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

Samuel Shribman[1,†], Thomas Marjot[2,†], Abubakar Sharif[3,†], Sunitha Vimalesvaran[4,†], Aftab Ala [5,6], Graeme Alexander[7], Anil Dhawan[4], James Dooley[7], Godfrey T Gillett[8], Deirdre Kelly[3], Alasdair McNeil[9], Thomas T Warner[1], Valerie Wheater[10], William Griffiths[11] and Oliver Bandmann[12] on behalf of the BASL Rare Diseases Special Interest Group

1. Reta Lila Weston Institute, UCL Queen Square Institute of Neurology, London, UK
2. Oxford Liver Unit, Oxford University Hospitals NHS Foundation Trust, John Radcliffe Hospital, Oxford, UK
3. Liver Unit (including small bowel transplantation), Birmingham Women & Children's Hospital, Birmingham, UK
4. Paediatric Liver, GI and Nutrition Centre and Mowat Labs, King's College Hospital, Denmark Hill, London, UK
5. Department of Gastroenterology and Hepatology, Royal Surrey NHS Foundation Trust, Guildford, UK
6. Institute of Liver Studies, Kings College Hospital, London, UK
7. University College London Institute of Liver and Digestive Health, London, UK
8. Department of Clinical Chemistry, Northern General Hospital, Sheffield, UK
9. Sheffield Children's NHS Foundation Trust, Sheffield, UK
10. Wilson's Disease Support Group UK
11. Cambridge Liver Unit, Addenbrooke's Hospital, Cambridge, UK
12. Department of Neuroscience, Sheffield Institute of Translational Neuroscience, University of Sheffield, UK

Author contributions:

Concept and design: WG, GA, OB

Chairing of working party: OB

Literature search and synthesis of evidence: SS, TM, AS, SV

Writing group: SS, TM, AS, SV, GA, AD, GTG, DK, TTW, WG, OB

Formulation of consensus recommendations: All authors

Writing and critical review of the manuscript: All authors

† Shared first co-authorship

Correspondence:

Dr William Griffiths
Consultant Hepatologist
Cambridge Liver Unit
Level 9, Box 210
Addenbrooke's Hospital, Hills Road
Cambridge CB20QQ
bill.griffiths@addenbrookes.nhs.uk

Prof Oliver Bandmann
Professor of Movement Disorders Neurology
Department of Neuroscience
Sheffield Institute for Translational Neuroscience (SITraN)
The University of Sheffield
385a Glossop Road
Sheffield, S10 2HQ, UK
o.bandmann@sheffield.ac.uk

Word count:

Electronic word count:
Number of figures: 1
Number of boxes: 6
Number of tables: 3

Conflicts of interest:

SS has received grants from the Guarantors of Brain via the Association of British Neurologists and Wilson's Disease Support Group UK. AA has received grants from Alexion, Orphalan and Univar, is on advisory boards for Alexion, Orphalan, Ultragenyx, Univar and Vivet, is on the speakers bureau for Orphalan and Univar and is a co-applicant on a patent for bis-choline tetrathiomolybdate. AD has received consulting fees and payments from Alexion and Univar and is on the advisory boards for Univar, Alexion and Orphalan. DK has received consulting fees from Orphalan. TTW is President of the Association of British Neurologists. WG is consulting for Jnana Therapeutics. OB has received research support from the Wilson's Disease Support Group UK and is Chair of the Movement Disorders Advisory Group at the

Association of British Neurologists. The remaining authors do not have any conflicts of interest to declare.

Acknowledgements:

SS is funded by the Guarantors of Brain via an ABN Clinical Research Training Fellowship and has received funding from the Wilson's Disease Support Group UK. TM is funded via a Wellcome Trust Clinical Research Training Fellowship (ref. 102176/B/13/Z). AA is supported by the NIHR and UKRI. We would like to thank several members of the BASL Rare Diseases Special Interest Group who provided feedback during the consultation process including Mary Bythell, Jan Coebergh, Jane Collier, Susan Davies, Miranda Durkie, Mary Fortune, Tammy Hedderly, Steve Masson, Joanna Moore and Rupert Purchase.

Key words:

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

Summary:

Wilson's disease is an autosomal-recessive disorder of copper metabolism which typically presents with hepatic, neurological, psychiatric and ophthalmological manifestations. The diagnosis can be challenging given that no single test can confirm or exclude the disease and diagnostic delays are common. Treatment protocols vary and adverse effects, including paradoxical worsening, can occur. Here, we provide recommendations on indications for testing, how to interpret results and when additional investigations are required. We cover how treatment should be initiated, 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.

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 European Association for the Study of the Liver and 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. Clinitrials.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.

ABBREVIATIONS

ABN	Association of British Neurologists
AIH	Autoimmune hepatitis
ALF	Acute liver failure
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BASL	British Association for the Study of the Liver
BSG	British Society of Gastroenterology
CVVH	Continuous veno-venous haemofiltration
DBS	Deep brain stimulation
FLAIR	Fluid attenuation inversion recovery
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
INR	International normalised ratio
KF	Kayser-Fleischer
LT	Liver transplantation
MARS	Molecular adsorbent recycling system
MLPA	Multiplex ligation-dependent probe amplification
MMSE	Mini-mental state examination
MoCA	Montreal cognitive assessment
MRI	Magnetic resonance imaging
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
NDRS	National Disease Registration Service
NWI	New Wilson index
PALF	Paediatric acute liver failure
PT	Prothrombin time
UWDRS	Unified Wilson’s disease rating scale
WD	Wilson’s disease
WDSG-UK	Wilson’s Disease Support Group - UK

CONTENTS

SUMMARY OF RECOMMENDATIONS

	ADULT	PAEDIATRIC
Indications for testing	*Hepatic* - All adults presenting with liver disease should have routine investigations for WD. - All adults with unexplained liver disease despite investigation with laboratory tests, liver imaging, and histology should have a wider screen for WD. - 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. *Neurological* - All adults who develop *progressive* postural tremor, dystonia or parkinsonism under the age of 50 years, except those with isolated cervical dystonia or blepharospasm, should have routine investigations for WD. - All adults who develop a mixed movement disorder and any of the following red flags should have routine investigations and a wider screen for WD, in addition to neuroimaging: • Subacute onset or progression • Early bulbar involvement • Executive dysfunction • Behavioural or personality changes • Suspected liver disease • Previous episodes of haemolysis	*Hepatic* - All children presenting with liver disease should have routine investigations and a wider screen for WD. *Haematological* - All children with an unexplained haemolytic anaemia should have routine investigations and a wider screen for WD. *Neurological* - All children who develop *progressive* postural tremor, dystonia or parkinsonism over the age of five should have routine investigations for WD. - All children who develop a mixed movement disorder and any of the following red flags should have routine investigations and a wider screen for WD, in addition to neuroimaging: • Subacute onset or progression • Early bulbar involvement • Executive dysfunction • Behavioural or personality changes • Suspected liver disease • Previous episodes of haemolysis

Interpretation of initial investigations	*Serum caeruloplasmin* - Serum caeruloplasmin <0.10 g/L is highly suggestive of WD but a wider screen for WD is usually required to make a diagnosis. - Serum caeruloplasmin 0.10 - 0.20 g/L can have numerous causes and a wider screen for WD is indicated. - Serum caeruloplasmin >0.20 g/L does not exclude diagnosis of WD but reduces the likelihood. *24-hour urine collection* - Patients should be offered written instructions for 24-hour urine collections and provided with non-acid washed containers. - Copper output >0.64 µmol/24 hours is suggestive of WD but further investigations are required to make a diagnosis. *Slit lamp examination* - The presence of KF rings on slit lamp examination is highly suggestive of WD. *Urgency* - Initial investigations should be performed as soon as possible given the risk of hepatic and neurological deterioration. - Patients suspected to have WD should be urgently discussed with a specialist centre.

Additional tests	*Liver imaging* - All patients with suspected WD should have a liver ultrasound scan irrespective of their clinical presentation. - Liver stiffness measurement by transient elastography should be performed in all adults without overt cirrhosis at the point of WD diagnosis. *Neuroimaging* - MRI brain is indicated in any patient with suspected WD who has neurological or psychiatric manifestations. - WD should be considered in patients with an unexplained movement disorder and signal abnormalities in basal ganglia, thalamus or brainstem. - All patients with a confirmed diagnosis of WD should have an MRI brain irrespective of their initial presentation. *Genetic testing* - Genetic testing is required in all patients with suspected WD but should not delay the initiation of treatment. *Liver biopsy* - A liver biopsy with hepatic dry weight parenchymal copper may help with the diagnosis of WD when other non-invasive tests have proved inconclusive. - 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. - Liver biopsy is not indicated in patients with a confirmed diagnosis of WD who have no evidence of liver involvement. - In the absence of cholestatic liver disease, a hepatic parenchymal copper content >209 µg/g dry weight tissue is highly suggestive of WD. *Serum copper* - Serum copper should not routinely be used alone to confirm or exclude a diagnosis of WD. - Clinicians should not delay initiation of treatment while serum copper is pending. *Copper-65 absorption test* - A Copper-65 test can be performed in specialist centres when other tests are inconclusive and clinical suspicion remains.

<table>
<tr><td rowspan="2">Initial management</td><td>Transplantation for adults
Adults with ALF should be urgently referred to a liver transplant centre.
Liver transplantation should be considered in all adults with acute liver failure.</td><td>Transplantation for children
Patients with PALF or decompensated liver disease should be urgently referred to a paediatric liver transplant centre.
Liver transplantation is indicated in decompensated liver disease with encephalopathy.
The new Wilson index (NWI) should be used for prognosis and facilitate decision making for liver transplantation.</td></tr>
<tr><td colspan="2">Chelation therapy
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.
Penicillamine should be introduced gradually with dose increments of 125-250 mg per week in children
Penicillamine should be introduced gradually with dose increments of 125-250 mg per week in adults with neurological or psychiatric symptoms.
Penicillamine can be introduced more quickly in adults presenting with isolated liver disease.
Trientine dihydrochloride or tetrahydrochloride can be used in children and adults intolerant to penicillamine.
Zinc salts
Zinc salts are considered a third-line treatment for adults and should only be initiated by specialist centres. They should not be initiated as monotherapy in patients with cirrhosis.
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.
Dietary copper restriction
Dietary copper intake should be restricted in the first year of treatment. Decisions to continue this should take into account response to treatment, adherence and impact on quality of life.</td></tr>
</table>

Monitoring & follow up	*Initial response to treatment* - A full blood count, renal profile, liver function tests 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. - Patients with neurological symptoms should have regular follow up with a movement disorders specialist for a minimum of 12 months after treatment initiation. - 24-hour urinary copper output while continuing medication ('on treatment') should be measured within the first two months to confirm an adequate copper excretion. *Maintenance therapy (typically after two years)* - 24-hour urinary copper output while continuing medications ('on treatment') should be 3-8 µmol/day with chelating agents and 0.5-1.2 µmol/day with zinc salts. - 24-hour urinary copper output after 48 hours of treatment cessation ('off treatment') should be 0.2-0.6 µmol/day for patients treated with chelating agents. - Non-caeruloplasmin-bound copper should be less than 2.4 µmol/L. *Risk of hepatocellular carcinoma* - HCC screening should be considered in patients with cirrhosis using 6-monthly ultrasound. *Family planning and pregnancy* - Chelation therapy can be continued throughout pregnancy. - Women on chelation therapy should not be advised against breastfeeding.
Family screening	- Clinical assessment and genetic screening should be offered to all first-degree relatives of patients diagnosed with WD. - Treatment of asymptomatic patients should only be initiated by specialist centres.

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, rheumatological and renal manifestations can occur and presentations in older adults are well described.[2,3] Clinical presentations are thus highly variable, often mimicking more common diseases, and diagnoses are frequently missed or delayed; the mean interval between symptoms onset and diagnosis is 2 years.[4] This has important implications because chelation therapy can prevent disease progression and the prognosis with early treatment is favourable.[5]

Deciding when and how to investigate for WD is a crucial step in making a prompt diagnosis. Routine investigations can be suggestive but specialised tests for WD are required to confirm the diagnosis. The sensitivity and specificity of these tests, however, are suboptimal and no single test can be used to confirm or exclude WD. Therefore, a combination of investigations, including some that are inconvenient, invasive or time-consuming are often required. Identifying when to perform these tests, determining their urgency, and interpreting results is not straightforward. If a diagnosis is made, then treatment should be initiated promptly. Serious or debilitating complications, including paradoxical neurological worsening, can arise after treatment initiation and close monitoring by a physician experienced in managing WD is required.

Several diagnostic scoring systems and treatment pathways for WD have been proposed in previous guidelines.[6-8] However, there is a need for a practical guide for the diagnosis and treatment of WD, in particular for secondary care physicians. 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 paediatric and adult physicians. Expertise among hepatologists and movement disorders specialists in England has recently been consolidated into paediatric and adult centres for WD. Points of contact at specialist centres are listed here. We describe how treatment should be initiated, ideally under the guidance of one of these specialist centres. We also cover the core principles of long-term management, including monitoring and family screening, which should be undertaken in a multi-disciplinary WD clinic at a specialist centre but may be relevant or of interest to secondary care physicians.

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) in order to provide direction for general physicians regarding the initial investigation and management of WD. The document was also intended to promote multidisciplinary working and to familiarise the reader with UK specialist centres and referral pathways. The working group compiling this guidance was chaired by OB and included experts in adult hepatology (GA, WG, TM), paediatric hepatology (DK, AD, AS, SV), adult neurology (OB, TTW, SS), genetics (AM), clinical chemistry (GTG) alongside patient representation (VW). The major subject areas were agreed via electronic correspondence and video teleconferencing, and allocated to individuals responsible for searching the literature to identify published research, conference abstracts, and existing guidelines (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 relevant members of the British Society of Gastroenterology (BSG), Association of British Neurologists (ABN), and Wilson's Disease Support Group UK (WDSG-UK) for review. This process took place over a total of 9 months (between January and September 2021) and resulted in the finalised recommendations presented in the executive summary.

CLINICAL PRESENTATION AND INDICATIONS FOR TESTING

Clinicians should try to distinguish between clinical presentations which are compatible but unlikely to represent WD, and scenarios which constitute a higher risk and require more thorough and urgent investigation. Based on our combined multidisciplinary experience, we advocate a pragmatic approach where routine investigations are performed in cases where there is a lower index of suspicion, with a wider screen reserved for when there are additional clinical features suggestive of WD. There are a number of additional tests that may be required in specific circumstances (**Table 1**).

Table 1. Investigations for Wilson's disease

Routine investigations	Wider screen	Additional tests
Full blood count	Full blood count	Liver imaging
Liver function tests	Liver function tests	Neuroimaging
Coagulation profile	Coagulation profile	Genetic testing
Serum caeruloplasmin	Serum caeruloplasmin	Liver biopsy
	24-hour urine collection	Serum copper
	Slit lamp examination	Copper-65 absorption test

The most striking clinical presentation where WD should be suspected is the combination of liver disease and a movement disorder.[9] Hepatologists therefore need to be familiar with neurological features and reciprocally neurologists and psychiatrists need to recognise liver disease and avoid common pitfalls, such as using normal serum transaminases to falsely exclude liver disease (including WD). All specialists should be aware of psychiatric manifestations, which are common and often precede other symptoms. We discuss hepatic, neurological and psychiatric features of WD, highlighting specific considerations in the paediatric population. Wider systemic manifestations are also summarised in **Table 2**.

Irrespective of the presentation, a family history of liver disease or a movement disorder in a sibling should raise suspicion given the presentation varies within families.[10] It is also important to ask specifically about a history of WD in wider family members given the carrier frequency of *ATP7B* mutations is relatively high. Historically, this has been quoted as 1 in 90.[11] More recent data on genetic prevalence in the UK suggests this is considerably higher.[12] When variants with low penetrance are excluded, prevalence of heterozygous carriers is estimated to be 1 in 70.[13]

Table 2. Typical manifestations of Wilson's disease at presentation

Hepatic	Asymptomatic raised transaminases Asymptomatic steatosis Acute hepatitis Chronic hepatitis Cirrhosis Acute-on-chronic liver failure Acute liver failure
Neurological	Dysarthria Tremor Dystonia Parkinsonism Ataxia Executive dysfunction
Psychiatric	Behavioural or personality changes Hypomania Depression Anxiety Psychosis
Ophthalmological	Kayser-Fleischer rings Sunflower cataracts
Haematological	Thrombocytopenia Coagulopathy Haemolytic anaemia
Rheumatological	Osteoarthritis Chondrocalcinosis Osteomalacia Osteoporosis
Renal	Renal calculi Renal tubular acidosis Fanconi syndrome

Patients presenting with suspected liver disease

Patients with hepatic disease tend to present at a younger age than those with neurologic manifestations.[14] Children are rarely symptomatic before the age of 5 years.[15] Hepatic presentations are also more common in women, whereas neurological presentations are more common in men although the reasons for this remain unclear.[4]

Accurately attributing liver disease to a diagnosis of WD remains challenging. This relates both to WD being a rare condition, and to the high variability in the clinical, laboratory and histological manifestations of liver disease. Virtually all patterns of liver involvement have been described in WD in both adult and paediatric populations. This includes asymptomatic derangements in liver biochemistry, self-limiting hepatitis-like illness, hepatic steatosis on imaging, hepatomegaly, severe acute hepatitis, haemolysis with episodic jaundice, cirrhosis

with or without portal hypertension, and acute liver failure.[16-20] When faced with any of these clinical presentations WD should form part of the differential diagnosis and routine investigations including full blood count, liver function tests, clotting profile and serum caeruloplasmin should be performed. However, many of these clinical scenarios will be accounted for by a range of more common liver insults including but not limited to alcohol, non-alcoholic fatty liver disease, viral hepatitis, autoimmune liver disease, and drug-induced liver injury. Therefore, greater weight should be given to a possible WD diagnosis in patients where an alternative aetiology for liver disease has not been identified, those with associated neurological and psychiatric features, or patients with a family history of undifferentiated liver disease. In these patients, a wider screen for WD should be done.

Whilst this represents a pragmatic approach to diagnosis, it is important to recognise that WD can co-exist with other liver pathology. Furthermore, WD can mimic other liver conditions further complicating diagnosis. This is particularly relevant in the context of hepatic steatosis identified on imaging or biopsy, which is common in WD and can be misattributed to alcohol or non-alcoholic steatohepatitis. WD should therefore be considered in all cases of hepatic steatosis, particularly in patients without an history of excess alcohol consumption, and who do not have metabolic risk factors (e.g. obesity, type 2 diabetes, hypertension). Similarly, the histological features of WD on liver biopsy can resemble autoimmune hepatitis (AIH) and therefore clinicians should keep an open mind for WD in those labelled with AIH who fail to respond to immunosuppressive medication, or who develop neurological symptoms.[21]

Left unrecognised and/or untreated, chronic WD can progress to fibrosis and ultimately cirrhosis which is present in 25-54% of patients at diagnosis.[22-25] Compensated cirrhosis is often asymptomatic, being identified radiologically or via features of evolving portal hypertension including splenomegaly, gastro-oesophageal varices and thrombocytopenia. This contrasts with decompensated cirrhosis which describes a systemic disease characterised by ascites, variceal haemorrhage, hepatic encephalopathy, renal dysfunction, and susceptibility to infection.

Acute Liver Failure

Up to 20% of paediatric and adult patients with WD will have severe acute hepatic (formerly ‘fulminant’) WD as their first presentation.[26] This severe liver injury can rapidly progress to acute liver failure (ALF) defined by the presence of jaundice, coagulopathy, ascites, renal failure and encephalopathy. The condition is rapidly fatal in nearly all cases without liver transplantation (LT) and WD accounts for 3-9% of all tertiary referrals for consideration of

super urgent LT.[27,28] The classical presentation of acute hepatic WD is characterised by a young patient presenting with encephalopathy, haemolytic anaemia, and high bilirubin to alkaline phosphatase ratio. Acute WD occurs more commonly in females than males (4:1), and KF rings are present in over 50% of cases.[29] Whilst traditionally the definition of ALF requires the absence of chronic liver disease, an exception is made in the case of WD where most patients will have underlying cirrhosis at the time of ALF presentation.[30] Acute WD often presents *de novo* and without warning, although there may be a concurrent viral trigger. Acute hepatic WD may also occur in patients with an established diagnosis of WD following an abrupt cessation of medication.

Liver biochemistry typically consists of profound jaundice, mild to moderately elevated transaminases, and a conspicuously normal or low alkaline phosphatase. In the setting of acute liver failure, the ALP to bilirubin ratio may have a role in differentiating between WD and non-WD pathology.[31]

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

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

Recommendation*: All adults presenting with liver disease should have routine investigations for WD.*

Recommendation*: All adults with unexplained liver disease despite investigation with laboratory tests, liver imaging, and histology should have routine investigations and a wider screen for WD.*

Recommendation*: All adults presenting with liver disease in combination with a movement disorder or unexplained haemolytic anaemia should have routine investigations and a wider screen for WD.*

Patients presenting with neurological or psychiatric symptoms

The most common movement disorder in children and adults with WD is a postural tremor of the upper limbs. It is usually irregular or jerky and can easily be examined by asking patients to hold their arms out. However, patients can present with other movement disorders including

dystonia, parkinsonism, ataxia and, less commonly, chorea (**Box 1**).[15,32,33] Patients may refer to shaking, clumsiness or loss of balance. Handwriting is often affected and it is helpful to ask about and examine this, particularly in children.[15]

Several clinical features can help differentiate movement disorders in WD from other aetiologies. Firstly, while symptoms are often chronic and slowly progressive, some patients have a subacute onset or progression that is unusual in other diseases and should prompt urgent investigation. Secondly, movement disorders often occur in combination, for example as dystonic tremor or dystonia-parkinsonism syndromes. Thirdly, there is early bulbar involvement with slurred speech, drooling and slow lateral tongue movements on examination. Slurred speech, or dysarthria, is reported in 52% of children and 74-91% of adults.[15,33] Patients may be mistaken for being intoxicated in public.[34] Some patients also have a characteristic grimacing facial expression (risus sardonicus) and seizures occur in around 10% of children with neurological presentations.[15,35]

Box 1. Glossary of neurological terms

Ataxia	Incoordination of voluntary movements
Chorea	An ongoing, random-appearing sequence of one or more discrete involuntary movements
Dysarthria	Impaired articulation or slurring of speech
Dystonia	Involuntary sustained or intermittent muscle contractions cause twisting and repetitive movements or abnormal postures
Executive dysfunction	Impairment in higher order cognitive abilities such as planning, reasoning, problem solving, inhibition and emotion regulation
Parkinsonism	Slowness of movement characterised by decrement in speed and amplitude of repetitive movements (bradykinesia) associated with rigidity and/or rest tremor

Cognitive function

Executive dysfunction is common in neurological presentations of WD but can be subtle and easily missed in a brief consultation.[36-38] This can manifest with difficulties in decision-making, multi-tasking, flexible thinking or concentration. Other cognitive domains, including processing speed, memory, visual function and social cognition may also be affected. Up to 60% of children and adolescent patients presenting with neurological symptoms report falling behind at school,[15] and asking about difficulties at school, college, university or work may be a useful screen for cognitive impairment in WD. Commonly used bedside tests for adults, including the

Mini-Mental State Examination (MMSE) or Montreal Cognitive Assessment (MoCA), are less sensitive for mild cognitive impairment and more detailed assessments, such as the Addenbrooke's Cognitive Examination, or formal neuropsychometry may be required.[39]

Psychiatric features

Behavioural or personality changes (incongruous behaviour, irritability, aggression and disinhibition), mood disorders (hypomania or depression) and anxiety are common.[40,41] Psychosis can also occur, typically with paranoid delusions.[16] 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.[41] While the yield from screening patients with isolated psychiatric symptoms is likely to be low, psychiatrists should be aware of hepatic and neurological features and urgently arrange initial investigations and onward referral if WD is suspected.[43]

Recommendation*: All children who develop progressive postural tremor, dystonia or parkinsonism over the age of five should have routine investigations for WD.*

Recommendation*: All adults who develop progressive postural tremor, dystonia or parkinsonism under the age of 50 years, except those with isolated cervical dystonia or blepharospasm, should have routine investigations for WD.*

Recommendation*: All patients who develop a mixed movement disorder and any of the following red flags should have routine investigations and a wider screen for WD, in addition to neuroimaging:*

- *Subacute onset or progression*
- *Early bulbar involvement*
- *Executive dysfunction*
- *Behavioural or personality changes*
- *Suspected liver disease*
- *Previous episodes of haemolysis*

INTERPRETING INITIAL INVESTIGATIONS

Liver function tests

Abnormal liver biochemistry is a well-recognised but non-specific feature of WD. Elevated transaminases (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]) are found in 40-60% of patients at presentation, typically ranging between 50-200 U/L, and can occur in patients presenting exclusively with neurological manifestations.[44] In a European cohort of 53 consecutive WD patients, ALT was elevated in 60% of patients presenting with chronic liver disease, and 30% of those presenting with neurological features alone.[23] Elevated bilirubin is present in 11-13% of patients at diagnosis and approximately 10% report a previous episode of clinically overt jaundice.[22,24] Hyperbilirubinaemia may reflect either liver injury or coombs-negative haemolysis (a well-recognised feature of WD; see below) or a combination of both, which may be clinically determined by the relative proportions of conjugated and unconjugated bilirubin.

Full blood count and clotting profile

Haematological abnormalities are common in WD occurring in a third of patients at diagnosis.[22] Coombs-negative haemolysis is a characteristic but under-recognised feature of WD, present in 4-10% of cases.[24,45,46] The clinical course of haemolysis may be chronic, although is often punctuated by episodes of anaemia and jaundice, or can manifest as acute haemolytic syndrome, particularly during childhood or adolescence. In a retrospective analysis of 321 UK patients with WD, acute haemolytic crises were found to be the initial presentation in 7% of cases.[47] Of these 22 patients, the diagnosis of WD was delayed in 18 (82%) with subsequent progressive liver injury and/or neurologic deterioration. This emphasises the importance of including WD in the differential for haemolysis. Chronic haemolysis may also predispose to pigment gallstones which are more common in patients with WD.[46] The pathogenic mechanisms leading to haemolysis remains incompletely understood. However, a direct effect of copper toxicity on red blood cells is likely and would account for the marked haemolysis seen in acute liver failure when excess copper is liberated during hepatic necrosis.

Thrombocytopenia and, less commonly, leukopenia, may occur in the setting of portal hypertension. In one cohort, a platelet count below 140 was seen in 63% of hepatic presentations and 52% of neurological presentations.[23] Elevated prothrombin time (PT) and international normalised ratio (INR) may occur in parallel with hepatic dysfunction but are not features of WD *per se.*[49] An INR of 1.3 or above is seen in 47% of hepatic presentation and 65% of neurological presentations.[48]

Serum caeruloplasmin

Caeruloplasmin is a copper carrying protein that is secreted by the liver and is responsible for the transport of >90% of circulating copper in healthy individuals. Serum levels are low in neonates, gradually rising with age and eventually peaking in mid-childhood before reducing during the pubertal period.[49] Caeruloplasmin testing should therefore only be performed after 1 year of age.[7] Most NHS laboratories currently use an immunological method to determine serum caeruloplasmin with normal values usually set at >0.20 g/L. However, this method tends to overestimate serum caeruloplasmin levels and although more accurate enzymatic assays have been developed, these have not moved into mainstream clinical practice.[50]

A very low serum caeruloplasmin (<0.1 g/dL) is characteristic of WD.[51] However, the interpretation of serum caeruloplasmin has several caveats and limitations. Firstly, whilst the majority (85%) of patients with neurological manifestations of WD will have serum caeruloplasmin <0.2 g/L, levels may be within the normal range in up to 40% of patients with active liver involvement,[22,52] including in ALF. This is due to upregulation of caeruloplasmin, an acute phase protein, in response to hepatic damage and inflammation. Serum caeruloplasmin may also be elevated secondary to any other cause of inflammation, pregnancy or oral contraceptive pill use.[53] Conversely, reduced serum caeruloplasmin is found in end-stage liver disease of any aetiology and copper deficiency due to malabsorption or zinc supplementation. Up to 30% of heterozygous *ATP7B* carriers have a mildly reduced serum caeruloplasmin (0.15-0.19 g/L).[54] Rarely, variants in the caeruloplasmin (*CP*) gene can cause reduced or undetectable serum caeruloplasmin. Patients with bi-allelic mutations develop acaeruloplasminemia, a very rare neurodegenerative disease associated with abnormal iron metabolism, anaemia and diabetes.[55] In the light of all these limitations, the diagnostic value of serum caeruloplasmin for WD when used in isolation is poor. For example, in a real world prospective cohort of 2,867 patients investigated for liver disease in secondary care, 17 (0.59%) had a serum caeruloplasmin <0.2g/L of whom only one was subsequently diagnosed with WD following comprehensive investigation.[56] This equates to a positive predictive value of only 6% for patients presenting with liver disease.

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.*

Recommendation*: Serum caeruloplasmin 0.10-0.20 g/L can have numerous causes and a wider screen for WD is indicated.*

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

24-hour urinary copper output

Urinary copper output varies throughout the day and 24-hour collections are therefore required. These are inconvenient for patients, require careful timing and may be challenging for those with movement disorders or executive dysfunction. Written instructions should be provided (**Box 2**). Laboratories often insist on using acid-washed containers, although this has recently been shown to be unnecessary.[57]

With a cut-off of 0.64 µmol (40 *µg) per* 24 hours, the sensitivity and specificity for diagnosing WD in children are 79% and 88%, respectively.[51] Data confirming an appropriate cut-off in adults are limited. A higher cut-off of 1.6 µmol (100 *µg) per* 24 hours is suggested to be diagnostic in a previous guideline.[58] In a study of 111 healthy adults from the UK,[59] mean copper output was 0.34 µmol (22 µg) per 24 hours and most clinical biochemists would consider a copper output >0.64 µmol in an adult to be abnormal. Other causes of increased urinary copper output include cholestatic liver diseases, autoimmune hepatitis, non-alcoholic fatty liver disease and nodular regenerative hyperplasia.[60] Cholestasis prevents the biliary excretion of copper and can lead to systemic copper overload with markedly elevated urinary copper output, particularly in children.[61]

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

Recommendation*: Copper output >0.64 µmol/24 hours is suggestive of WD but further investigations are required to make a diagnosis.*

Box 2. Instructions for performing a 24-hour urine collection

- Empty bladder into toilet on waking and record this as the start time
- Collect all the urine passed that day and night into the container
- Empty bladder into container on waking and record this as the stop time
- Return container with any relevant forms to the hospital

Slit lamp examination

Copper deposits within Descemet's membrane, known as Kayser-Fleischer (KF) rings, are characteristic of WD and occur in 71-90% of patients with neurological features at presentation

and 24-47% of patients with hepatic presentations.[52,62] They may be seen with systemic copper overload due to cholestasis, for example in primary biliary cholangitis, and, very rarely, alcoholic hepatitis and multiple myeloma[63,64] KF rings are often visible with the naked eye as a yellowish-green or golden-brown discoloration at periphery of each cornea, which on closer inspection, is distinct from the underlying iris. They always appear first as a crescent at 12 o'clock, next being manifest at 6 o'clock, before joining up to form a complete ring. It can take a matter of seconds to make a tentative diagnosis of WD if a clinician spots KF rings at the bedside but only if the clinician actively looks for them. A video demonstrating how to examine for them can be found here (**Video 1**). They may not be detectable at the bedside and slit lamp examination by an experienced Ophthalmologist may therefore be required to confirm or exclude the presence of KF rings when WD is suspected. Where there is doubt of the presence or absence of KF rings, anterior segment ocular coherence tomography (AS-OCT) may be helpful.[65] Sunflower cataracts can be visible to the naked eye and do not require slit-lamp examination to reveal their presence.

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

Have I made the diagnosis yet?

The diagnosis is relatively straightforward if there is a low serum caeruloplasmin (<0.2 g/L), high urinary copper output (>0.64 µmol/24 hours) and KF rings.[26] 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. There is some value in the Leipzig scoring system (see **Appendix**) for the diagnosis of WD but we would recommend this is only used in conjunction with discussion with a specialist centre for WD. Points of contact at specialist centres in England are listed here.

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 or undiagnosed disease. These complications can be fatal, particularly in the context of acute liver failure, 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 the WDSG-UK (www.wilsonsdisease.org.uk) for additional information and support.[26]

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

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

ADDITIONAL INVESTIGATIONS

Liver imaging

Hepatic steatosis is demonstrated by increased liver echogenicity on ultrasound or cross-sectional imaging and is a common finding in WD occurring in 35-88% of patients.[66,67] However, this is highly nonspecific being found in a range of other more prevalent conditions including alcohol related and non-alcoholic fatty liver disease. Ultrasound does have an important role in staging liver disease severity and should be requested in any patient with suspected WD and abnormal liver function tests, thrombocytopenia, or clinical features of chronic liver disease. Cirrhosis may be suggested by an irregular liver edge, with or without portal hypertensive features including reversed portal vein flow, increased spleen size, and the presence of ascites. Cross sectional imaging with 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. In a case series of 53 consecutively diagnosed patients with a neurological phenotype, all patients had at least one ultrasound feature consistent with liver disease.[23] Certain radiological features have been suggested to be specific to WD including multiple hyper- and hypoechoic nodular lesions, a perihepatic fat layer, and the absence of caudate lobe hypertrophy in a cirrhotic liver. However, these have only been demonstrated in small series and should not be considered diagnostic.[66,68] The role of ultrasound in the surveillance and diagnosis of hepatocellular carcinoma in patients with cirrhosis is discussed below.

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

Liver stiffness measurement (LSM) by transient elastography (TE) may be used as an additional tool for non-invasive fibrosis staging in WD, alongside clinical assessment, laboratory investigations, and liver imaging. A LSM cut-off of ≥9.9kPa has good accuracy in identifying cirrhosis in adults with a new WD diagnosis (PPV; 74%, NPV; 100%).[69] In most treated WD patients, LSM remains stable over time and therefore routine monitoring is not required.[69] However, TE may be useful in patients with clinical evidence of disease progression or in cases of poor treatment adherence or response, accepting that data in these settings are limited. Studies evaluating the performance of LSM in children with WD are lacking.

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

Neuroimaging

Specialists need to consider whether an MRI of the brain is indicated and whether any previous neuroimaging is consistent with WD. Hyperintensities on T2-weighted or FLAIR sequences, often referred to as 'lesions', are typically seen bilaterally in the basal ganglia, thalamus and/or brainstem in patients with neurological presentations but also occur in cerebral white matter (**Figure 1**).[70-72] Atrophy of the cerebral cortex, brainstem and/or cerebellum is also common at diagnosis. The vast majority (90-100%) of patients with a neurological presentation will have at least one of these abnormalities although these findings are also not uncommon in patients with hepatic presentations of WD and those identified through family screening.[70,71]

Figure 1. Neuroradiological abnormalities in WD.

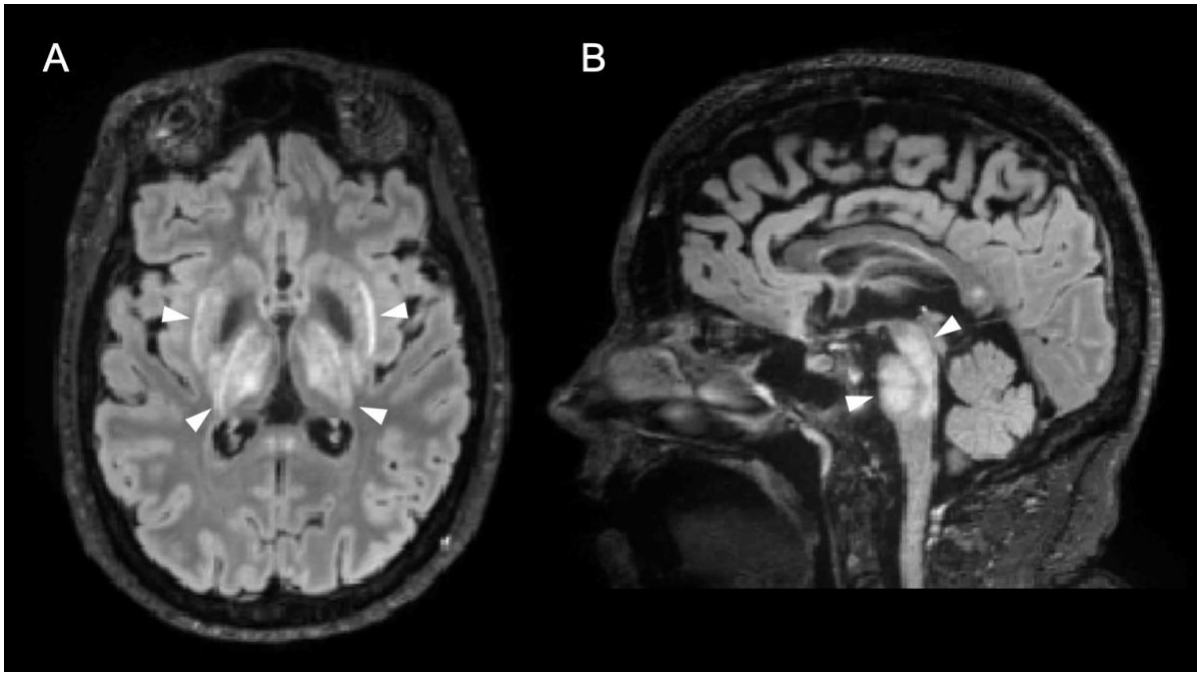

Fig. 1 Axial (A) and sagittal (B) views of a FLAIR sequence demonstrate hyperintense signal abnormality in the basal ganglia, thalamus and brainstem (arrowheads). Image courtesy of Samuel Shribman.

Lesions in the posterior midbrain (tectal plate), pons or simultaneously involving the basal ganglia and brainstem appear to be highly specific for WD among other causes of movement disorders.[73] Susceptibility-weighted imaging is often abnormal and T1-weighted hyperintensities in the basal ganglia, which can occur with cirrhosis of any cause, may be

seen.[74-76] Neurologists should also be aware that WD can rarely cause confluent white matter abnormalities similar to a leukodystrophy.[77,78]

Neuroimaging findings have important prognostic implications given lesions in the thalamus and brainstem are associated with paradoxical neurological worsening.[79,80] They are also relevant in patients with hepatic presentations, 20% of whom will go on to develop neurological symptoms and may subsequently require MRI.[44]

Recommendation*: MRI brain is indicated in any patient with suspected WD who has neurological or psychiatric manifestations.*

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

Recommendation*: All patients with a confirmed diagnosis of WD should have an MRI brain irrespective of their initial presentation.*

Penicillamine challenge test

Historically, measuring urinary copper excretion following the administration of penicillamine (penicillamine challenge test) was employed in the diagnostic work-up of WD, particularly in children. However due to inconsistent dosing and timing of penicillamine, results have proved unreliable and this test is no longer recommended for symptomatic or asymptomatic patients with suspected WD irrespective of their age.

Genetic testing

More than 700 pathogenic mutations in *ATP7B* have been described although some variants may have reduced clinical penetrance. A genetic diagnosis should therefore always be corroborated with clinical, biochemical and radiological findings.[81] Importantly, the absence of two pathogenic mutations does not exclude a diagnosis of WD. In a genetic study of 181 patients from the UK, two pathogenic mutations were identified in 98% of participants when using a combination of Sanger sequencing (coding regions, splice sites and promoter region) and multiplex ligation-dependent probe amplification (MLPA, for identifying deletions and duplications).[82] Exome sequencing identified only 88% of patient with WD in a cohort from Poland.[83] Genetic testing should not delay initiation of chelation therapy when other features are diagnostic. It also has an important role in family screening.

NHS England offers next generation sequencing for *ATP7B* through the National Genomic Test Directory with an estimated turnaround time of around six weeks. Multiplex ligation-dependent probe amplification can be arranged on request. Next generation sequencing is also available through a number of neurology, hepatology and paediatric gene panels.

Recommendation*: Genetic testing is required in all patients with suspected WD but should not delay the initiation of treatment.*

Liver biopsy

Where the diagnosis is uncertain, measurement of hepatic parenchymal copper content through liver biopsy may confirm the diagnosis of WD in children and adults. Furthermore, liver histology may help stage liver disease severity and exclude alternative or comorbid pathology. In the early stages of WD, macrovesicular steatosis may be the only histological feature, detected in 70% of cases. Portal inflammation and fibrosis, similar to autoimmune hepatitis, is a further pattern although often in association with steatosis. Vacuolated nuclei, degenerate hepatocytes, inflammation and Mallory-Denk bodies may also be seen, reminiscent of non-alcoholic or alcohol-related liver disease. Over time, fibrosis may accumulate culminating in established cirrhosis which is identified in up to 50% of patients at the point of biopsy diagnosis.[25] However, these histological features are not specific to WD. Copper and copper-associated proteins may be identified by histochemical stains before cirrhosis and is usually periportal; with cirrhosis irregular deposition is present within and between nodules.

Given the diagnostic challenges in interpreting liver morphology, measurement of hepatic parenchymal copper concentration forms an important part of the liver biopsy work up of WD and part of the sample should be obtained/retained for this. The normal copper content in the liver is <50 µg/g of dry weight. A threshold of ≥250 µg/g has traditionally been regarded as diagnostic of WD.[25] However, this threshold has since been revised downward to 209 µg/g following a large prospective diagnostic accuracy study in 3350 consecutive patients undergoing liver biopsy, of which 178 were ultimately diagnosed with WD.[84]

A practical guide to the processing of liver tissue including common pitfalls is presented in **Box 3.** A variety of stains can be used to highlight copper deposits (e.g. rhodamine or orcein), however they can be unreliable and absence of staining does not exclude WD. In addition, copper staining is non-specific for WD, being seen in a range of other cholestatic liver conditions including primary biliary cholangitis, biliary atresia, prolonged extrahepatic biliary

obstruction, primary/secondary sclerosing cholangitis, and heterozygous carriers of ATP7B gene variants. With regards the method of biopsy, percutaneous is preferable but a transjugular approach should be considered if there is concern regarding bleeding risk

***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.*

***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.*

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

***Recommendation**: In the absence of cholestatic liver disease, a hepatic parenchymal copper content >209 µg/g dry weight tissue is highly suggestive of WD.*

Box 3. Liver tissue sample handling for measurement of dry weight copper

- Liaise with histopathologist prior to obtaining liver biopsy to determine local protocols and available expertise
- The minimum amount of tissue required for dry weight copper analysis is 0.3 mg, approximately equivalent to a 0.5 cm length of tissue from a 22-gauge needle, or 0.3 cm length of tissue from an 18-gauge needle. To account for potential losses during sample handling, biopsy material in excess of these quantities should be obtained
- Specimen should be transferred in a copper-free container and to laboratory with necessary expertise for performing copper quantification
- Do not put the tissue sample for copper estimation in formaldehyde
- Sample does not need to be frozen

Serum copper

The serum copper concentration reflects copper incorporated into caeruloplasmin and non-caeruloplasmin-bound copper, also known as the 'free' copper. The latter is thought to be the toxic component and is loosely bound to albumin, smaller peptides and amino acids. The caeruloplasmin-bound copper is reduced in proportion to the degree of hypocaeruloplasminaemia. Patients with a low serum caeruloplasmin will likely have a low

serum copper and patients with a high serum caeruloplasmin will likely have a higher serum copper (which may fall within the reference interval), irrespective of the underlying cause.[85] 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.[47,86]

The non-caeruloplasmin-bound copper can be calculated (**Box 4**) and 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.[87] In particular, the calculated non-caeruloplasmin-bound copper may be paradoxically low or negative as a result of inaccurate caeruloplasmin assays.[88] Clinical biochemists familiar with the performance of local assays may find the serum copper useful when interpreting caeruloplasmin results and may suggest arranging a serum copper as a second-line test (or be able to perform copper analysis on the same sample). Unlike the serum caeruloplasmin, the turnaround time for this test is usually at least several weeks.

Recommendation*: Serum copper should not routinely be used alone to confirm or exclude a diagnosis of WD.*

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

Box 4. Calculation for serum non-caeruloplasmin-bound ('free') copper concentrations[87]

serum non-caeruloplasmin bound ('free') copper	=	serum copper	-	47	x	serum caeruloplasmin
(µmol/L)		(µmol/L)				(g/L)

Copper-65 absorption test

The majority of copper in the body has atomic weight 63 Da (^{63}Cu) and a small proportion exists as a stable, non-radioactive isotope with atomic weight 65 Da (^{65}Cu). This test involves administering 3mg of ^{65}Cu in solution, approximately 2-3 times the recommended daily allowance for copper intake (https://www.nhs.uk/conditions/vitamins-and-minerals/others/). The ^{65}Cu/^{63}Cu ratio is measured in serum samples at baseline and after 1, 2, 6 and 72 hours. Patients with WD have a characteristic pronounced early peak in the ^{65}Cu/^{63}Cu ratio before a gradual decline as they fail to incorporate ^{65}Cu into caeruloplasmin. Healthy controls and heterozygote carriers have a small initial peak with a gradual increase in the ^{65}Cu/^{63}Cu ratio

as ^{65}Cu is incorporated into caeruloplasmin. In the UK, the test is currently available at the Scottish Trace Element and Micronutrient Diagnostic and Research Laboratory based in Glasgow (www.trace-elements.co.uk) (**Box 5**). The protocol is available here. The ^{65}Cu solution can be sent, and resulting serum samples returned, via courier.

This test has been validated in a cohort of 13 WD patients, 12 heterozygote carriers and 10 healthy controls from the UK.[89] Results were similar to that of radioactive copper isotope assay that has been used in Poland for several decades.[90] Some experts on the panel have found this test invaluable in difficult cases and suggest it should be more widely used. Adverse effects include nausea after drinking the ^{65}Cu solution and the negligible theoretical risk of giving a patient with suspect WD a small copper supplement.

Recommendation*: A Copper-65 test can be performed in a specialist centre when other tests are inconclusive and clinical suspicion remains.*

Box 5. Arranging a Copper-65 absorption test

- Contact the Scottish Trace Element and Micronutrient Diagnostic and Research Laboratory to request Copper-65 test and latest protocol
- Confirm date for test, including collection of 72-hour sample, with patient
- Liaise with local pathology department to coordinate receipt of Copper-65 solution prior to and delivery of serum samples after date of test.
- Identify scientist in local pathology department who will be receiving samples in advance
- Take baseline serum sample and deliver sample to scientist.
- Administer Copper-65 solution as per protocol
- Take serum sample after 1, 2, 6 and 72 hours delivering each sample to scientist by hand
- Confirm with local pathology department that samples are being couriered to Glasgow

INITIAL MANAGEMENT

Acute liver failure in adults

Acute hepatic WD and the evolution of acute liver failure (ALF) is a medical emergency. Early recognition, rapid diagnostic work-up, prompt supportive management, and referral to a specialist centre are therefore paramount. All patients should have slit-lamp examination for KF rings, and imaging to examine liver texture and hepatic vasculature. Liver biopsy, preferably by the transjugular route, can be useful to quantify parenchymal copper content and to identify cirrhosis, malignancy or alcohol-induced liver injury. Serum caeruloplasmin is of limited diagnostic value being reduced in 50% of all types of ALF, and may also be normal or elevated as part of an acute phase response. Urinary copper is markedly increased and 24-hour collection should be attempted even in the emergency setting.

The new Wilson disease prognostic index, calculated from AST, albumin, bilirubin, INR, and white cell count, is highly accurate in predicting mortality with listing for liver transplantation generally recommended for a score ≥11.[29,91] In the interim, optimal management of ALF outside of intensive care involves aggressive fluid resuscitation, sepsis control, and continued reassessment for progressive organ dysfunction. Plasmapheresis, hemofiltration, and exchange transfusion may offer some protection against copper-mediated renal tubular damage and can be considered as a bridge to transplantation. Acute chelation therapy can be introduced, but only isolated case reports exist of survival in severe acute WD (revised WPI ≥11) without liver transplantation.

In patients with deteriorating cirrhosis who do not meet super-urgent listing criteria (https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/22847/pol195.pdf), elective transplantation may be indicated.

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

Recommendation*: Liver transplantation should be considered in all adults with acute liver failure.*

Acute liver failure in children

Paediatric ALF (PALF) is defined as acute onset liver injury with PT >15 seconds or INR >1.5 not corrected by vitamin K in the presence of clinical HE, or a PT ≥20 seconds or INR ≥2.0 regardless of the presence or absence of HE[92]. This differs from adults where the presence of encephalopathy is regarded as an essential diagnostic component of ALF.[93] Children with

PALF or decompensated liver disease, characterized by jaundice, signs of portal hypertension including gastrointestinal bleeding, ascites or encephalopathy, should be managed in a paediatric liver transplant centre (See **appendix** for contact details). In addition to early intensive care support, medical treatment with penicillamine or combination therapy with penicillamine and zinc salts is appropriate in children with decompensated liver disease without encephalopathy as a bridge to avoid liver transplantation.[94]

Bridging therapies to transplantation have been used with varying results, including, continuous veno-venous hemodialysis (CVVH), plasmapheresis and MARS (molecular adsorbent recycling system). These methods can facilitate liver transplantation and, in some case reports, even prevent the need for urgent transplantation.[95] Decision to transplant can be difficult and various indices have been proposed including the new Wilson index (NWI) (See **appendix**).[29]

Recommendation*: Patients with PALF or decompensated liver disease should be urgently referred to a paediatric liver transplant centre.*

Recommendation*: Liver transplantation is indicated in decompensated liver disease with encephalopathy.*

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

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. 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. Both need to be taken on an empty stomach. 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.[5,96] A clinical commissioning policy produced by NHS England in 2018 outlines that trientine is commissioned for patients who are intolerant of penicillamine and should only be prescribed by, or in consultation with, a specialist centre.[97] Specific indications for switching to trientine and relative contraindications for starting penicillamine, such as history of autoimmune disease, severe thrombocytopenia or renal disease and allergy to penicillin, are summarised in the policy and the appendix below.

Two formulations of trientine have been approved for use in the UK, the salts trientine dihydrochloride and trientine tetrahydrochloride. Trientine dihydrochloride capsules are marketed by Univar, with the trade name Cufence, and by Tillomed. Trientine tetrahydrochloride tablets are marketed by Orphalan with the trade name Cuprior. All three products can be stored at room temperature until their recommended expiry dates.

Importantly, advice about the dose of trientine in previous guidelines, which were published prior to the introduction of trientine tetrahydrochloride, refers to the content of the salt, trientine dihydrochloride. However, European Medicines Agency (EMA) approval for Cufence and Cuprior now requires these two drugs to be labelled with respect to the content of trientine base. The label for Cufence is ‘Cufence 200 mg hard capsules’ – each hard capsule contains 300 mg trientine dihydrochloride equivalent to 200 mg trientine. The label for Cuprior is ‘Cuprior 150 mg film-coated tablets’ – each film-coated tablet contains 300 mg trientine tetrahydrochloride equivalent to 150 mg trientine. The label for trientine dihydrochloride produced by Tillomed continues to refer to the content of trientine dihydrochloride and not trientine base.

In addition, the bioavailability of the trientine base differs between Cuprior and Cufence in healthy indivudals.[98] Based on pharmacokinetic data, the manufacturer of Cuprior has suggested that, therapeutically, 1000 mg Cufence (base), i.e. five capsules, are equivalent to 600 mg Cuprior (base), i.e. four tablets. However, the relative efficacy of these drugs when applying this dose conversion has not yet been determined in patients with WD and the absorption and bioavailability of both drugs may be diminished by trientine-diet interactions. Patients are therefore advised to take trientine between meals.

There are no universally accepted dosing schedules for penicillamine or trientine and adverse effects are usually dose-dependent (**Table 3**). 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 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 **Box 6** for all patients starting chelation therapy.

Randomised controlled trials comparing bis-choline tetrathiomolybdate to standard of care for de-coppering and maintenance therapy (NCT03403205) and trientine tetrahydrochloride to penicillamine for maintenance therapy (NCT03539952) are ongoing.

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.*

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

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

Recommendation*: Penicillamine can be introduced more quickly in adults presenting with isolated liver disease.*

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

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.*

Box 6. Checklist for all patients starting chelation therapy

- Measure height and weight
- Perform urine dipstick*
- Advise patient to take chelation therapy on an empty stomach
- Warn patient about adverse effects, including neurological worsening
- Provide written instructions for dose escalation and monitoring

It is desirable for all patients to be assessed by a hepatologist and a movement disorders specialist prior to starting treatment

* Microscopic haematuria and mild proteinuria are common even in untreated patients with WD. Urine dipstick is therefore required to confirm whether haematuria or proteinuria are present at baseline rather than being misinterpreted later as a drug side effect.

Some clinicans offer pyridoxine (Vitamin B6) supplementation to patients being treated with Penicillamine on the basis that high doses of Penicillamine have been shown disrupt pyridoxine metabolism. The evidence to support this is limited. In a study of 19 patients with WD,[99] one individual who was receving a Pencillamine dose of 48 mg/kg was found to have increased excretion of xanthurenic acid, an intermediate metabolite, after oral loading of tryptophan and this improved with pyridoxine supplementation. 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.

Table 3. Dosing and adverse effects for penicillamine, trientine, and zinc salts.

	Dosing	Adverse effect
Penicillamine	**Children:** 125 –250 mg/day slowly increasing by 125-250 mg/week to initial target of 20 mg/kg/day in two divided doses (maximum 1500 mg/day) **Adults WITHOUT neurological or psychiatric symptoms:** Initial target of 1000-1500 mg/day in two divided doses **Adults WITH neurological or psychiatric symptoms:** 125-250 mg/day, slowly increasing by 125-250 mg/week, to initial target of 1000-1500 mg/day in two divided doses. ***Maintenance dose (typically after two years):*** 10-20mg/kg/day in two divided doses.	***Early reactions*** Hypersensitivity reactions (fever, rash) Proteinuria Bone marrow suppression (thrombocytopenia, neutropaenia) Altered sense of taste/smell Paradoxical neurological worsening ***Late reactions*** Lupus-like syndrome Goodpastures syndrome Elastosis perforans serpiginosa Cutis Laxa Poor wound healing
Trientine	**Children:** 150-200mg/day slowly increasing by 150-200 mg/week to initial target of 400-1000 mg/day for trientine dihydrochloride (Cufence) or 225-600 mg/day for trientine tetrahydrochloride (Cuprior) in two divided doses. **Adults WITHOUT neurological or psychiatric symptoms:** 800-1600 mg/day for trientine dihydrochloride (Cufence) or 450-975 mg/day for trientine tetrahydrochloride (Cuprior) in two divided doses. **Adults WITH neurological or psychiatric symptoms:** 150-200 mg/day slowly increasing by 150-200 mg/week to initial target of 800-1600 mg/day for trientine dihydrochloride (Cufence) or 450-975 mg /day for trientine tetrahydrochloride (Cuprior) in two divided doses. ***Maintenance dose (typically after two years):*** 800-1600 mg/day for trientine dihydrochloride (Cufence) or 450-975 mg /day for trientine tetrahydrochloride (Cuprior) in two divided doses.	Urticaria/rash Arthralgia/myalgia Proteinuria Haematuria Sideroblastic anaemia Paradoxical neurological worsening
Zinc salts	**< 6 years:** 25mg twice daily **6 – 16 years or if <50kg:** 25mg three time daily **>16 years or if >50kg:** 50mg three times daily	Nausea Abdominal pain Gastritis and gastric ulcers Paradoxical neurological worsening

Dosing for penicillamine and zinc salts are based on experience and for trientine dihydrochloride and tetrahydrochloride are based on summary of product characteristics. The recommended doses of trientine dihydrochloride and tetrahydrochloride are expressed as mg of trientine base as opposed to trientine salt.

Zinc salts

Zinc salts inhibit the absorption of dietary copper by increasing metallothionein expression in enterocytes. Zinc acetate is licensed for the treatment of WD, unlike zinc sulphate, which is a dispersible formulation. Their role in the treatment of WD remains controversial given reports of progression of liver disease in patients taking zinc monotherapy.[100] Marcellini *et al.* reported that zinc salts can effectively control the disease and prevent its progression over the course of 10 years, with a reduction in hepatic copper concentration.[101] However, Santiago et al. found serum transaminase levels increased in 18/23 (78%) of children diagnosed through family screening.[102]

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 and should only be initiated by specialist centres. They should not be initiated as monotherapy in patients with cirrhosis.*

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. As a result, clinicians vary significantly in their practice. In a recent International survey by Sturm et al, the majority of respondents from North America advise lifelong copper restricted diet (<1 mg/day) and from Europe advise dietary copper restriction in the first year of treatment or until liver function tests normalize.[103] Almost a quarter of respondents from Europe did not advise their patients to reduce dietary copper intake. The literature mentions avoiding chocolate, nuts, liver (and other offal), shellfish and mushrooms.[6,8] 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 should take into account response to treatment, adherence and impact on quality of life.*

Paradoxical neurological worsening

Between 11-30% of patients with neurological symptoms at presentation develop paradoxical worsening after initiation of chelation therapy, which is irreversible in around half of cases.[80,104,105] There are reports of patients with hepatic presentations developing irreversible neurological disability with treatment but this appears to be rare.[106,107] The mean interval between treatment initiation and deterioration is two months but it can occur at any time in the first six months. The pathophysiological basis for this phenomenon is unclear but risk factors may include prominent neurological involvement at baseline, brainstem/thalamic lesions on MRI and concurrent anti-psychotic use.[80]

Paradoxical neurological worsening can occur with penicillamine, trientine and zinc salts and data on the risk of worsening with each treatment are conflicting.[5,108] 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. Managing this clinical situation can be extremely challenging, and it can be difficult to decipher whether early deterioration represents paradoxical neurological worsening or undertreatment. Clinicians therefore 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, add zinc or consider other treatment options, such as a course of intramuscular Dimercaprol.[109] 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.[110]

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

Response to treatment

Chelation therapy is usually effective for managing liver disease but neurological outcomes are less predictable. In a study of 163 patients from Germany, liver function improved in 79%, remained stable in 8% and deteriorated in 13%.[44] Of 58 patients with neurological presentations, 54% improved, 22% remained stable and 24% deteriorated. 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 at least several years before neurological recovery reach a plateau.[111]

The 24-hour urinary copper output and non-caeruloplasmin-bound ('free') copper can be used to monitor the biochemical response to chelation therapy. Chelation therapy induces a marked cupriuresis in the first few months of chelation therapy, which typically peaks at around 6 months with penicillamine and around 18 months with trientine.[112] The urinary copper output can either be measured while patients continue their medication ('on *treatment*') or after 48 hours of treatment cessation ('off treatment').[113]

An 'on treatment' collection (or spot urine copper) can be useful for confirming that there is an adequate cupriuresis, i.e. the urinary copper output is significantly higher than prior to starting treatment. 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, usually decreases over the first and second year of treatment for patients on penicillamine but takes longer for patients on trientine.[112] It is not usually helpful to measure this in the first six months of treatment.

Despite methodological concerns, the non-caeruloplasmin-bound ('free') copper can be useful in monitoring treatment response if it is consistently measured at the same laboratory and should gradually decrease with treatment.

Recommendation*: The 24-hour urinary copper output while continuing medication ('on treatment') should be measured in the first few months of treatment to confirm adequate urinary copper excretion.*

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 a 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 in patients with movement disorders to monitor response to treatment. Adherence and any wider concerns about medications should be addressed. The 24-hour urine output should be measured on an annual basis or more often if there are concerns over clinical or biochemical deterioration. Those patients who present with KF rings should be examined at the bedside and, if necessary by an experienced ophthalmologist, to confirm whether and when they resolve. Metabolic bone disease is common in WD and Vitamin D supplementation should be encouraged.

Copper indices

Clinicians vary in whether they recommend 'on treatment' or 'off treatment' collections during maintenance therapy. An 'on treatment' collection has the advantage that it confirms an ongoing cupriuresis but can be misleading if patients are non-adherent during the collection. An 'off treatment' collection provides a measure of residual copper balance. It 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 and a safe copper output for one patient may be more concerning for another. The trend may be more important than the exact value. However, in general, most clinicians aim for an 'on treatment' copper output of 3-8 µmol (200-500 µg) per 24 hours or an 'off treatment' copper output of 0.2-0.6 µmol (12-40 µg) per 24 hours for patients treated with chelating agents or 0.5-1.2 µmol (30-70 µg) per 24 hours for patients treated with zinc salts. If calculated, the serum non-caeruloplasmin-bound copper is usually <2.4 µmol/L (15 µg/dL) in stable patients.[114] Values above these various thresholds may indicate undertreatment or non-adherence.

Some patients require high doses of chelating agents or combination therapy in the initial de-coppering stages but should then ideally be changed to lower doses during maintenance therapy to reduce the risk of over-treament in the longterm. Complications of chelation-induced, iatrogenic copper deficiency such as sideroblastic anaemia and myelopathy have been reported in overtreated patients. Dermatological adverse effects of Penicillamine such

as elastosis perforans serpiginosa or cutis laxa, are dose-dependent and further emphasize the need for a careful review of the penicillamine maintenance dose. An 'off treatment' urinary copper output < 0.2 umol/24 hours may indicate overtreatment. Patients should be carefully monitored if doses are reduced.

***Recommendation**: 24-hour urinary copper output while continuing medications ('on treatment') should be 3-8 µmol/day for patients treated with chelating agents and 0.5-1.2 µmol/day for patients treated with zinc salts during maintenance therapy.*

***Recommendation**: 24-hour urinary copper output after 48 hours of treatment cessation ('off treatment') should be 0.2-0.6 µmol/day for patients treated with chelating agents.*

***Recommendation**: Non-caeruloplasmin-bound copper should be less than 2.4 µmol/L during maintenance therapy.*

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. Examples include (but are not limited to) mental health, speech and language therapy, physiotherapy, occupational therapy and dietetics services. Clear care pathways should be established locally to ensure reliable, timely access to professionals in these associated specialties.

Wilson's Disease Support Group UK

This volunteer organisation provides excellent support for people living with WD, their families and friends, particularly those who are newly diagnosed. It runs an active Facebook Group with over 1000 members and liaises with leading WD consultants in the UK for appropriate advice. Members receive an annual newsletter and meet annually. It holds a UK WD Patient Register and supports research into WD. Further information including medical articles, dietary advice and patient stories can be found on their website (www.wilsonsdisease.org.uk).

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,[115] are more likely to improve with chelation therapy than others and symptomatic treatments, either through beneficial or adverse effects, can make the interpretation of the clinical response to chelation therapy more challenging. There are case reports of patients with disabling tremor and dystonia having deep brain stimulation surgery (DBS) and a clinical trial for DBS in WD is ongoing (NCT02552628).[116-118] This invasive treatment may be appropriate for a small minority of carefully selected patients who have reached a plateau in neurological recovery despite at least several years of intensive chelation therapy.

Driver and Vehicle Licensing Agency (DVLA) guidance states that patients with any chronic neurological disorder that may affect vehicle control because of impaired coordination and muscle strength must notify the DVLA. They may continue to drive as long as safe vehicle control is maintained at all times. For car and motorcycle (Group 1) drivers, a licence valid for 1, 2, 3 or 5 years may be issued provided medical enquiries by the DVLA confirm that driving perofrmance is not impaired. For bus and lorry (Group 2) drivers, a licence will be refused or revoked if the individual's condition is progressive or disabling

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. In a retrospective study across three WD cohorts from UK and Sweden, Walshe *et al.* reported nine cases of intra-abdominal malignancy in those followed up >10 years (n=159) including two cases of HCC.[119] Similarly, Van Meer *et al* reported only two cases of HCC in 130 patients followed up over 15 years equating to an annual HCC risk of 0.09% in the total cohort and 0.14% in those with cirrhosis. The overall annual incidence of HCC appears slightly higher in Chinese WD populations (0.23%).[45] By comparison, the annual risk of HCC in patients with alcohol or hepatitis B virus (HBV) related cirrhosis is around 3%. Several other European long-term follow up studies have reported no cases of HCC in WD patients.[44,120] The reasons for the rarity of HCC in WD compared to other causes of chronic liver disease remains unclear and is at odds with rodent models of WD which demonstrate high rates of hepatocarcinogenesis.[121] However, despite the low incidence reported in observational studies, HCC nonetheless remains a recognised and severe complication of WD. In 2013, Thattil et al summarised 28 case reports of HCC in patients with WD.[122] In this series all diagnoses of HCC occurred in patients with cirrhosis of which 85% were male. Furthermore, UK electronic health record data identified HCC as the underlying cause of death in 3/51 (3%) WD patients between 2008-2018 (not peer reviewed;

available as abstract only). Due to the paucity of data, it has so far been impossible to assess the impact of de-coppering therapy on cancer risk. However, it is worth noting that HCC has been reported in patients with excellent treatment compliance and normal copper indices.

Whilst the annual incidence of HCC in WD falls well below the 1.5% threshold traditionally used to justify screening in patients with cirrhosis regardless of aetiology,[123] HCC remains a recognised complication of the disease and an understandable concern for both patients and clinicians. 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 dysfunction. This should be performed using 6-monthly ultrasound in line with the European Association for the Study of the Liver (EASL) consensus guidelines for HCC screening in cirrhosis.[123] Contrast-enhanced MRI may be required for patients where ultrasound imaging is unreliable for screening purposes due to anatomical or technical reasons.

We recognise that some hepatologists also measure alpha fetoprotein (AFP) for HCC screening in cirrhosis. While we cannot say that this in incorrect, we feel the current data does not support its use in WD in the absence of a superimposed aetiology and would prefer to leave this to individual choice.

Recommendation*: HCC screening should be considered in WD patients with cirrhosis using 6-monthly ultrasound.*

Adherence

Non-adherence to treatment leads to progression of liver disease and neurological symptoms.[115,124-127] In a retrospective cohort of 170 newly diagnosed, symptomatic patients from Poland, 26% stopped their treatment once for at least three months or twice for at least two months during the follow up period.[127] Those patients who were not persistent with treatment were more likely to experience disease progression (52% vs 2%). After diagnostic failure, non-adherence is also the second most common cause of death in patients with WD.[128]

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 case series.[131] Conversely, drug discontinuation during pregnancy has been associated with

acute hepatic WD and acute liver failure.[132,133] 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.[134]

Recommendation*: Chelation therapy can be continued throughout pregnancy.*

Recommendation*: Women on chelation therapy should not be advised against breastfeeding.*

FAMILY SCREENING

Each sibling of an affected patient has a 25% chance of having WD. Diagnoses across multiple generations have been described and so screening is usually offered to all first-degree relatives, including parents (not just siblings or offspring). Several approaches to screening have been recommended in previous guidelines.[6-8] In our view, both clinical assessment and genetic testing should be offered to all first-degree relatives:

Clinical assessment

Up to 69% of patients diagnosed through family screening have clinical features of liver or neurological disease.[10] Undiagnosed, asymptomatic manifestations of WD in first degree relatives of index cases may require urgent further investigations and initiation of treatment. We therefore recommend clinical assessment and routine investigations for WD (**Table 1**) in all first-degree relatives. Slit lamp examination and 24-hour urine collection should be considered, especially in siblings of affected index cases.

Genetic testing

All families should be routinely referred to Clinical Genetics for genetic screening. Family screening for WD should follow standard Clinical Genetics practice for autosomal recessive conditions. Genetic testing can be helpful to confirm that both parents are heterozygous carriers and hence that the variants are *in trans* (on separate chromosomes). The parents could then be asked to contact their own siblings to make them aware that they have a chance of being a carrier for WD and that they could be referred for carrier testing. A “to whom it may concern” letter could be provided for this purpose. Risks to relatives outside of the nuclear family are likely to be low. In consanguineous families, the chance of other relatives being affected is much higher and these families should be referred to Clinical Genetics.

As explained above, the siblings of an index patient have a ¼ (25%) chance of inheriting bi-allelic *ATP7B* variants and being affected. The rationale for testing should be explained so that siblings understand that they may have sub-clinical disease and that this may be amenable to treatment. As such, we would not recommend following a prolonged predictive genetic testing pathway (e.g. as is usual for Huntington disease). Since targeted testing is being undertaken for a known familial variant, extensive consent processes discussing issues such as secondary findings are not appropriate. If bi-allelic variants have been identified in the proband, identification of a single variant in a relative can be taken as strong evidence that they are clinically unaffected carriers in the absence of clinical or biochemical features of WD.

Partners of index patients or heterozygous carriers may wish to undergo genetic screening when planning a family. These individuals should be referred to Clinical Genetics. It may be appropriate to discuss reproductive medicine options for couples who are carriers of ATP7B variants. Both prenatal diagnosis with selective termination of affected foetuses or preimplantation genetic testing (PGT) would be feasible.

Recommendation*: Clinical assessment and genetic screening should be offered to all first-degree relatives of patients diagnosed with WD.*

Recommendation*: Treatment of asymptomatic patients should only be initiated by specialist centres.*

MISCELLANEOUS

Participation in research

All WD patients should be informed about and actively encouraged to participate in research activities. Information about opportunities to participate in observational studies or clinical trials can be found through the BASL Special Interest Group on WD or the WDSG-UK. Patients interested in participating in research in future may wish to join the research register maintained by the WDSG-UK.

National Rare Disease Registration Service

The National Disease Registration Service (NDRS) has been working in collaboration with the BASL Rare Diseases Special Interest Group to identify methods to achieve national (for England) ascertainment of people with WD. It collects data from multiple sources, including clinically reported cases, death certificates, hospital episode statistics, genetic test results, laboratory and primary care prescribing data. These data are then used to develop data linkage methods to increase the validity of ascertaining people with WD in the routinely collected data. This process results in less biased, more complete case ascertainment than clinical reporting alone. The resulting data are then used to carry out healthcare planning, descriptive epidemiology, including cancer outcomes, and are available to be used by those with the legal basis to access it. NDRS welcomes direct reporting of cases of WD from treating clinicians and diagnostic laboratories. NDRS has legal permission granted under section 251 of the NHS Act 2006 to collect and hold data about known or suspected cases of rare disease without patients' consent. Please contact jeanette.aston@nhs.net for more information.

Diagnostic criteria

An international consensus of experts proposed a diagnostic scoring system for WD, often referred to as the Leipzig criteria, in 2001.[26] This score incorporates clinical, biochemical, histopathological and genetic findings to determine if a diagnosis of WD is highly likely, probable or unlikely and is widely used in clinical research (**Appendix**). In children presenting with liver disease, the Ferenci score provides a good combination of sensitivity (98%) and specificity (97%) for the diagnosis of WD.[135] The score has not, to our knowledge, been validated in adults and is primarily used for research. Alternative diagnostic algorithms that prioritise early genetic testing and minimise the need for liver biopsy have been proposed more recently.

Rating scales

The Unified Wilson's Disease Rating Scale (UWDRS) can be used to quantify neurological involvement in WD and has been validated in several patient populations (**Appendix**).[136,137] The neurological section consists of 9 items for neurological disability items based on the Barthel index and 18 items for neurological examination based on the Unified Parkinson's Disease Rating Scale and Burkhe-Fahn-Marsden Dystonia Scale, among others.

REFERENCES

1. Wijayasiri P, Hayre J, Nicholson ES, et al. Estimating the clinical prevalence of Wilson's disease in the UK. *JHEP Rep.* 2021;3(5):100329.
2. Bandmann O, Weiss KH, Kaler SG. Wilson's disease and other neurological copper disorders. *The Lancet Neurology.* 2015;14(1):103-113.
3. Ala A, Walker AP, Ashkan K, Dooley JS, Schilsky ML. Wilson's disease. *The Lancet.* 2007;369(9559):397–408.
4. Litwin T, Gromadzka G, Członkowska A. Gender differences in Wilson's disease. *J Neurol Sci.* 2012;312(1-2):31–35.
5. Weiss KH, Thurik F, Gotthardt DN, et al. Efficacy and safety of oral chelators in treatment of patients with Wilson disease. *Clin Gastroenterol Hepatol.* 2013;11(8):1028–1035.
6. EASL Clinical Practice Guidelines: Wilson's disease. *J Hepatol.* 2012;56(3):671–685.
7. Socha P, Janczyk W, Dhawan A, et al. Wilson's Disease in Children: A Position Paper by the Hepatology Committee of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition. *J Pediatr Gastroenterol Nutr.* 2018;66(2):334–344.
8. Roberts EA, Schilsky ML, (AASLD). Diagnosis and treatment of Wilson disease: an update. *Hepatology.* 2008;47(6):2089-2111.
9. Shribman S, Warner TT, Dooley JS. Clinical presentations of Wilson disease. *Ann Transl Med.* 2019;7(2):S60.
10. Chabik G, Litwin T, Członkowska A. Concordance rates of Wilson's disease phenotype among siblings. *J Inherit Metab Dis.* 2014;37(1):131–135.
11. Scheinberg IH, Sternlieb I. *Wilson's disease.* W B Saunders; 1984.
12. Coffey AJ, Durkie M, Hague S, et al. A genetic study of Wilson's disease in the United Kingdom. *Brain.* 2013;136(5):1476-1487.
13. Wallace DF, Dooley JS. ATP7B variant penetrance explains differences between genetic and clinical prevalence estimates for Wilson disease. *Hum Genet.* 2020;139(8):1065-1075.
14. Ferenci P, Stremmel W, Członkowska A, et al. Age and Sex but Not ATP7B Genotype Effectively Influence the Clinical Phenotype of Wilson Disease. *Hepatology.* 2019;69(4):1464–1476.
15. Walshe JM, Yealland M. Wilson's disease: the problem of delayed diagnosis. *J Neurol Neurosurg Psychiatry.* 1992;55(8):692–696.
16. Pandit A, Bavdekar A, Bhave S. Wilson's disease. *Indian J Pediatr.* 2002;69(9):785–791.

17. Eisenbach C, Sieg O, Stremmel W, Encke J, Merle U. Diagnostic criteria for acute liver failure due to Wilson disease. *World J Gastroenterol.* 2007;13(11):1711–1714.
18. Roberts EA, Yap J. Nonalcoholic Fatty Liver Disease (NAFLD): Approach in the Adolescent Patient. *Curr Treat Options Gastroenterol.* 2006;9(5):423–431.
19. Alam S, Lal BB. Metabolic Liver Diseases Presenting as Acute Liver Failure in Children. *Indian Pediatr.* 2016;53(8):695–701.
20. Członkowska A, Litwin T, Dusek P, et al. Wilson disease. *Nat Rev Dis Primers.* 2018;4(1):21.
21. Milkiewicz P, Saksena S, Hubscher SG, Elias E. Wilson's disease with superimposed autoimmune features: report of two cases and review. *J Gastroenterol Hepatol.* 2000;15(5):570-574.
22. Stremmel W, Meyerrose KW, Niederau C, Hefter H, Kreuzpaintner G, Strohmeyer G. Wilson disease: clinical presentation, treatment, and survival. *Ann Intern Med.* 1991;115(9):720–726.
23. Przybyłkowski A, Gromadzka G, Chabik G, Wierzchowska A, Litwin T, Członkowska A. Liver cirrhosis in patients newly diagnosed with neurological phenotype of Wilson's disease. *Funct Neurol.* 2014;29(1):23–29.
24. Moores A, Fox S, Lang A, Hirschfield GM. Wilson disease: Canadian perspectives on presentation and outcomes from an adult ambulatory setting. *Can J Gastroenterol.* 2012;26(6):333–339.
25. Ferenci P, Steindl-Munda P, Vogel W, et al. Diagnostic value of quantitative hepatic copper determination in patients with Wilson's Disease. *Clin Gastroenterol Hepatol.* 2005;3(8):811–818.
26. Ferenci P, Caca K, Loudianos G, et al. Diagnosis and phenotypic classification of Wilson disease. *Liver Int.* 2003;23(3):139–142.
27. Gow PJ, Jones RM, Dobson JL, Angus PW. Etiology and outcome of fulminant hepatic failure managed at an Australian liver transplant unit. *J Gastroenterol Hepatol.* 2004;19(2):154–159.
28. Ostapowicz G, Fontana RJ, Schiødt FV, et al. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. *Ann Intern Med.* 2002;137(12):947–954.
29. Dhawan A, Taylor RM, Cheeseman P, De Silva P, Katsiyiannakis L, Mieli-Vergani G. Wilson's disease in children: 37-year experience and revised King's score for liver transplantation. *Liver Transpl.* 2005;11(4):441–448.
30. Davies SE, Williams R, Portmann B. Hepatic morphology and histochemistry of Wilson's disease presenting as fulminant hepatic failure: a study of 11 cases. *Histopathology.* 1989;15(4):385-394.

31. Korman JD, Volenberg I, Balko J, et al. Screening for Wilson disease in acute liver failure: a comparison of currently available diagnostic tests. *Hepatology.* 2008;48(4):1167–1174.
32. Czlonkowska A, Litwin T, Dziezyc K, Karlinski M, Bring J, Bjartmar C. Characteristics of a newly diagnosed Polish cohort of patients with neurological manifestations of Wilson disease evaluated with the Unified Wilson's Disease Rating Scale. *BMC Neurol.* 2018;18(1):34.
33. Machado A, Chien HF, Deguti MM, et al. Neurological manifestations in Wilson's disease: Report of 119 cases. *Mov Disord.* 2006;21(12):2192–2196.
34. Choudhary N, Joshi L, Duggal A, Puri V, Khwaja GA. Isolated lingual involvement in Wilson's disease. *J Neurosci Rural Pract.* 2015;6(3):431–433.
35. Dening TR, Berrios GE, Walshe JM. Wilson's disease and epilepsy. *Brain.* 1988;111:1139–1155.
36. Seniów J, Bak T, Gajda J, Poniatowska R, Czlonkowska A. Cognitive functioning in neurologically symptomatic and asymptomatic forms of Wilson's disease. *Mov Disord.* 2002;17(5):1077-1083.
37. Hegde S, Sinha S, Rao SL, Taly AB, Vasudev MK. Cognitive profile and structural findings in Wilson's disease: a neuropsychological and MRI-based study. *Neurol India.* 2010;58(5):708–713.
38. Frota NA, Barbosa ER, Porto CS, et al. Cognitive impairment and magnetic resonance imaging correlations in Wilson's disease. *Acta Neurol Scand.* 2013;127(6):391–398.
39. Senda M, Terada S, Takenoshita S, et al. Diagnostic utility of the Addenbrooke's Cognitive Examination - III (ACE-III), Mini-ACE, Mini-Mental State Examination, Montreal Cognitive Assessment, and Hasegawa Dementia Scale-Revised for detecting mild cognitive impairment and dementia. *Psychogeriatrics.* 2020;20(2):156–162.
40. Svetel M, Potrebic A, Pekmezovic T, et al. Neuropsychiatric aspects of treated Wilson's disease. *Parkinsonism Relat Disord.* 2009;15(10):772–775.
41. Dening TR, Berrios GE. Wilson's disease. Psychiatric symptoms in 195 cases. *Arch Gen Psychiatry.* 1989;46(12):1126–1134.
42. Akil M, Brewer GJ. Psychiatric and behavioral abnormalities in Wilson's disease. *Adv Neurol.* 1995;65:171–178.
43. Demily C, Parant F, Cheillan D, et al. Screening of Wilson's disease in a psychiatric population: difficulties and pitfalls. A preliminary study. *Ann Gen Psychiatry.* 2017;16:19.
44. Merle U, Schaefer M, Ferenci P, Stremmel W. Clinical presentation, diagnosis and long-term outcome of Wilson's disease: a cohort study. *Gut.* 2007;56(1):115–120.

45. Cheung KS, Seto WK, Fung J, Mak LY, Lai CL, Yuen MF. Epidemiology and natural history of Wilson's disease in the Chinese: A territory-based study in Hong Kong between 2000 and 2016. *World J Gastroenterol.* 2017;23(43):7716–7726.
46. Walshe JM. Hepatic Wilson's disease: initial treatment and long-term management. *Curr Treat Options Gastroenterol.* 2005;8(6):467–472.
47. Walshe JM. The acute haemolytic syndrome in Wilson's disease--a review of 22 patients. *QJM.* 2013;106(11):1003–1008.
48. Przybyłkowski A, Gromadzka G, Chabik G, Wierzchowska A, Litwin T, Członkowska A. Liver cirrhosis in patients newly diagnosed with neurological phenotype of Wilson's disease. *Funct Neurol.* 2014;29(1):23-29.
49. Kelly J, Raizman JE, Bevilacqua V, et al. Complex reference value distributions and partitioned reference intervals across the pediatric age range for 14 specialized biochemical markers in the CALIPER cohort of healthy community children and adolescents. *Clin Chim Acta.* 2015;450:196–202.
50. Merle U, Eisenbach C, Weiss KH, Tuma S, Stremmel W. Serum ceruloplasmin oxidase activity is a sensitive and highly specific diagnostic marker for Wilson's disease. *J Hepatol.* 2009;51(5):925–930.
51. Ryan A, Nevitt SJ, Tuohy O, Cook P. Biomarkers for diagnosis of Wilson's disease. *Cochrane Database Syst Rev.* 2019(11).
52. Steindl P, Ferenci P, Dienes HP, et al. Wilson's disease in patients presenting with liver disease: a diagnostic challenge. *Gastroenterology.* 1997;113(1):212-218.
53. Burrows S, Pekala B. Serum copper and ceruloplasmin in pregnancy. *Am J Obstet Gynecol.* 1971;109(6):907–909.
54. Mak CM, Lam CW, Tam S. Diagnostic accuracy of serum ceruloplasmin in Wilson disease: determination of sensitivity and specificity by ROC curve analysis among ATP7B-genotyped subjects. *Clin Chem.* 2008;54(8):1356-1362.
55. Marchi G, Busti F, Lira Zidanes A, Castagna A, Girelli D. Aceruloplasminemia: A Severe Neurodegenerative Disorder Deserving an Early Diagnosis. *Front Neurosci.* 2019;13:325.
56. Cauza E, Maier-Dobersberger T, Polli C, Kaserer K, Kramer L, Ferenci P. Screening for Wilson's disease in patients with liver diseases by serum ceruloplasmin. *J Hepatol.* 1997;27(2):358–362.
57. Robson AF, Lockett P, Tetlow L, Chaloner C. Evaluation of 24-h urine containers for urine copper measurement by inductively coupled plasma mass spectrometry. *Ann Clin Biochem.* 2020;57(3):246–248.
58. EASL Clinical Practice Guidelines: Wilson's disease. *J Hepatol.* 2012;56(3):671-685.

59. Sieniawska CE, Jung LC, Olufadi R, Walker V. Twenty-four-hour urinary trace element excretion: reference intervals and interpretive issues. *Ann Clin Biochem.* 2012;49(4):341-351.
60. Nicastro E, Ranucci G, Vajro P, Vegnente A, Iorio R. Re-evaluation of the diagnostic criteria for Wilson disease in children with mild liver disease. *Hepatology.* 2010;52(6):1948–1956.
61. Sezer OB, Perk P, Hoşnut F, Köse SK, Özcay F. Is it necessary to re-evaluate diagnostic criteria for Wilson disease in children? *Turk J Gastroenterol.* 2014;25(6):690–695.
62. Bruha R, Marecek Z, Pospisilova L, et al. Long-term follow-up of Wilson disease: natural history, treatment, mutations analysis and phenotypic correlation. *Liver Int.* 2011;31(1):83–91.
63. Tauber J, Steinert RF. Pseudo-Kayser-Fleischer ring of the cornea associated with non-Wilsonian liver disease. A case report and literature review. *Cornea.* 1993;12(1):74–77.
64. Williams EJ, Gleeson D, Burton JL, Stephenson TJ. Kayser-Fleischer like rings in alcoholic liver disease: a case report. *Eur J Gastroenterol Hepatol.* 2003;15(1):91–93.
65. Broniek-Kowalik K, Dzieżyc K, Litwin T, Członkowska A, Szaflik JP. Anterior segment optical coherence tomography (AS-OCT) as a new method of detecting copper deposits forming the Kayser-Fleischer ring in patients with Wilson disease. *Acta Ophthalmol.* 2019;97(5):e757-760.
66. Akhan O, Akpinar E, Karcaaltincaba M, et al. Imaging findings of liver involvement of Wilson's disease. *Eur J Radiol.* 2009;69(1):147–155.
67. Cançado EL, Rocha MeS, Barbosa ER, et al. Abdominal ultrasonography in hepatolenticular degeneration. A study of 33 patients. *Arq Neuropsiquiatr.* 1987;45(2):131–136.
68. Li W, Zhao X, Zhan Q, et al. Unique CT imaging findings of liver in Wilson's disease. *Abdom Imaging.* 2011;36(1):69–73.
69. Paternostro R, Pfeiffenberger J, Ferenci P, et al. Non-invasive diagnosis of cirrhosis and long-term disease monitoring by transient elastography in patients with Wilson disease. *Liver Int.* 2020;40(4):894–904.
70. Litwin T, Gromadzka G, Członkowska A, Gołębiowski M, Poniatowska R. The effect of gender on brain MRI pathology in Wilson's disease. *Metab Brain Dis.* 2013;28(1):69–75.
71. Li X, Feng Z, Tang W, et al. Sex Differences in Clinical Characteristics and Brain MRI Change in Patients With Wilson's Disease in a Chinese Population. *Front Physiol.* 2018;9:1429.

72. Sinha S, Taly AB, Ravishankar S, et al. Wilson's disease: cranial MRI observations and clinical correlation. *Neuroradiology.* 2006;48(9):613–621.
73. Prashanth LK, Sinha S, Taly AB, Vasudev MK. Do MRI features distinguish Wilson's disease from other early onset extrapyramidal disorders? An analysis of 100 cases. *Mov Disord.* 2010;25(6):672–678.
74. Yang J, Li X, Yang R, et al. Susceptibility-Weighted Imaging Manifestations in the Brain of Wilson's Disease Patients. *PLoS One.* 2015;10(4):e0125100.
75. Fritzsch D, Reiss-Zimmermann M, Trampel R, Turner R, Hoffmann KT, Schafer A. Seven-tesla magnetic resonance imaging in Wilson disease using quantitative susceptibility mapping for measurement of copper accumulation. *Invest Radiol.* 2014;49(5):299–306.
76. Zhou XX, Qin HL, Li XH, et al. Characterizing brain mineral deposition in patients with Wilson disease using susceptibility-weighted imaging. *Neurol India.* 2014;62(4):362-366.
77. Patell R, Dosi R, Joshi HK, Storz D. Atypical neuroimaging in Wilson's disease. *BMJ Case Rep.* 2014;2014.
78. Hori H, Kudo Y, Kuroiwa Y, Tanaka F. Azure Lunulae and Leukoencephalopathy in Wilson Disease. *Intern Med.* 2020.
79. Prashanth LK, Taly AB, Sinha S, et al. Prognostic factors in patients presenting with severe neurological forms of Wilson's disease. *QJM.* 2005;98(8):557–563.
80. Litwin T, Dzieżyc K, Karliński M, Chabik G, Czepiel W, Czlonkowska A. Early neurological worsening in patients with Wilson's disease. *J Neurol Sci.* 2015;355(1-2):162–167.
81. Wallace DF, Dooley JS. ATP7B variant penetrance explains differences between genetic and clinical prevalence estimates for Wilson disease. *Hum Genet.* 2020;139(8):1065–1075.
82. Coffey AJ, Durkie M, Hague S, et al. A genetic study of Wilson's disease in the United Kingdom. *Brain.* 2013;136(5):1476–1487.
83. Kluska A, Kulecka M, Litwin T, et al. Whole-exome sequencing identifies novel pathogenic variants across the ATP7B gene and some modifiers of Wilson's disease phenotype. *Liver Int.* 2019;39(1):177–186.
84. Yang X, Tang XP, Zhang YH, et al. Prospective evaluation of the diagnostic accuracy of hepatic copper content, as determined using the entire core of a liver biopsy sample. *Hepatology.* 2015;62(6):1731–1741.
85. Papanikolopoulos K, Alexopoulou A, Dona A, Hadziyanni E, Vasilieva L, Dourakis S. Abnormalities in Cu and Zn levels in acute hepatitis of different etiologies. *Hippokratia.* 2014;18(2):144–149.

86. Attri S, Sharma N, Jahagirdar S, Thapa BR, Prasad R. Erythrocyte metabolism and antioxidant status of patients with Wilson disease with hemolytic anemia. *Pediatr Res.* 2006;59(4):593–597.
87. Duncan A, Yacoubian C, Beetham R, Catchpole A, Bullock D. The role of calculated non-caeruloplasmin-bound copper in Wilson's disease. *Ann Clin Biochem.* 2017;54(6):649-654.
88. Poujois A, Trocello JM, Djebrani-Oussedik N, et al. Exchangeable copper: a reflection of the neurological severity in Wilson's disease. *Eur J Neurol.* 2017;24(1):154-160.
89. Lyon TD, Fell GS, Gaffney D, et al. Use of a stable copper isotope (65Cu) in the differential diagnosis of Wilson's disease. *Clin Sci (Lond).* 1995;88(6):727–732.
90. Członkowska A, Rodo M, Wierzchowska-Ciok A, Smolinski L, Litwin T. Accuracy of the radioactive copper incorporation test in the diagnosis of Wilson disease. *Liver Int.* 2018;38(10):1860-1866.
91. Petrasek J, Jirsa M, Sperl J, et al. Revised King's College score for liver transplantation in adult patients with Wilson's disease. *Liver Transpl.* 2007;13(1):55–61.
92. Squires RH, Jr., Shneider BL, Bucuvalas J, et al. Acute liver failure in children: the first 348 patients in the pediatric acute liver failure study group. *J Pediatr.* 2006;148(5):652–658.
93. EASL Clinical Practical Guidelines on the management of acute (fulminant) liver failure. *J Hepatol.* 2017;66(5):1047–1081.
94. Dhawan A, Taylor RM, Cheeseman P, De Silva P, Katsiyiannakis L, Mieli-Vergani G. Wilson's disease in children: 37-year experience and revised King's score for liver transplantation. *Liver Transpl.* 2005;11(4):441-448.
95. Proost R, Cassiman D, Levtchenko E, Morava-Kozicz E, Neirynck J, Witters P. Fulminant Wilson Disease in Children: Recovery After Plasma Exchange Without Transplantation. *J Pediatr Gastroenterol Nutr.* 2020;71(6):720–725.
96. Appenzeller-Herzog C, Mathes T, Heeres MLS, Weiss KH, Houwen RHJ, Ewald H. Comparative effectiveness of common therapies for Wilson disease: A systematic review and meta-analysis of controlled studies. *Liver Int.* 2019;39(11):2136–2152.
97. Clinical commissioning policy: Trientine for Wilson disease (all ages). https://www.england.nhs.uk/wp-content/uploads/2018/12/Trientine-for-Wilson-disease-all-ages-1.pdf (*accessed September 2021*).
98. Weiss KH, Thompson C, Dogterom P, et al. Comparison of the Pharmacokinetic Profiles of Trientine Tetrahydrochloride and Trientine Dihydrochloride in Healthy Subjects. *Eur J Drug Metab Pharmacokinet.* 2021;46(5):665-675.
99. Gibbs K, Walshe JM. Penicillamine and pyridoxine requirements in man. *Lancet.* 1966;1(7430):175-179.

100. Weiss KH, Gotthardt DN, Klemm D, et al. Zinc monotherapy is not as effective as chelating agents in treatment of Wilson disease. *Gastroenterology.* 2011;140(4):1189–1198.
101. Marcellini M, Di Ciommo V, Callea F, et al. Treatment of Wilson's disease with zinc from the time of diagnosis in pediatric patients: a single-hospital, 10-year follow-up study. *J Lab Clin Med.* 2005;145(3):139-143.
102. Santiago R, Gottrand F, Debray D, et al. Zinc Therapy for Wilson Disease in Children in French Pediatric Centers. *J Pediatr Gastroenterol Nutr.* 2015;61(6):613–618.
103. Sturm E, Piersma FE, Tanner MS, Socha P, Roberts EA, Shneider BL. Controversies and Variation in Diagnosing and Treating Children With Wilson Disease: Results of an International Survey. *J Pediatr Gastroenterol Nutr.* 2016;63(1):82–87.
104. Kalita J, Kumar V, Chandra S, Kumar B, Misra UK. Worsening of Wilson disease following penicillamine therapy. *Eur Neurol.* 2014;71(3-4):126–131.
105. Walshe JM, Yealland M. Chelation treatment of neurological Wilson's disease. *Q J Med.* 1993;86(3):197-204.
106. Brewer GJ, Turkay A, Yuzbaziyan-Gurkan V. Development of neurologic symptoms in a patient with asymptomatic Wilson's disease treated with penicillamine. *Arch Neurol.* 1994;51(3):304–305.
107. Glass JD, Reich SG, DeLong MR. Wilson's disease. Development of neurological disease after beginning penicillamine therapy. *Arch Neurol.* 1990;47(5):595–596.
108. Czlonkowska A, Gajda J, Rodo M. Effects of long-term treatment in Wilson's disease with D-penicillamine and zinc sulphate. *J Neurol.* 1996;243(3):269–273.
109. Walshe JM, Munro NA. Zinc-induced deterioration in Wilson's disease aborted by treatment with penicillamine, dimercaprol, and a novel zero copper diet. *Arch Neurol.* 1995;52(1):10–11.
110. Poujois A, Sobesky R, Meissner WG, et al. Liver transplantation as a rescue therapy for severe neurologic forms of Wilson disease. *Neurology.* 2020;94(21):e2189-2202.
111. Weisner B, Hartard C, Dieu C. CSF copper concentration: a new parameter for diagnosis and monitoring therapy of Wilson's disease with cerebral manifestation. *J Neurol Sci.* 1987;79(1-2):229–237.
112. Pfeiffenberger J, Lohse CM, Gotthardt D, et al. Long-term evaluation of urinary copper excretion and non-caeruloplasmin associated copper in Wilson disease patients under medical treatment. *J Inherit Metab Dis.* 2019;42(2):371–380.
113. Dziezyc K, Litwin T, Chabik G, Czlonkowska A. Measurement of urinary copper excretion after 48-h d-penicillamine cessation as a compliance assessment in Wilson's disease. *Funct Neurol.* 2015;30(4):264-268.

114. Członkowska A, Litwin T. Wilson disease - currently used anticopper therapy. *Handb Clin Neurol.* 2017;142:181-191.
115. Hefter H, Tezayak O, Rosenthal D. Long-term outcome of neurological Wilson's disease. *Parkinsonism Relat Disord.* 2018;49:48–53.
116. Low HL, Alexander SK, Misbahuddin A, Gillett GT. Posterior subthalamic area deep brain stimulation for treatment of tremor and dystonia in Wilson's disease. *Brain Stimul.* 2019;12(5):1304–1306.
117. Beaulieu-Boire I, Aquino CC, Fasano A, et al. Deep Brain Stimulation in Rare Inherited Dystonias. *Brain Stimul.* 2016;9(6):905–910.
118. Sidiropoulos C, Hutchison W, Mestre T, et al. Bilateral pallidal stimulation for Wilson's disease. *Mov Disord.* 2013;28(9):1292–1295.
119. Walshe JM, Waldenström E, Sams V, Nordlinder H, Westermark K. Abdominal malignancies in patients with Wilson's disease. *QJM.* 2003;96(9):657–662.
120. Beinhardt S, Leiss W, Stattermayer AF, et al. Long-term outcomes of patients with Wilson disease in a large Austrian cohort. *Clin Gastroenterol Hepatol.* 2014;12(4):683–689.
121. Jong-Hon K, Togashi Y, Kasai H, Hosokawa M, Takeichi N. Prevention of spontaneous hepatocellular carcinoma in Long-Evans cinnamon rats with hereditary hepatitis by the administration of D-penicillamine. *Hepatology.* 1993;18(3):614–620.
122. Thattil R, Dufour JF. Hepatocellular carcinoma in a non-cirrhotic patient with Wilson's disease. *World J Gastroenterol.* 2013;19(13):2110–2113.
123. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. *J Hepatol.* 2018;69(1):182–236.
124. Walshe JM, Dixon AK. Dangers of non-compliance in Wilson's disease. *Lancet.* 1986;1(8485):845–847.
125. Dziezyc K, Karlinski M, Litwin T, Czlonkowska A. Compliant treatment with anti-copper agents prevents clinically overt Wilson's disease in pre-symptomatic patients. *Eur J Neurol.* 2014;21(2):332–337.
126. Maselbas W, Chabik G, Czlonkowska A. Persistence with treatment in patients with Wilson disease. *Neurol Neurochir Pol.* 2010;44(3):260–263.
127. Masełbas W, Członkowska A, Litwin T, Niewada M. Persistence with treatment for Wilson disease: a retrospective study. *BMC Neurol.* 2019;19(1):278.
128. Walshe JM. Cause of death in Wilson disease. *Mov Disord.* 2007;22(15):2216–2220.
129. Rubinfeld Y, Maor Y, Simon D, Modai D. A progressive rise in serum copper levels in women taking oral contraceptives: a potential hazard? *Fertility and sterility.* 1979;32(5):599-601.

130. Haimov-Kochman R, Ackerman Z, Anteby EY. The contraceptive choice for a Wilson's disease patient with chronic liver disease. *Contraception.* 1997;56(4):241-244.
131. Brewer GJ, Johnson VD, Dick RD, Hedera P, Fink JK, Kluin KJ. Treatment of Wilson's disease with zinc. XVII: treatment during pregnancy. *Hepatology.* 2000;31(2):364-370.
132. Scheinberg IH, Sternlieb I. Pregnancy in penicillamine-treated patients with Wilson's disease. *New England Journal of Medicine.* 1975;293(25):1300-1302.
133. Shimono N, Ishibashi H, Ikematsu H, et al. Fulminant hepatic failure during perinatal period in a pregnant woman with Wilson's disease. *Gastroenterologia Japonica.* 1991;26(1):69-73.
134. Kodama H, Anan Y, Izumi Y, Sato Y, Ogra Y. Copper and zinc concentrations in the breast milk of mothers undergoing treatment for Wilson's disease: a prospective study. *BMJ Paediatr Open.* 2021;5(1):e000948.
135. Koppikar S, Dhawan A. Evaluation of the scoring system for the diagnosis of Wilson's disease in children. *Liver Int.* 2005;25(3):680–681.
136. Leinweber B, Möller JC, Scherag A, et al. Evaluation of the Unified Wilson's Disease Rating Scale (UWDRS) in German patients with treated Wilson's disease. *Mov Disord.* 2008;23(1):54–62.
137. Volpert HM, Pfeiffenberger J, Groner JB, et al. Comparative assessment of clinical rating scales in Wilson's disease. *BMC Neurol.* 2017;17(1):140.

APPENDIX

New Wilson Index

	0 Points	1 Point	2 Points	3 Points	4 Points
Serum bilirubin, µmol/L	0-100	101-150	151-200	201-300	>301
Aspartate aminotransferase, U/L	0-100	101-150	151-300	301-400	>401
International normalized ratio	0-1.29	1.3-1.6	1.7-1.9	2.0-2.4	>2.5
White blood cell count, 10^9/L	0-6.7	6.8-8.3	8.4-10.3	10.4-15.3	>15.4
Albumin, g/L	>45	34-44	25-33	21-24	<20

A score of ≥11 points is associated with a high probability of death without liver transplantation and is an indication for liver transplantation. Adapted from Dhawan A et al.[29]

Contact details for liver transplant units

Paediatric liver transplant units

London - King's Paediatric Liver Centre, King's College Hospital (0203 2999000)

Birmingham – Liver Unit, Birmingham Children's Hospital (0121 333 9999)

Leeds – Children's Liver Unit, Leeds General Infirmary (0113 2432799)

Adult liver transplant units

London (North) – Sheila Sherlock Liver Centre, Royal Free Hospital (0207 794 0500)

London (South) - King's Liver Transplant Unit, King's College Hospital (0203 299 9000)

Birmingham – Liver Unit, Queen Elizabeth Hospital (0121 627 2000)

Leeds – Leeds Liver Unit, St James's University Hospital (0113 243 3144)

Newcastle – Liver Unit, Freeman Hospital (0191 233 6161)

Cambridge – Cambridge Liver Unit, Addenbrooke's Hospital (0122 324 5151)

Edinburgh – Scottish Liver Transplant Unit, Edinburgh Royal Infirmary (0131 536 1000)

NHS England commissioning criteria for trientine dihydrochloride

The following sections quote the clinical commissioning policy directly[97]:

Patients intolerant of penicillamine with symptomatic disease

Patients are eligible for trientine dihydrochloride if they experience the following early side effects in the first weeks/months whilst on penicillamine and symptoms have not resolved and/or copper levels have not normalised:

- Fever
- Rash*
- Enlarged lymph nodes
- Neutropenia
- Thrombocytopenia
- Proteinuria
- Severe persistent nausea

*Transient rashes and fever may occur early in therapy with penicillamine; if persistent, antihistamines or temporary withdrawal of treatment with or without a short course of steroids may be necessary. Penicillamine may be re-introduced at a lower dosage. If steroids are given, penicillamine should be reintroduced before steroid withdrawal.

Trientine dihydrochloride can be considered as an alternative to penicillamine in the following circumstances:

- Patient has a past history of an autoimmune tendency
- Patient has concurrent severe thrombocytopenia or renal disease
- Patients who are hypersensitive to penicillin – patients may react rarely to penicillamine

Patients who become intolerant of penicillamine at a later time (see list below) and are without symptomatic disease and patients who have stable disease

Trientine hydrochloride is a recognised option but these patients could also be considered for zinc maintenance therapy by the tertiary care specialist centre, with the requirement for regular clinical and laboratory monitoring.

Late events (months to years after starting penicillamine) are usually but not exclusively in the list below:

- Nephrotic syndrome
- Glomerulonephritis
- Total bone marrow aplasia
- Skin changes (cutis laxa, elastosis perforans serpiginosa, pemphigus)
- Myasthenia gravis
- Polymyositis
- Goodpastures syndrome
- Optic neuritis
- Proteinuria 1-2 g/day or equivalent in children
- Haematuria (if cause unknown)
- Thrombocytopenia, leukopenia
- Bleeding related to above
- Lupus like syndrome (haematuria, proteinuria, positive antinuclear antibody)
- Arthralgia

Leipzig criteria for the diagnosis of WD

Score	-1	0	1	2	4
Neurologic or psychiatric features (including typical MRI abnormalities)		Absent		Present	
KF rings (slit lamp examination)		Absent		Present	
Coombs negative hemolytic anaemia		Absent		Present	
Urine copper output		Normal	1-2x ULN	>2x ULN	
Urine copper output after penicillamine challenge (if baseline normal)				>5x ULN	
Liver copper content	Normal		1-5x ULN	>5x ULN	
Rhodanine-stained hepatocytes		Absent	Present		
Serum ceruloplasmin (mg/dL)		Normal	10-20	<10	
Pathogenic ATP7B mutations		None	One		Two

A total score of four or more indicates WD is highly likely, two to three indicates WD is probable (and more investigations required) and a score of zero to one indicates WD is unlikely. Adapted from Ferenci P et al.[26]

UWDRS neurological examination subscore

Item	Score
10. Speech	0 - Normal
	1 - Slight dysarthria or slight loss of expression, diction and/or volume
	2 - Moderate dysarthria or monotone, slurred speech. Still understandable
	3 - Marked impairment, difficult to understand
	4 - Unintelligible
11A. Facial expression - Oromandibular dystonia If >2, skip item 11B	0 - No dystonia present
	1 - Slight. Occasional grimacing or other mouth movements
	2 - Mild. Movement present less than 50% of the time
	3 - Moderate dystonic movements or contractions present most of the time
	4 - Severe dystonic movements or contractions present most of the time
11B. Facial expression - Hypomimia	0 - Normal
	1 - Minimal hypomimia, could be normal “Poker Face”
	2 - Slight but definitely abnormal diminution of facial expression
	3 - Moderate hypomimia; lips parted some of the time
	4 - Masked or fixed facies with severe or complete loss of facial expression
12. Tremor at rest Scores for RUL, LUL, RLL and LLL	0 - Absent
	1 - Slight and infrequently present
	2 - Mild in amplitude and persistent. Or moderate but intermittent
	3 - Moderate in amplitude and present most of the time
	4 - Marked in amplitude and present most of the time
13. Head tremor	0 - None
	1 - Slight or hardly perceptible tremor. May be intermittent
	2 - Moderate amplitude (<2 cm). May be intermittent
	3 - Marked amplitude (2-4 cm)
	4 - Severe amplitude (>4 cm)
14. Rigidity Scores for Neck, RUL, LUL, RLL and LLL	0 - Absent
	1 - Slight or detectable only when activated by mirror or other movements
	2 - Mild to moderate
	3 - Marked, but full range of motion easily achieved
	4 - Severe, range of motion achieved with difficulty
15. Finger taps Score for RUL and LUL	0 - Normal
	1 - Mild impairment
	2 - Moderate impairment
	3 - Severe impairment
	4 - Cannot perform the task
16. Rapid alternating movements of hands Score for RUL & LUL	0 - Normal
	1 - Mild impairment
	2 - Moderate impairment
	3 - Severe impairment
	4 – Cannot perform task
17. Handwriting	0 - Normal
	1 - Slightly impaired
	2 - Moderately impaired; all words are legible
	3 - Severely impaired; few words are legible
	4 - Cannot hold a pen
18A. Tremor in arms - Postural Score for RUL and LUL	0 - None
	1 - Slight or hardly perceptible postural tremor. May be intermittent
	2 - Moderate amplitude (<2 cm). May be intermittent
	3 - Marked amplitude (2-4 cm)
	4 - Severe amplitude (> 4 cm)
18B. Tremor in arms - Wing-beating	0 - None
	1 - Slight or hardly perceptible wing-beating tremor. May be intermittent
	2 - Moderate amplitude (< 2 cm). May be intermittent
	3 - Marked amplitude (2-4 cm)

Score for RUL and LUL	4 - Severe amplitude (> 4 cm)
19. Finger-to-nose-test Score for RUL and LUL	0 - Normal
	1 - Mild impairment
	2 - Moderate impairment
	3 - Severe impairment
	4 - Cannot perform the task
20. Leg agility Score for RLL and LLL	0 - Normal
	1 - Mild impairment
	2 - Moderate impairment
	3 - Severe impairment
	4 - Cannot perform the task
21. Postural tremor in legs Score for RLL and LLL	0 - None
	1 - Slight or hardly perceptible tremor. May be intermittent
	2 - Moderate amplitude (<2 cm). May be intermittent
	3 - Marked amplitude (2-4 cm)
	4 - Severe amplitude (> 4 cm)
22. Cervical dystonia	0 - No dystonia present
	1 - Slight. Occasional pulling
	2 - Obvious torticollis, but mild
	3 - Moderate pulling
	4 - Extreme pulling
23. Arm and hand dystonia Score for RUL and LUL	0 - No dystonia present
	1 - Slight dystonia. Clinically insignificant
	2 - Mild. Obvious dystonia, but not disabling
	3 - Moderate. Able to grasp, with some manual function
	4 - Severe. No useful grasp
24. Arising from chair	0 - Normal
	1 - Slow; or may need more than one attempt
	2 - Needs arms of seat as support
	3 - Tends to falls back and may have to try several times
	4 - Unable to arise without help
25A. Posture - Trunk dystonia If >2, skip items 25B and 25C	0 - No dystonia present
	1 - Slight bending; clinically insignificant
	2 - Definite bending, but not interfering with standing
	3 - Moderate bending; interfering with standing
	4 - Extreme bending of trunk preventing standing
25B. Posture - Ataxia of stance	0 - Absent
	1 - Slight (swaying only present without visual feedback)
	2 - Moderate (moderate swaying; still able to stand with feet together)
	3 - Marked (marked swaying; unable to stand with feet together)
	4 - Severe to most severe (unable to stand without support or bedridden)
25C. Posture Parkinsonism	0 - Normal erect
	1 - Not quite erect, slightly stooped posture; could be normal for older person
	2 - Moderately stooped posture, definitely abnormal; can be slightly leaning
	3 - Severely stooped posture with kyphosis; can be moderately leaning
	4 - Marked flexion with extreme abnormality of posture
26A. Gait - Leg dystonia Score for RLL and LLL If >2, skip items 26B and 26C	0 - No dystonia present
	1 - Slight dystonia, but not causing impairment; clinically insignificant
	2 - Mild dystonia. Walks briskly and unaided
	3 - Moderate dystonia. Severely impairs walking or requires assistance
	4 - Severe. Unable to walk on involved leg
26B. Gait - Ataxia	0 - Absent
	1 - Slight (ataxia only visible, when walking on tandem or without visual feedback)

	2 - Moderate (ataxia visible in normal walking; difficulties when walking on tandem)
	3 - Marked (broad-based, staggering gait; unable to walk on tandem)
	4 - Severe (unable to walk without support, wheelchair-bound, bedridden)
26C. Gait - Parkinsonism	0 - Normal
	1 - Walks slowly, may shuffle with short steps, but no festination or propulsion
	2 - Walks with difficulty, requires little or no assistance; may have festination
	3 - Severe disturbance of gait, requiring assistance
	4 - Cannot walk at all, even with assistance.
27C. Chorea Score for face, trunk, RUL, LUL, RLL and LLL	0 - Absent
	1 - Slight/ intermittent
	2 - Mild/ common or moderate/ intermittent
	3 - Moderate/ common
	4 - Marked/ prolonged

Adapted from Leinweber B et al.[136]