Review Article

Clinical practice guidelines in Wilson disease

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Abstract: Three guidelines in Wilson disease (WD) have been issued to date: by the American Association for the Study of Liver Diseases (AASLD) in 2003 with revision in 2008, by the European Association for the Study of the Liver (EASL) in 2012, and most recently by the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) in 2018. The following review aims to compare and contrast the approach to diagnosis and management of WD outlined in each guidance. Diagnostic criteria for WD are variable, with the AASLD proposing a clinical/biochemical algorithmic approach, while EASL and ESPGHAN favor use of the Leipzig score. Screening of first-degree relatives differs in modality: clinical and genetic testing in AASLD and ESPGHAN, versus genetic testing alone in EASL. There is general consensus regarding treatment of WD, though ESPGHAN favors zinc over chelators in maintenance phase and for asymptomatic patients. Liver transplantation is indicated in cases of acute liver failure (ALF) due to WD, but not primarily for neuropsychiatric disease in all guidelines. EASL and ESPGHAN advocate for use of the revised King's score to guide transplant listing. There are limited recommendations on special circumstances including pregnancy, surgery, and malignancy risk in WD. Though current recommendations address the management of liver disease due to WD, future guidelines may include a more detailed discussion of neurological and psychiatric manifestations of WD.

Keywords: Wilson disease (WD); guideline; liver

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Background

One of the challenges in Wilson disease (WD) that is common to many rare diseases is the scarcity of randomized and high-quality clinical studies to inform recommendations. Therefore, guidelines in WD have relied less on randomized trial data and more on case series and expert consensus to complement the limited study data available. In addition, the wide range of phenotypic manifestations of WD with overlapping ages of presentation and multisystem involvement makes it more complicated to draft a comprehensive guidance for diagnosis and treatment. Three guidelines have been developed to date, all focused on liver disease in WD: the American Association for the Study of Liver Diseases (AASLD) issued their guideline in 2003 with revision in 2008 (1), the European Association for the Study of the Liver (EASL) in 2012 (2) and most recently the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) in 2018 (3). While these are comprehensive with respect to liver issues, they are limited with respect to consensus care for neurological and psychiatric manifestations of WD and with respect to certain special circumstances. We will explore the commonalities and differences of these three guidelines in their approach to diagnosis and management of WD (summarized in *Table S1*). Given their temporal distribution,

the comparative review of these recommendations below ultimately reflects the evolution of WD care over the past decade.

Diagnosis

Diagnostic testing

The three guidelines differ in their approach to diagnostic testing: reliance on liver biopsy and role of genetic mutational analysis represent some areas of divergence. The AASLD advocates for an algorithmic approach to diagnosis, using clinical and biochemical parameters: slit lamp exam for Kayser-Fleischer (KF) rings, serum ceruloplasmin and 24-hour urine copper. Liver biopsy for histology and copper quantification is recommended if initial testing is non-concordant, and molecular testing is reserved for cases where biopsy is non-diagnostic. Slight differences in the diagnostic algorithm are specified if presentation is unexplained liver disease *vs.* neuropsychiatric disorder with or without liver disease, whereas other guidelines make no such distinction.

The EASL and ESPGHAN guidelines both advocate for the use of the Leipzig score to establish a diagnosis of WD. This scoring system includes a combination of clinical, biochemical and genetic testing (4). Individual components included presence or absence of KF rings, neurological symptoms, level of serum ceruloplasmin, presence or absence of Coombs-negative hemolytic anemia, liver copper quantification, urinary copper excretion over 24 hours (spontaneous or after penicillamine challenge) and mutation analysis for *ATP7B* mutations. Each component is weighted with respect to its presence or absence or degree of change from normal, and a diagnosis of WD is deemed "unlikely", "probable" or "highly likely" based on the number of points accrued, similar to the revised original scoring system of the International autoimmune hepatitis group (5). One of the limitations of the Leipzig scoring system is that it is expert-derived, and no specific data support the weighting ascribed to individual components or the prognostic value of their combination. However its use has been validated in adult and pediatric populations (6,7).

Calculation of the Leipzig score is the primary diagnostic approach presented in the EASL guidelines. Interestingly, this guideline proposes a slight variation on the interpretation of the score, whereby scores of 2 are classified as "unlikely" rather than "probable" as in the original scoring system. They further recommend that "unlikely" and "possible" cases be stratified based on urinary copper excretion, hepatic copper content and *ATP7B* mutational analysis to definitively rule in or out the diagnosis of WD.

The ESPGHAN guidelines incorporate the Leipzig score into a broader, stepwise approach to diagnosis. The first step consists of clinical evaluation (hepatosplenomegaly, ascites and KF rings), liver biochemistry and measures of copper metabolism (ceruloplasmin, 24-hour urinary copper). The second step focuses on molecular testing. One mutation is considered sufficient to diagnose WD in the presence of "definite" signs and symptoms, whereas 2 mutations are required in an asymptomatic child. Liver biopsy for copper quantification is designated as the third and final step. Leipzig score is calculated at each step, and testing concluded once a score of 4 points (high likelihood of WD) is achieved.

An algorithmic approach to diagnostic testing, as proposed by AASLD, is likely most helpful clinically in guiding the evaluation of a patient with suspected WD. However, a formal scoring system such as the Leipzig score, carries the advantage of being standardized, measurable and easily comparable and is ideally suited for the research setting. Perhaps the best strategy combines features of both approaches, as put forward by ESPGHAN where periodic Leipzig score calculation is embedded within a clinical algorithm. Moreover, EASL and ESPGHAN propose a strategy where liver biopsy plays a lesser role overall, in favor of increased reliance on mutational analysis, a shift which likely reflects a broader thrust towards non-invasive testing and wider availability and affordability of genetic analysis over the past decade.

Diagnosis of ALF due to WD

Contrary to the setting of unexplained liver disease, no formal algorithm or scoring system exists to diagnose acute liver failure (ALF) due to WD. All three guidelines recommend a combination of clinical and laboratory findings, which in the appropriate setting point to a diagnosis of ALF secondary to WD. The AASLD guidelines note the following features: Coombs negative hemolytic anemia, coagulopathy, renal failure, modest transaminitis, normal or markedly subnormal alkaline phosphatase (ALP), ALP to bilirubin ratio less than 2, female predominance. EASL specifies a ratio of ALP to bilirubin less than 4, and AST to ALT ratio greater than 2.2 in combination with other signs and symptoms. They also formally suggest confirmation on liver biopsy if possible (histology and copper quantitation),

or on explant in the setting of transplant. ESPGHAN highlights hyperbilirubinemia (greater than 17.5 mg/dL), low transaminases (100–500 IU/L), low ALP, and ALP to bilirubin ratio less than 1 as supportive but not pathognomonic of ALF secondary to WD.

Family screening

All three societies agree that family screening for WD should be pursued in first-degree relatives of affected patients but differ somewhat in preferred mode of screening. AASLD recommends that siblings be screened via *ATP7B* mutation analysis or haplotype studies when possible. Children of affected patients as well as other first-degree relatives in whom genetic testing is not available should receive a comprehensive panel (slit lamp, ceruloplasmin, 24 hours urine copper, liver tests, complete blood count, international normalized ratio) with or without liver biopsy for copper quantification. EASL proposes that all first-degree relatives should receive genetic screening alone, ideally *ATP7B* mutation analysis. In situations where the specific mutation of the affected patient is unknown, they recommend pedigree analysis using haplotypes based on known polymorphisms. However, this guideline does not comment on what to do if genetic testing is unavailable. ESPGHAN advocates that all first-degree relatives be screened using physical exam, liver function, serum ceruloplasmin as well as *ATP7B* mutational analysis or haplotype studies. It seems likely given continued advances in genetic testing that mutational analysis will become the prime mode of screening for WD, as suggested by EASL. Therefore, outlining alternative approaches remains relevant to situations where such testing is not available.

Treatment

Medical therapy

Medical therapy in WD is broadly divided into initial and maintenance phases. The presence or absence of clinical symptoms also modulates choice of therapy. There is general agreement between both adult guidelines on approach to treatment, but some differences when compared to pediatrics where zinc plays a more prominent role. All three guidelines support the view that initial therapy in a symptomatic patient should be a chelating agent (penicillamine or trientene). AASLD and ESPGHAN specify a potential role for combination therapy with zinc in the setting of decompensated cirrhosis. EASL guidelines also propose a role for zinc as initial choice in neurological patients.

AASLD and EASL both suggest maintenance-dose chelator or zinc as acceptable options for maintenance therapy as well as for first-line therapy in asymptomatic patients. ESPGHAN rather favors zinc in both these scenarios. The AASLD and EASL guidelines mention an emerging role for tetrathiomolybdate, though this agent is still under investigation. They also cite vitamin E as a potential adjunctive therapy, though without evidence for its efficacy in studies with patients with WD.

All three guidelines mention the importance of a low copper diet in concert with medical therapy, particularly within the first year of treatment. The ESPGHAN guidelines further recommend maintenance of a low copper diet in combination with chelator therapy until remission of symptoms and normalization of liver enzymes. They uniquely specify no need for dietary restriction if on zinc therapy, however. This could be problematic if zinc treatment is not consistent or if the amount of ingested copper is relatively high.

Treatment monitoring

The main indicators of copper balance used for treatment monitoring in all three society guidelines are the 24-hour urine copper and non-ceruloplasmin bound copper. There is agreement between all guidelines on the target range of urinary copper excretion while on maintenance chelator therapy: 200–500 μg (3–8 μmol) per day with slight differences expected between d-penicillamine and trientine since the former chelates more copper on a mole for mole basis. The EASL guidelines specify an additional target: that 24-hour urinary copper be measured after 2 days of cessation of chelation therapy, with values less than 100 μg (1.6 μmol) per day indicating adequate control.

Some slight differences are apparent for zinc therapy. The AASLD recommends aiming for urinary copper excretion less than 75 μg (1.2 μmol) per day while on zinc. EASL allows up to 100 μg (1.6 μmol) per day, while ESPGHAN, similar to AASLD, specifies 30–75 μg (0.5–1.2 μmol) per day. ESPGHAN recommends monitoring serum and urinary zinc while on zinc therapy. Periodically following zinc metabolism is mentioned in the AASLD and EASL guidelines as well, but without carrying the weight of a formal recommendation as it does in ESPGHAN.

Normalization of non-ceruloplasmin bound copper is cited as a secondary treatment target in all three guidelines,

though difficulties with commercial assays which most often utilize immunologic detection may limit its use clinically.

AASLD and EASL recommend following liver biochemistry and function, serum copper, ceruloplasmin and physical exam twice yearly, and urinary copper at least yearly. For patients on chelation therapy, blood count and urinalysis require biannual monitoring as well. ESPGHAN suggests similar monitoring parameters, however, as may be expected in the pediatric setting, at more frequent intervals: weekly during the first month of therapy, then every 1–3 months until remission, and every 3–6 months thereafter.

Transplant

All three guidelines endorse the position that indications for liver transplantation in WD include ALF and decompensated cirrhosis unresponsive to medical management, and that extrahepatic disease (neuropsychiatric) does not constitute a primary indication for transplant. ESPGHAN goes as far as stating that severe neuropsychiatric disease represents a contraindication to transplant, likely a reflection of poor reversibility and its potential impact on long-term adherence.

A prognostic index, the revised King's score, was developed using a combination of biochemical parameters (bilirubin, aspartate aminotransferase, international normalized ratio, white blood cell count and albumin) to assess mortality in liver failure due to WD (8). EASL and ESPGHAN formally recommend its use to guide need for transplant listing (score of 11 or greater).

Special circumstances

Acute liver failure

All three societies agree on liver transplantation as the principal treatment modality in ALF due to WD. AASLD further delineates some bridging therapies that may be helpful, particularly for renal protection: plasmapheresis, hemofiltration, exchange transfusion and albumin dialysis. A potential role for extracorporeal liver support systems such as the molecular adsorbents recirculating system (MARS) is mentioned by both AASLD and ESPGHAN as a bridge to transplant.

Pregnancy

AASLD and EASL make similar recommendations on management of WD during pregnancy and in the postpartum period. Both support continuing WD therapy during pregnancy, with some modifications. Given concerns for potential teratogenicity as well as for wound healing post-partum, dose-reduction of chelators is recommended for the full duration of pregnancy. It is suggested that zinc be maintained without dose-adjustment. Both societies agree that breastfeeding is contraindicated on penicillamine, with few data available on the safety of trientene and zinc in this setting.

The EASL guidelines uniquely address the question of contraception: spermicide, barrier methods and progesterone-only preparations are suggested given the impact of estrogen on copper metabolism, though based on limited data using older formulations with high-dose estrogens.

Surgery

AASLD is unique in suggesting dose-reduction of chelator therapy in the event of a surgical procedure, given potential concern for wound healing. No adjustment of zinc therapy is recommended, similar to recommendations during pregnancy.

Liver cancer and WD

Hepatobiliary malignancies, namely hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma, occur rarely in WD, with a reported prevalence of 1.2% in a large multicentre cohort (9). The AASLD specifies that no screening is currently recommended for HCC in WD and makes no recommendation on screening for cholangiocarcinoma. EASL and ESPGHAN do not comment on the topic of hepatic malignancy in WD.

Conclusions

Guidelines in WD highlight current challenges and opportunities: a lack of consensus on the best diagnostic strategy in a disease known to have wide phenotypic variability, the expansion of genetic testing and its applications and evolving treatment options. Future guidelines may include a more detailed discussion of extrahepatic manifestations of WD and their management, as well as management of ALF due to WD, pregnancy and a better characterization of malignancy risk. Ultimately, more high-quality data is needed to inform future recommendations, as WD guidance transitions away from

expert opinion and more towards evidence-based guidance.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Supplementary

Table S1 Summary of guideline recommendations in WD

Society guidelines	Diagnosis			Treatment			Special circumstances		
	Diagnostic testing	Diagnosis of ALF due to WD	Family screening	Medical therapy	Treatment monitoring	Transplant	ALF	Pregnancy	Surgery
AASLD 2008	Clinical and biochemical algorithmic approach	Laboratory and clinical assessment	Siblings: genetic testing*. Children, other first-degree relatives: clinical assessment	*Initial:* chelator +/– zinc. *Maintenance and asymptomatic:* chelator or zinc	24-hour urine copper	*Indication:* decompensated cirrhosis, not primarily for neuropsychiatric disease	Bridging therapies, transplant	Dose-reduction of chelator, no adjustment for zinc	Dose-reduction of chelator, no adjustment for zinc
EASL 2012	Leipzig score	Laboratory and clinical assessment	First-degree relatives: genetic testing	*Initial:* chelator. *Maintenance and asymptomatic:* chelator or zinc	24-hour urine copper	*Indication:* decompensated cirrhosis, not primarily for neuropsychiatric disease. *Prognosis:* revised King's Wilson score	Transplant	Dose-reduction of chelator, no adjustment for zinc	–
ESPGHAN 2018	Clinical and biochemical algorithm and Leipzig score	Laboratory and clinical assessment	First-degree relatives: clinical assessment and genetic testing*	*Initial:* chelator +/– zinc. *Maintenance and asymptomatic:* zinc	24-hour urine copper. If zinc therapy: serum zinc, 24-hour urine zinc	*Indication:* decompensated cirrhosis, exclude severe neuropsychiatric disease. *Prognosis:* revised King's Wilson score	Bridging therapies, transplant	–	–

*, if genetic testing unavailable, standard biochemical and clinical testing. WD, Wilson disease.