label phase I/II trial for adeno-associated viral (AAV) vector-based gene therapy is ongoing (NCT04537377). We anticipate that further collaboration between specialist centres, both nationally and internationally, will be needed to maximise opportunities for translational research and participation in clinical trials going forward.

CONCLUSION

WD is a rare and complex disorder which requires early recognition and treatment in order to prevent critical hepatic and neurological complications. Many patients with this condition will first present to primary and secondary care and it is crucial that general physicians are familiar with the spectrum of clinical manifestations, indications for testing, and diagnostic tools available. This multidisciplinary guidance, supported by major hepatology and neurology societies, provides a clear, practical, and accessible framework for the investigation of those with suspected WD. It also emphasises the need for early consultation with specialist centres in order to establish the diagnosis, initiate treatment, and establish long-term pathways for follow up. Our advice reflects recent data on imaging abnormalities in the liver and brain, cut-offs for hepatic copper quantification, ATP7B variants, paradoxical neurological worsening and the relative efficacy of common therapies in WD.^{67,71,72,82,91,99} It also considers broader changes in clinical practice associated with increasing access to transient elastography, neuroimaging and genetic testing and decreasing reliance on liver biopsy and penicillamine challenge tests. Through promoting greater awareness of the challenges and pitfalls of WD management we hope to mitigate the evolution of life-threatening and disabling complications of this eminently treatable condition.

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FIGURE LEGENDS

Figure 1. This figure graphically summarises the major learning points and consensus recommendations in this guidance document. It places particular emphasis on the recognition of clinical features, indications for testing, early specialist referral, and the fundamental components of initial and long-term management. ALF, acute liver failure; ACLF, acute-on-chronic liver failure; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate transaminase; FH, family history; HCC, hepatocellular carcinoma; KF, Kayser-Fleischer; RTA, renal tubular acidosis; TE, transient elastography. Figure created using biorender.com.

Figure 2. Neuroradiological abnormalities in WD. Axial (A) and sagittal (B) views of a FLAIR sequence demonstrate hyperintense signal abnormality in the basal ganglia, thalamus and brainstem (arrowheads). The images are included with patient consent. FLAIR, fluid attenuated inversion recovery.